Psoriasis as netopathy.
Model of pathogenesis with unique netosis role.

Edition e1.2

Mikhail Peslyak, Nikolay Korotky

Antipsoriatic Association
"The Natural Alternative"
Moscow, 2020

UDC 616.5:616-092;

Mikhail Yuryevich Peslyak[1,2], Nikolay Gavrilovich Korotky[1].
Psoriasis as netopathy. Model of pathogenesis with unique netosis role.
Edition e1.2,
M.: Antipsoriatic Association "The Natural Alternative", 2020. - 73 pages.

ISBN 978-5-905504-08-2

[1] **Pirogov Russian National Research Medical University**
[2] **Antipsoriatic Association "The Natural Alternative"**

Electronic Publication Date:
Edition e1.2: Dec 8, 2020. DOI: 10.5281/zenodo.4310086
DOI of latest edition: 10.5281/zenodo.4310085

Web: www.psorias.info, E-mail: info@psorias.info

The given book is authorized translation of the book (edition r1.2), published in Russian: ISBN 978-5-905504-07-5, DOI: 10.5281/zenodo.4310079**. Translation has been carried out with active support of "Status Translation" agency. Reprinting at occurrence of new materials or detection of serious errors is supposed. Further, updated texts (Russian and English) of the book will be placed in Internet.**
Details and links on www.psorias.info.

Supplements

Psoriasis as netopathy. Model of pathogenesis with unique netosis role. Supplements.
(e1.2, pdf-format, DOI: 10.5281/zenodo.4310107)

Abstract

An analytical survey of results of experimental and theoretical works on psoriatic disease has been carrried out. A new YN-model of pathogenesis of psoriasis as skin manifestation of systemic psoriatic process SPPN is formulated. The model presupposes a crucial role of small intestine hyperpermeability for bacterial products and growth of populations of Gram(-) TLR4-active and Gram+ NOD2-active bacteria (including those presumed psoriagenic PsB) in small intestine microbiome. PsB – bacteria presumed psoriagenic – are given a definition based on existence of genes responsible for forming peptidoglycan interpeptide bridges, similar to Str.pyogenes. All known such species are identified.

The central subprocess of systemic psoriatic process SPPN is PAMP-nemia, namely chronic kPAMP-load on blood phagocytes, also leading to increased kPAMP-level in blood.The key PAMP (kPAMP) are LPS, PG (including PG-Y - peptidoglycan of PsB) and bacDNA. PAMP-nemia causes increased kPAMP-carriage of phagocytes and growth of prenetotic neutrophil fraction in blood. SPPN severity is proportional to total kPAMP-load on blood phagocytes and to their total (PG-Y)-carriage. SPPN severity predetermines possibility of initiating and supporting psoriasis.

Senescent kPAMP+ blood neutrophils do not completely degrade kPAMP as they preserve the latter for delivery into bone marrow. Many of them become attracted into inflamed skin, undergo netosis, and kPAMP (including PG-Y) appear in extracellular space. Dermal monocytes and dendritic cells endocyte PG-Y, then they transform to mature maDC-Y and carry out Y-antigen presentation to specific TL-Y, activating them. Skin immune system interprets Y-antigen presentation as a sign of dermal PsB expansion and turns on one of its protection mechanisms – epidermal hyperproliferation.

Pinpoint psoriatic plaque is initiated during dermal inflammatory process L2, causing innate response, particularly at L2(DEMP) - dermal expansion of commensal microbiome with PsB. For L2(DEMP), a phase-by-phase initiation of pinpoint plaque and of its subsequent growth is constructed. Y-priming level (presence and concentration of Y-specific T-lymphocytes in prepsoriatic dermis and lymphnodes) determines possibility of plaque initiation.

Severity and growth of plaque is determined by intensity of Y-antigen income to dermis inside kPAMP+ phagocytes. New kPAMP+ phagocytes and Y-specific T-lymphocytes are constantly attracted into plaques, which supports inflammatory reaction. With decrease of SPPN severity, natural remission of plaques occurs, up to their total disappearance.

Psoriasis is regarded as reaction of skin immune system to imaginary dermal PsB expansion supported by netosis of (PG-Y)+ neutrophils. Within YN-model, psoriasis is classified as netopathy.

Key words

bacterial DNA, bacterial products, cytokines, dendritic cells, innate and adaptive response, keratinocytes, kPAMP-carriage, lipopolysaccharide, microbiome, model of pathogenesis, muramyl dipeptide, netosis, neutrophils, PAMP-nemia, peptidoglycan, phagocytes, psoriagenic bacteria, psoriasis, small intestine permeability, systemic psoriatic process, T-lymphocytes.

Content

«Is it true that firemen put fires out instead of going to start them?»

Ray Bradbury, «Fahrenheit 451»

1. Psoriasis

Epidermis self-renewal is regular process. New cells are born in basal layer. They mature, vary, migrate outside and form external horny layer. Then they die away and exfoliate. Standard duration of epidermis cell life (renewal period) for areas of skin with average thickness is 20-25 days. Psoriasis accelerates self-renewal. Cells live 4-10 days (Doger 2007, Weatherhead 2011, Zhang 2015). Cells migrating outside have no time to differentiate and they aren't quite functional. Psoriatic plaques have red shade. They are tender, they are covered by white flakes due to intensive lost of cells and they are much thicker.

Psoriasis isn't contagious. There are various types of psoriasis: vulgaris or plaque (L40.0), flexural or inverse (L40.83-4), erythrodermic (L40.85), pustular (L40.1-3, L40.82), guttate (L40.4). Codes of diseases are given according to ICD-10. Chronic plaque psoriasis (CPs) is the most frequent type (more than 80% of total number of cases). Up to 15% of psoriatics also suffer from psoriatic arthritis (L40.5).

Psoriasis strikes about 2% of population (~150 million people). New diagnosis of psoriasis gets ~5 million people every year. Disease appears after birth or in extreme old age. Psoriasis is a chronic disease so there are periods of aggravation and remission. Sometimes there is no cause for period change and sometimes aggravation can be decreased as a result of treatment. Serious psoriasis can result in disability. Psoriasis course is similar in men and women. Afro-Americans, Indians, Chineses and Japaneses suffer from psoriasis less frequently and Eskimos don't suffer from psoriasis at all (Gudjonsson 2007, Parisi 2013, Michalek 2017).

Psoriasis is registered in "Online Mendelian Inheritance in Man" at number OMIM*177900. Psoriasis is disease with hereditary predisposition: concordance of uniovular twins is 70%. If one parent suffers from psoriasis children are diagnosed the disease in 15-25% of cases; if both parents suffer from psoriasis children are diagnosed the disease in more than 40-60% of cases. The interrelation of allele HLA-Cw*0602 (chromosome 6p21) and psoriasis of the first type which is characterized by early beginning is proved. This allele is found in more than 60% of PP (not more than 15% of healthy persons). Locuses of other chromosomes have weaker interrelations. Psoriasis can't begin only in presence of genetical deflections. External exposure is necessary for beginning and maintenance of psoriasis. Infections, skin traumas, stresses, reaction to medications, climatic changes and other causes can provoke onset of psoriasis or its aggravation.

2. Models of pathogenesis and unknown antigen

There are several models of pathogenesis of psoriasis, but none of them is universally accepted. The systemic BF-model (Fig.A1) and Y-model are described in (Baker 2006b) and (Peslyak 2012a, Peslyak 2012b) respectively. The local N-model (Di Meglio 2011, Perera 2012), GK-model (Guttman-Yassky 2011) and TC-model (Tonel 2009) and GL-model (Gilliet 2008) are considered and given a comparative analysis in the monograph (Peslyak 2012b). Local models by other authors (on the whole, similarly constructed) have been published in recent years. They include the specified GKH-model (Hawkes 2017); FM-model (Fig.A2, Delgado-Rizo 2017); SE-model (Fig.A3, Schon 2018) and BMM-model (Benhadou 2018, fig.1).

The modern idea of skin immune system functioning is outlined in the video "Immunology of Skin" directed by Miriam Merad and James Kruger. Part two of the video deals with the wrong work of skin immune system during psoriatic inflammation. The key role of the "unknown antigen" (hereinafter Y-antigen) in psoriatic inflammation is also highlighted (Fig.2A). Subsequently, a number of new studies devoted to psoriasis were published. But none of them has yet given exact answers to the questions:

- What is the origin of Y-antigen?
- What is the chemical structure of Y-antigen?

Four versions of the origin of Y-antigen are submitted (Fig.2B):

Version V1. Origin is resident and host. It is the main version of authors of local models of pathogenesis. Y-antigens are autoantigens descended from host resident skin cells. All local models of pathogenesis presume that the main reasons for initiation and support of psoriasis are located only in skin (and, including, unknown antigen). Such potential autoantigens were studied repeatedly (keratin 17, LL37, lipid antigens, ADAMTSL5, PLA2G4D and others) (Albanesi 2018, Arakawa 2015, Benhadou 2018, Cheung 2016, Di Domizio 2019, Fuentes-Duculan 2017, Hawkes 2017, Lowes 2014, Schon 2018,

Ten Bergen 2020, Valdimarsson 2009). Specific to them T-lymphocytes are found in psoriatic skin, but not in all psoriatic patients. Therefore any of them cannot be Y-antigen, specific T-lymphocytes to which must be found in _each_ psoriatic patient. The presence of antibodies to the autoantigens listed above can be explained by their high concentration in psoriatic skin and, consequently, in blood. This concentration is a consequence, and not a cause of psoriatic inflammation. Numerous attempts to prove the validity of version V1 have not been successful yet.

Version V2. Origin is non-resident from external environment (of course, non-host). Y-antigens are fragments of chemicals or bacteria, fungi, viruses or proteins secreted by them coming on or into the skin from external environment. The given version already existed in the 20th century. For many years this version was considered as the main one. But numerous studies to prove version V2 inadequate (Baker 2008).

Version V3. Origin is non-resident from within (for example, from blood flow) and non-host. Y-antigens are fragments of chemicals or bacteria, fungi, viruses or proteins secreted by them. Come to psoriatic skin from other body organs (e.g. in blood phagocytes). The main version of the authors of systemic models of pathogenesis: BF-model. Barbara Baker and Lionel Fry (Fig.A1, Baker 2006a, Baker 2006b); Y-model. Peslyak MY and Korotky NG (Korotky 2005, Peslyak 2012a, Peslyak 2012b); YN-model (Fig.4, Fig.5, Fig.6, Fig.7). The known facts do not contradict version V3. The question of presumed chemical structure of Y-antigen is discussed in (Peslyak & Korotky 2019).

Version V4. Origin is non-resident from within (for example, from blood flow) and host. Y-antigens are autoantigens descended from host non-resident cells. Coming to skin from other body organs (for example, fragments of phagocytes of blood). It is part from potential autoantigens (LL37, ADAMTSL5, PLA2G4D) listed in version V1 description. They descend not only from resident skin phagocytes (neutrophils, dendritic and mast cells), but also and from non-resident phagocytes attracted from blood flow during psoriatic inflammation. The version V4 is not proved (for the same reasons, as version V1) (Frasca 2019, Lande 2014, Schon 2019).

3. Prerequisites

Some of the studies underlying this work are listed below.

- **In psoriatic patients, there is an increased macromolecular small intestinal permeability.** Zhanna Rudkovskaya with co-workers, PRNRMU, Institute of food of Russian Academy of Medical Science, Moscow, Russia (Rudkovskaya 2003, Stenina 2004); Eugeny Kharkov with co-workers, Krasnoyarsk state medicine university, Krasnoyarsk, Russia (Harkov 2005, Harkov 2006, Harkov 2008, Shiryaeva 2007)
- **Majority of PP had SIBO (small intestine bacterial overgrowth).** More than 10^5 CFU/ml found in 95 of 121 PP (78.5%). Natalia Potaturkina-Nesterova with co-workers. Ulyanovsk State University, Ulyanovsk, Russia (Gumayunova 2009a, Gumayunova 2009b, Gumayunova 2009c, Gumayunova 2016).
- **Majority of PP had high blood LPS-level.** Zuhra Garaeva with co-workers. Kazan Medicine Academy, Kazan, Russia (Garaeva 2007).
- **Systemic model of pathogenesis (BF-model).** The antigenic role of streptococcal peptidoglycan outside skin (gut, tonsils, blood flow) and inside psoriatic skin. Barbara Baker and Lionel Fry (2006-7). Faculty of Medicine, Imperial College, London, UK (Baker 2006a, Baker 2006b, Baker 2006c).
- **New systemic model of pathogenesis (Y-model).** Development of BF-model. Detailed coordinated description of systemic and local subprocesses. (Peslyak 2012a, Peslyak 2012b).
- **Netosis of neutrophils in psoriatic patients' blood and skin.** Demonstration of the correlation between netotic neutrophil percentage in blood and psoriasis severity. Correlation between netotic neutrophil percentage in control blood of healthy patients under the influence of serum from psoriatic patients and severity of their PASI. Estimation of netotic neutrophil quantity in psoriatic skin. Cheng-Che E. Lan et al., Department of Dermatology, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan. (Hu 2016).

Fragments of bacterial products of small intestine bacteria contain PAMP: lipopolysaccharide (LPS) and peptidoglycan (PG), including specific peptidoglycan (PG-Y) and bacDNA. With increased macromolecular small intestine permeability (Korotky & Peslyak 2005, Harkov 2005, Harkov 2006, Harkov 2008, Camilleri 2019, Ely 2018, Graziani 2019, Guerville 2016) in psoriatic patients, these bacterial products get to systemic blood flow, form the chronically increased PAMP level in blood and chronically increased kPAMP-load on blood phagocytes. Specifically, they form the increased LPS-level (Garaeva 2007).

Phagocytes are neutrophils, monocytes and dendritic cells (Nagl 2002).

The specific peptidoglycan PG-Y contains Y-antigen, i.e. peptide which includes interpeptide bridges (L-Ala)-(L-Ala) and/or (L-Ser)-(L-Ala). Such bridges are found in nearly all species of Streptococcus, in Enterococcus faecalis, and also in many species from Leuconostoc and Weissella genera (Fig.3 and Table 6). Such species are presumed psoriagenic (Baker 2006a, Baker 2006b, Peslyak 2012a, Peslyak 2012b, Ely 2018), hereinafter designated PsB (section SP2.1).

After publication of Y-model (Peslyak 2012a, Peslyak 2012b).there appeared results of new researches, primarily connected with netosis of neutrophils (Delgado-Rizo 2017, Grayson 2016, Hasler 2016, Kenny 2017, Papayannopoulos 2018, Pinegin 2015, Rai 2019), including that associated with psoriasis. It became known that a considerable proportion of blood neutrophils in psoriatic patients is in the activated (prenetotic) state (Hu 2016, fig.1 and 3; Lin 2011, fig.4; Shao 2016, Shao 2019).

Within new YN-model such a prenetotic condition of blood neutrophils is also dictated by chronically increased kPAMP-load (section SPN4).

Getting into inflamed psoriatic skin, many blood neutrophils undergo netosis (Lin 2011, fig.3; Hu 2016, fig.4). As a result, in the intercellular space there can appear non-degraded bacterial products which were earlier endocyted by neutrophils in blood, including Y-antigens. Bacterial products lost during netosis are endocyted by all skin phagocytes. Monocytes Mo and dendritic cells DC which endocyte non-degraded fragments of PG-Y become Y-antigen carriers (hereinafter Mo-Y and DC-Y) (Fig.6). Under the influence of pro-inflammatory cytokines some monocytes Mo-Y are transformed to dendritic cells MoDC-Y.

In pro-inflammatory environment MoDC-Y and DC-Y continue transformation and transform to mature dendritic cells maDC-Y. These maDC-Y present Y-antigen to effector TL-Y (Y-specific T-lymphocytes) (subprocess L8a, Fig.6 and Fig.7). This presentation initiates and supports adaptive answer to imaginary dermal expansion of PsB, one of its consequences being hyperproliferation of keratinocytes (subprocess L8b). The transfer of Y-antigen in psoriatic skin from neutrophils to monocytes and dendritic cells due to netosis is the main difference between YN-model and Y-model (Fig.6).

A detailed description of all the differences between YN-model and Y-model can be found in Supplement A8. Within the project (Peslyak & Korotky 2019) it is proposed to receive new facts in support of several basic hypotheses underlying systemic Y-model and YN-model (Table A12).

A model cannot be called “new” if it does not contain new fragments that are absent in other models, including hypothetical (sub)processes and-or dependencies. All new fragments of YN-model do not contradict to commonly accepted facts.

4. Neutrophils in YN-model

We have collected and extended information on the known and presumed roles of neutrophils at psoriasis. In the text above, the reasons why neutrophils, apart from blood monocytes and dendritic cells, play a major role in YN-model are enumerated. The requirement of blood phagocyte tolerization which was crucial for Y-model (for monocytes and dendritic cells) is also omitted. Activated blood neutrophils (unlike monocytes and dendritic cells) retain the opportunity of being attracted to inflamed tissues, as LPS impact on them, albeit reduces CXCR4 expression, at the same time contributes to considerable CCR2 expression (Shen 2017).

Senescent neutrophils can take endocyted (in blood flow) bacterial products into bone marrow (which is stimulated by growth of CXCR4 expression), so these products find themselves in extracellular space after apoptosis of these neutrophils. Notably these bacterial products retain their PAMP properties. Such a function of senescent neutrophils is meant for training monocyte progenitors during their maturing in bone marrow (Tacke 2006, Rankin 2010).

During systemic psoriatic process SPPN (due to chronic kPAMP-load) some part of senescent blood neutrophils (along with other neutrophils) is constantly attracted into inflamed psoriatic skin instead of bone marrow. It happens due to constant CCR1 expression and probably owing to change of CXCR4 expression to CCR2 expression (Uhl 2016, Ortmann 2018). In psoriatic skin CCL2, CCL5 (CCR1 ligands) and CCL2, HBD2 and HBD3 (CCR2 ligands) are actively secreted (Supplement A12).

As a result, these senescent blood neutrophils appear in the place, where they were not supposed to appear, at the same time (presumably) retaining non-degraded bacterial products in them. Due to the fact that there are many factors of netosis in psoriatic skin (Table 3), there occurs netosis of part of these neutrophils (local subprocess L3b), especially since senescent neutrophils have a greater potential to netosis (Ortmann 2018).

In YN-model the list of kPAMP is extended: bacDNA is added to LPS and PG. This is done because neutrophils have not only endosomal, but also membrane TLR9 receptor (Lindau 2013). That means that bacDNA (as well as LPS) can contribute to activating (transforming to prenetotic state) neutrophils even at external contact or binding. Activation intensity largely depends on the percentage of CpG fragments in bacDNA, depending on bacterial species (Dalpke 2006). Interaction of CpG fragments with TLR9 also reduces the tendency of neutrophils to apoptosis (Jozsef 2004), which can contribute to increasing the proportion of neutrophils terminating their existence by netosis.

Section subprocess L3b contains detailed analysis of factors (real and presumed) contributing to netosis at psoriasis (Table 3). Among them there is no bacDNA, as at the moment there are no published studies of bacDNA influence on netosis.

Intensity of phagocyte activation under the influence of several PAMP considerably increases (synergic effect). There is also synergic influence of a few factors (not only PAMP) on netosis (Table 3).

5. Systemic psoriatic process SPPN.

SPPN is similar to SPP, but it is less complicated. Process SPPN involves GIT, hepatobiliary, vascular and immune systems, elimination organs; fragments of bacterial products containing PAMP (including kPAMP) chronically enter the blood from small intestine as part of this process. Therefore kPAMP-load (contact, linkage, and endocytosis) on blood phagocytes (including Mo and DC) becomes constant, which leads to the emergence of a considerable proportion of kPAMP-carriers among them.

Chronically increased blood level LPS is called endotoxemia and chronically increased LPS-load on phagocytes is the main sign of endointoxication. Set of these deflections (in case of influence of several PAMP) was named "PAMP-nemia", and set of PAMP causing these deflections - key PAMP (Peslyak 2012a). In YN-model key PAMP (kPAMP) are LPS, PG (including PG-Y) and bacDNA (subprocess SPN4).

Source of PG-Y entering the blood can be not only GIT microbiome, but also temporary local infections, for example tonsillar infection (subprocess SP6). Subprocesses forming process SPPN are on (Fig.4 and Fig.5.).

SPPN severity is proportional to the total kPAMP-load on blood phagocytes as well as to their total (PG-Y)-carriage. First and foremost, this applies to neutrophils. Their attraction into inflamed skin and their subsequent netosis is the main condition of initializing and sustaining psoriatic plaque.

5.1. Subprocess SP1. Small intestine hyperpermeability for bacterial products with PAMP.

Subprocess is known; its influence on psoriasis was investigated.

Normally, bacterial products keep getting into blood through intestine wall, which is confirmed by blood analyses of healthy people (Fukui 2016a, Paisse 2016). Bacterial products containing PAMP are mainly macromolecules. Their income into blood occurs primarily in small intestine, controlled by its barrier function (Camilleri 2019, Graziani 2019, Guerville 2016).

Within YN-model, it is assumed that total income of bacterial products into blood from colon is considerably lower than from small intestine, and is therefore disregarded. The concentration of lumen colic microbiome is certainly considerably higher than the concentration of lumen small intestine microbiome.

However, firstly, the total area of absorption in colon is considerably lower. This is explained by the height and quantity of villis and microvillis on enterocytes and colonocytes, the total area of absorption of small intestine being estimated at 32 m^2 and in colon - at 1 m^2 (Helander 2014).

Secondly, in colon, macromolecular permeability for bacterial products (intercellular and transcellular) is lower due to thicker mucus layer covering colon walls, which restricts direct contacts of microbiome with colonocytes (Camilleri 2019, Capaldo 2017, Johnson 2012). In small intestine there is only one mucus layer. This layer does not restrict direct contacts of microbiome with enterocytes, and notably mucosal microbiome is located in this single layer.

Thirdly, this is so because transcellular pathways determined both by Goblet's cells and by chylomicron, which are present in small intestine, are absent in colon (Guerville 2016). It has recently been demonstrated that normally it is the transcellular way in small intestine that is the basic one for LPS income into blood and lymph flow. This income occurs at LCFA absorption (long chain fatty acids), dependent, among other factors, on CD36 receptor (Akiba 2020). LCFA absorption, in its turn, primarily occurs in small intestine (partly owing to the fact that CD36 expression in colonocytes is considerably lower than in enterocytes) (Johnson 2012, chapters 59, 60). Currently the authors carry out the work devoted to studying the ways of LPS income into blood and lymph flow through colon and to determining colic permeability for LPS (Akiba 2020).

It is endotoxemia, notably die to increased small intestine permeability, that acts as one of the key factors for many diseases (Graziani 2019). Within YN-model, it is LPS, getting into blood and possessing TLR4 activity, that is supposed to be one of the key factors (along with peptidoglycan and bacDNA). Notably, only small intestine permeability (but not colic permeability) increases during endotoxemia (Guerville 2016, van Lier 2019).

The above-mentioned differences between colon and small intestine make it possible, within YN-model, to consider the income volume of bacterial products into blood flow from small intestine to be much higher than the similar income from colon.

However, in case of serious chronic violations in the condition of colonocytes, of their intercellular contacts and/or in the condition of colic mucus, the income volume of bacterial products into blood from colon can be comparable to the one from small intestine. Apparently, in such a situation colic permeability and colic microbiome (within subprocesses similar to SP1 and SP2) should be taken into account.

As a result of genetical predisposition or gastroenterologic diseases barrier function of small intestine is interrupted and volume of bacterial product income into blood increases (Fukui 2016a, Parfenov 1999). Long-term therapy of glucocorticoids (hydrocortizone, betamethasone, etc.) or cytostatics (methotrexate, cyclophosphamide, etc.) also can promote the process. Additionally permeability can increase as a result of disturbed mechanism of transcytosis around Peyer's patches and lymphoid follicles through associated epithelium (Male 2006, Mu 2017).

The causes of chronic barrier function disturbance can be related to diet, to dysperistalsis, to the condition of small intestine microbiome (insufficiency of immune response to concentration growth and/or change of composition) or to GIT diseases (De Santis 2015). Specifically, increased small intestine permeability occurs at inflammatory bowel disease, at alcoholic and non-alcoholic fatty disease of liver, at steatohepatitis, cirrhosis, heavy acute pancreatitis, bile cholangitis, diabetes and depression (Fukui 2016b, Graziani 2019, Mu 2017).

Numerous assumptions have been made recently that bacterial products getting into blood due to increased small intestine permeability play an important part in pathogenesis of psoriasis (Polkowska-Pruszyńska 2020, Sicora 2019, Myers 2019, Visser 2019).

For more detail on small intestine permeability at psoriasis see (Supplement A1).

SP1 depends on SP2. Some intestine bacteria are capable to influence barrier function, in particular by LPS (Chin 2006, Fasano 2004, Fukui 2016b, He 2019, O'Hara 2008). So increased small intestine permeability can be a direct result of composition of small intestine microbiome, especially in SIBO (Husebye 2005, Mu 2017, Ojetti 2006), including Gram(-)TLR4-active microflora.

SP1 depends on SP3. Small intestine permeability depends on quantitative and qualitative composition of bile entering small intestine (Assimakopoulos 2007, Song 2019). Chronic insufficiency of its entering interrupts barrier function and increases small intestine permeability, including for bacterial products with PAMP (Fukui 2016b, Khardikova 2000).

SP1 depends on SPN4. Significant rising of blood LPS level interrupts small intestine barrier function (Guerville 2016, van Lier 2019).

SP1 depends on SP5.1

5.2. Subprocess SP2. Growth of populations of Gram(-) TLR4-active and Gram+ NOD2-active bacteria in small intestine microbiome.

Subprocess is known; its influence on psoriasis was partly investigated.

Subprocess, as a rule, takes place within the limits of SIBO (small intestine bacterial overgrowth) (Bures 2010, Husebye 2005, Leite 2020, Quigley 2019, Bondarenko 2007, Martynov 2016).

However, subprocess SP2 may also not be accompanied with SIBO.

Detailed researches of transient enteric microflora at PP have been made for the first time by authors of the following works (Peslyak 2012c, Gumayunova 2009a, Gumayunova 2016, Nesterov 2009). Their results have confirmed the presence of serious dysbiotic deviations at BLC+PP (with blastocystosis) and at BLC(-)PP (without blastocystosis). The information about blastocystosis and its role in the change of colic microbiome can be found in the following works (Glebova 2007, Tan 2008).

For more detail on determining, diagnostics and causes of SIBO as well as on the results of PP research confirming its presence see Supplement A2.

Within the limits of subprocess SP2 special subprocess SP2.1 takes place (Fig.5).

Subprocess SP2.1. Growth of populations of psoriagenic PsB

Small intestine microbiome nearly always contains bacteria of Streptococcus genus (Supplement A2). Many of this genus, as well as some others, are presumed psoriagenic (Peslyak 2012c, Peslyak 2012a, Peslyak 2012b). These are bacteria having peptidoglycan similar to Str.pyogenes, i.e. containing (L-Ala)-(L-Ala) and/or (L-Ser)-(L-Ala) interpeptide bridges. Formation of these bridges in peptidoglycan is conditioned by the existence of enzymes of murM and murN type.

murM is an enzyme, providing serine/alanine addition (the first amino acid starting with Lys) when forming an interpeptide bridge at peptidoglycan. In the absence of this enzyme, there will be hardly any bridges. What exactly is added (serine or alanine) depends on the allele of murM-gene (Filipe 2001, Fiser 2003).

murN is an enzyme, providing alanine addition (the second amino acid starting with Lys) when forming an interpeptide bridge at peptidoglycan. In the absence of this enzyme, the bridge will be one amino acid in length.

Data base KEGG makes it possible to determine all (listed in it) bacterial strains which have genes providing secretion of both enzymes, i.e. both of murM type and murN type. Formation of interpeptide bridges in different bacteria is provided by various murMN-genes. All species of such bacteria included (Table 6). All strains of each of these species have (L-Ala)-(L-Ala) and/or (L-Ser)-(L-Ala) interpeptide bridges, i.e. their peptidoglycan is similar to Str.pyogenes peptidoglycan.

These species are presumed psoriagenic (labeled PsB).

Psoriatic patients have SIBO with PsB (Supplement A2).

SP2.1 depends on SP6. PsB (Table 6) are predominantly facultative nonpathogenic inhabitants of small intestine mucosa (Bouhnik 1999, Ciampolini 1996, Leite 2019, Leite 2020, Zilberstein 2007, Gumayunova 2009a). Some of them move from oral cavity and fauces mucosa (where they are commensals) to upper parts of small intestine. They can also move in case of gingivitis (Dhotre 2018) or tonsillar infections (Bartenjev 2000, Gudjonsson 2003, Thorleifsdottir 2016a).

At psoriasis and psoriatic arthritis, there are indirect and/or direct manifestations of the presence of bacterial products from PsB in skin and/or blood in the absence of local PsB-infections (Baker 2006a, Baker 2003, Baker 2000, Berthelot 2003, Cai 2009, El-Rachkidy 2007, Munz 2010, Sabat 2007, Weisenseel 2002, Weisenseel 2005). The authors of these studies, however, did not regard intestine microbiome as a potential source of PsB and therefore did not investigate it. In most cases, what was presumed was old PsB-infection with subsequent long persistence and/or deposition of bacterial products, e.g. in tonsillar tissue (Gudjonsson 2004) or directly in skin.

The assumption that PsB can be part of small intestine microbiome and can be the primary source of such bacterial products has been first made in work (Korotky & Peslyak 2005).

SP1 and SP2 are to be considered in interaction, as it is their combination that influences SPN4. Specifically, SPN4 can be present at significant SP1 level and insignificant SP2 level and vice versa.

SP2 depends on SP3. Bile has bactericidal properties to many non-commensal small intestine bacteria and ability to inactivate PAMP, containing in bacterial products, or to degrade it to non-toxic fragments thereby reducing level of entering in blood (Gunn 2000, Gyurcsovics 2003). Decrease of production or quality of bile and/or irregularity of its secretion result in decrease of bile bactericidal properties. It promotes bacterial growth in small intestine (Begley 2005, Hofmann 2006).

SP2 depends on SP5.1.

5.3. Subprocess SP3. Disturbance of production and/or circulation of bile acids (BA).

Subprocess is well-known. It was investigated in patients with psoriasis (Gyurcsovics 2003, Ely 2018, Baltabaev 2005, Matusevich 2000). Subprocess SP3 is essential part of vicious cycle (Fig.5, letter A) because it directly influences SP1 and SP2.

Disturbance of enterohepatic circulation can be a result of weakening of hepatic function of extraction and conjugation of BA from portal blood. So some part of BA constantly enters peripheral blood. BA pool is reduced, if liver possibilities on BA generation are limited. So the level of BA in bile is low. High blood BA level can be toxic for tissues and cause rising of permeability of membranes and local inflammation. Cholanic acid derivatives can interrupt integrity of blood vessel walls, increase their permeability and dilate lumens of vessels of dermis papillary layer (i.e. to influence rate of entering tissues by phagocytes) (Supplement A3).

SP3 depends on SP5.2. Chronic diseases or congenital defects of hepatobiliary organs result in depression of BA production. Obstructive jaundice or gallbladder excision completely stops their income to small intestine. Chronic overload of liver by bacterial products recycling also reduces BA production.

5.4. Subprocess SPN4. PAMP-nemia. Increased kPAMP-load on blood phagocytes. Increased kPAMP level in blood. kPAMP are LPS, PG and bacDNA.

This subprocess is well-known for various diseases (including for psoriasis) for LPS (Fukui 2016a, Gnauck 2016a, Guerville 2016, Jialal 2014, Munford 2016, van Lier 2019, Garaeva 2005, Garaeva 2007) and for bacDNA (Korotky 2020, Paisse 2016). But there were only few studies on PG and none on psoriasis (Fitting 2012, Kobayashi 2000).

Previously endotoxins were considered as any products of bacterial degradation (as against exotoxins - toxic secreted products of bacterium vital activity). But now term "endotoxin" means only LPS, term "endotoxemia" means increased blood LPS level (Fukui 2016a, Gnauck 2016a, Guerville 2016, Jialal 2014, Munford 2016, van Lier 2019). LAL-test is used for measuring blood free LPS level. Standard values are in range from 0 to 1 Eu/ml (0.1 Eu/ml or 10 pg/ml on average). It depends on rate of LPS entry from small intestine into portal blood and quality of LPS-elimination made by hepatobiliary system (up to 95% of LPS are destroyed by system of hepatic macrophages before they enter systemic blood flow and excreted with bile). Additionally it depends on porto-caval shunts (portal blood entry in systemic blood flow, i.e. not through liver) and activity of antiendotoxic immunity (Supplement A4).

PAMP-nemia and endotoxemia have the same cause. The cause is combined action of SP1 and SP2. Besides, overload and/or disturbance of detoxication systems (SP5) influence its level. Thus, detoxication systems do not have enough time to eliminate excess volume of bacterial products entering the blood, or they are weakened because of diseases and they don't stand usual load.

kPAMP-load on blood phagocytes increases while blood kPAMP-level raises slowly during initial stage of PAMP-nemia. kPAMP-load can be critical for psoriasis possibility at this stage. kPAMP-consumption (phagocyte-dependent and phagocyte-independent) can't stand kPAMP-income at the second stage. Blood kPAMP-level becomes even higher and can be critical for psoriatic arthritis beginning (Supplement A5).

Endotoxemia can accompany any Gram(-) infections and become the cause of many systemic diseases, but not psoriasis. kPAMP-load on phagocytes influences volume and bacterial products composition inside these phagocytes (subprocess SPN8). kPAMP-load influences prenetotic state of blood neutrophils, it influences volume and types of cytokines, secreted by phagocytes, including by synergy between kPAMP (Myhre 2006, Traub 2006).

Psoriatic patients frequently develop metabolic syndrome (Albareda 2014, Holmannova 2020, Romaní 2013), one of the causes of which is endotoxemia (Jialal 2014).

Endotoxemia in psoriatic patients can also be determined indirectly, by increased expression of TLR4 gene in blood cells (Garcia-Rodriguez 2011) or by increased concentration of elafin in blood (Elgharib 2019, McMichael 2005).

Although TLR4 is membranous receptor, but linkage with LPS and subsequent endocytosis make complex TLR4-LPS able to enter endosomes and cell (Coll 2010, Husebye 2006). The main receptors for PG (NOD2) and bacDNA (TLR9) are intracellular.

Within the limits of subprocess SPN4 special subprocess SP4.1 takes place (Fig.5)

Subprocess SP4.1. (PG-Y)-nemia.

(PG-Y)-nemia is called raised (PG-Y)-load on blood phagocytes in combination to increased level PG-Y in blood. All populations of Gram(+) and Gram(-) bacteria (not only PsB) of zones of hyperpermeability of small intestine, define total income of PG into blood and total PG-load on phagocytes. But only growth of PsB populations (SP2.1) is at the bottom of (PG-Y)-nemia.

PG concentration in blood is normal (control group of 14 people) on average - 20 pg/ml (from 0 to 90), PG concentration in blood in patients with sepsis from 50 pg/ml (Fitting 2012) to 190 ng/ml (Kobayashi 2000). PG concentration in psoriatic patients' blood has not been previously determined.

SP4.1 depends on SP2.1. (PG-Y)-nemia severity is proportional to growth of PsB-populations on small intestine microbiome.

SP4.1 depends on SP6. Tonsillar PsB-infection (as well as any other local PsB-infection) results in temporary (PG-Y)-nemia: temporary increase of (PG-Y)-level and (PG-Y)-load.

SPN4 depends on SP1 and SP2. If there are no local and/or systemic bacterial infections the main source of bacterial products entering the blood is small intestine microbiome.

SPN4 depends on SP5. Normal state of detoxication systems inhibits PAMP-nemia increase and, on the contrary, their diseases and/or overload promote its increase. Complex therapy of psoriasis always includes investigation of hepatobiliary organs, kidneys and urinary tract and their treatment if it is required.

5.5. Subprocess SP5. Overload and/or disorders of detoxication systems.

Detoxication systems role in psoriasis was described earlier (Korotkii & Peslyak 2005); also see Supplement A4. Taking into account various influence of the components of the given subprocess on other subprocesses, we will allocate disorders in GIT (SP5.1) and in hepatobiliary system (SP5.2):

Subprocess SP5.1. GIT

Researches show that functional and structural disorders in GIT aggravate psoriasis, and the combined treatment aimed at normalization of its functioning lead to good and long-term results (Pietrzak 2009, Pietrzak 2017, Garaeva 2005, Pagano 2008, Harkov 2008, Uspenskaya 2016, Shagova 2009). Certainly any helminthiasis aggravates the current of psoriasis, in particular, opisthorchiasis (Matusevich 2000, Khardikova 2005, Kuranova 2009) or parasitic disease, in particular, blastocystosis (Gumayunova 2009a, Nesterov 2009). Successful treatment of helminthiases and/or parasitic diseases and correction of dysbiotic deviations lead to much more successful and stable results in psoriasis treatment.

Subprocess SP5.2. Hepatobiliary system

Chronic endotoxemia in psoriasis (Garaeva 2005) can result in dysfunction of liver. Dysfunction severity depends on its level, duration and concomitant diseases (Matusevich 2000). The organic pathology of biliary tract and/or its functional disorders aggravate psoriasis, and cholestasia degree correlates with PASI (Gyurcsovics 2003, Ibliyaminova 2009).

It is well known that liver diseases aggravate psoriasis and make its treatment more complicated. For example, symptoms of non-alcoholic fatty liver disease (NAFLD) have been found at 47% of PP (n=130), while in the control group of healthy - only at 28% (of 260). PP with NALFD symptoms have higher PASI (14.2 against 9.6), than PP without NAFLD symptoms (Gisondi 2009, Mantovani 2016). Other studies demonstrate that the prevalence of NAFLD among PP (n=151) amounts to 21% against 7.8% in HP (n=51) (Awosika 2018).

It should be mentioned that implication of NAFLD can correlate with the disturbance of circulation and transportation of bile acids (Trauner 2010, Wenk 2011).

SP5 depends on SPN4. PAMP-nemia provides constant load on all detoxication systems.

5.6. Subprocess SP6. Tonsillar PsB-infection

Subprocess is well-known; it was repeatedly investigated for psoriasis, including tonsillectomy (Bartenjev 2000, Rachakonda 2015, Thorleifsdottir 2016a, Thorleifsdottir 2017). Tonsillar PsB-infection (as well as other local PsB-infection) provides temporary, but significant bacterial products from PsB (including PG-Y) entry in blood. The detailed analysis of these events may be found at (Baker 2006b) (Fig.A1).

About 30% of patients with primary guttate psoriasis recover spontaneously. However it regenerates to chronic plaque psoriasis at once or after remission in 70% of cases (Baker 2000). Probably tonsillar PsB-infection causing primary guttate psoriasis, also becomes a source of stable PsB-populations in upper parts of small intestine (SP2.1). It can result in development of chronic psoriasis. Chronic psoriasis aggravation during tonsillar PsB-infections is caused by because significant additional bacterial products from PsB (including PG-Y) entry in blood.

Tonsillar PsB-infection also causes adaptive immune response to Y-antigen. Effector Tem-Y (in dermis) and central Tcm-Y (in regional lymphnodes) are retained in the maximum concentration in priming plaque, in smaller concentration around the plaque, but also in all skin (phase N0, Fig.A8) (De Jesus-Gil 2018, Ferran 2013).

The authors of work (Fry 2007a) discussed preventive streptococcal vaccination for risk groups (genetic or family signs) if psoriasis hasn't yet begun (see also Supplement A6).

5.7. Subprocess SPN8. Growth of prenetotic neutrophils fraction. Increased kPAMP-carriage of blood phagocytes.

This subprocess (including SPN8.1) is final for systemic process SPPN as a whole. Chronically increased kPAMP-load causes constant endocytosis of bacterial products by blood phagocytes. Phagocytes do not manage to completely degrade part of bacterial products with PAMP (including kPAMP). As a result, fractions of kPAMP+ phagocytes are formed. The largest of them is the fraction of kPAMP+ neutrophils, some of which subsequently passes into activated (prenetotic) state.

Prenetotic blood neutrophils mostly have low density, i.e. are LDG (=LDN) (Grayson 2016, Pinegin 2015). LDG percentage among all neutrophils in PP (n=81) is 1.3 times higher than in HP (n=36), whereas their concentration in blood correlates with PASI (beta = 0.28; p = 0.01). Substantially reduced CD62L expression compared to other neutrophils characterizes activation of all LDG (Teague 2019).

Platelets play a special role: they form complexes with neutrophils (Neu-Pla). Due to LPS influence (through receptors of both platelets and neutrophils) there occurs neutrophil activation and their transition to prenetotic state. Neu-Pla complexes either undergo netosis in blood or are attracted to the place of inflammation. Neu-Pla complexes possess an enhanced ability to chemotaxis, adhesion to endothelium and transmigration through vessel walls (Chiang 2019, Kim 2016, Pinegin 2015, Papayannopoulos 2018, Teague 2019). Concentration of Neu-Pla complexes in blood of PP (n=12) amounts to 16%, which is higher than in blood of HP (n=10) - 8% (Teague 2019, fig.4B). Such complexes contain neutrophils of any density. Neu-Pla complexes can be found not only in blood, but also in psoriatic skin (Herster 2019).

Within YN-model, increase of LDG concentration and Neu-Pla concentration in blood of PP occurs, for instance, at endotoxemia caused by chronic LPS-load (subprocess SPN4) (Kim & Jenne 2016, Rodriguez-Rosales 2019, Taudorf 2007). It has been consistently demonstrated that Neu concentration in PP blood is increased, and NLR (correlation of neutrophil concentration and lymphocyte concentration) and PLR (correlation of platelet concentration and lymphocyte concentration) correlate with PASI severity (Paliogiannis 2019, Supplement A4). Similar changes are also observed at endotoxemia.

LPS-load on neutrophils brings them to prenetotic state, culminating in netosis after a certain time (up to 50 minutes). Since prenetotic neutrophils retain chemotaxis ability, netosis can occur in a place remote from the initial one. For neutrophils, a sequence of events has been experimentally organized: nanomaterial phagocytosis, transition to prenetotic state under LPS influence, chemotaxis, and netosis with ejection of non-degraded nanomaterial (Meyer 2020). Within YN-model, a similar sequence of events is expected, in which nanomaterial is substituted by kPAMP (LPS, PG, PG-Y and bacDNA). Neutrophils endocyte kPAMP in blood, transfer them to skin and, in non-degraded state, eject them to extracellular space during netosis.

Some prenetotic neutrophils in PP undergo netosis in blood (Hu 2016, fig.1 and 3; Lin 2011, fig.4; Shao 2019, fig.1; Teague 2019). Others are attracted to prepsoriatic and psoriatic skin, where prenetotic neutrophils (along with others) can also undergo netosis (Hu 2016, fig.4, Lin 2011, fig.3 and 6; Skrzeczynska-Moncznik 2012, Shao 2019) (subprocess L3b).

Growth of fractions of tolerized monocytes and dendritic cells (including kPAMP-carriers) in blood is possible, but not obligatory (described in Y-model).

Within subprocess SPN8, subprocess SPN8.1 takes place (Fig.5).

Subprocess SPN8.1. Increased (PG-Y)-carriage of blood phagocytes.

Subprocess SPN8.1 takes place only if SP4.1 is at work, i.e. when kPAMP-load on blood phagocytes (SPN4) includes (PG-Y)-load. Rate of PG-Y income (in Neu-Y) into skin determines psoriatic plaque sustenance.

Growth of fractions of tolerized monocytes and dendritic cells acting as (PG-Y)-carriers in blood is possible, but not obligatory (described in Y-model).

SPN8.1 depends on SP4.1. Total (PG-Y)-carriage of blood phagocytes depends on (PG-Y)-load on them.

Within YN-model, in all local processes monocytes and dendritic cells are designated as Mo and DC, irrespective of the fact whether they are tolerized and/or kPAMP-carriers.

SPN8 depends on SPN4. The size of prenetotic neutrophil fraction and total kPAMP-carriage of blood phagocytes depend on kPAMP-load in blood.

5.8. Discussion about SPPN

Systemic psoriatic process SPPN is a dynamic interaction of all listed subprocesses. The chronic increased kPAMP-load (subprocess SPN4) lays constant impact on blood immune system and includes chronic proinflammatory and anti-inflammatory mechanisms.

SPPN affects all organs because phagocytes participate in homeostatic and/or inflammatory renewal of pool of any tissue phagocytes. However problems can begin if bacterial products brought by them contains enough antigenic material wrongly accepted by local immune system as proof of presence of pathogenic bacteria. Antigenic material in psoriasis is PG-Y (in bacterial products) accepted by local immune system as proof of Str.pyogenes presence in skin.

Chronically increased kPAMP-load causes an increase in the fraction of activated (prenetotic) neutrophils, some of which undergo netosis. Those neutrophils which have not undergone netosis in blood can be attracted to inflamed skin. Among them, there will be Neu-Y, i.e. (PG-Y)-carriers. For more detail on local processes in skin see the following chapter.

Systemic psoriatic process SPPN defined by set of interconnected subprocesses (Fig.5):

- **Small intestine hyperpermeability for bacterial products with PAMP (SP1)**
- **Specific small intestine dysbiosis (SP2)**
- **Disorder of production and/or circulation of bile acids (SP3).**
- **Chronic PAMP-nemia (SPN4)**
- **Overload and/or disorder of detoxication systems (SP5)**
- **Growth of prenetotic blood neutrophils fraction (SPN8)**
- **Increased (PG-Y)-carriage of blood phagocytes (SPN8.1)**

SPP severity is proportional to total kPAMP-load on blood phagocytes and their total (PG-Y)-carriage.

Each of these subprocesses can be caused or strengthened by genetic and/or functional deviations.

Basic hypotheses connected with SPPN (Table A12)

- **Systemic psoriatic process SPPN as the main factor of psoriasis initialization and maintenance**
- **Psoriagenic bacteria PsB as a key factor (SP2.1, hypothesis H1-2)**
- **PAMP-nemia and (PG-Y)-nemia as key factor.**
  kPAMP are LPS, PG and bacDNA (SPN4, hypothesis HN3)
- **Growth of prenetotic blood neutrophils fraction (SPN8, hypothesis HN4)**
- **Increased (PG-Y)-carriage of blood phagocytes (SPN8.1, hypothesis HN6)**

6. Local processes

6.1. Some facts

The top layer of skin, epidermis, provides the first barrier of protection against external influence. Dermis is separated from epidermis by the basal membrane, and contains vascular network for supplying with nutrients epidermis, which is lacking its own blood vessels.

Apparently healthy skin of PP without plaques (uninvolved, nonlesional, symptomless) is also called "prepsoriatic" or the abbreviation NLS is used (NonLesional Skin). Psoriatic skin is designated by the abbreviation PLS (Psoriatic Lesional Skin). Further, these terms and abbreviations will be used everywhere.

NLS is characterized by mild dermal inflammation (not exceeding basal layers of epidermis), increased vascularity, itch, dryness, decrease of barrier function of the cornual layer, larger vulnerability. After psoriatic plaque (further PLS-plaque or plaque) appearance, active priming of surrounding skin occurs (increase of Tem concentration). The width of the priming ring depends on the severity, size and growth rate of plaque and can reach 5-10 centimeters. The internal border of the ring (directly near to plaque) by its characteristics is very close to condition of skin inside the focus of plaque. At relapses and aggravations the width of the ring increases, at natural remission - decreases (Cameron 2002, van de Kerkhof 1996, Vissers 2004).

Immunocytes are present in both dermis and in epidermis. These are epidermal dendritic LC (Langerhans cells) and dermal DC (DDC), macrophages (MF), mast cells and T-lymphocytes (TL). In the absence of inflammation, insufficient number of B-lymphocytes and NK cells is present in dermis, and plasmacytoid DC (PDC) and neutrophils (Neu) are practically absent. All epidermal LC, as well as a big part of DDC (about 60%) at the homeostatis state are originated from the precursors constantly presented in skin. However, a smaller part (about 40%) of DDC and practically all MF are originated from attracted blood DC and Mo. At inflammation, LC pool starts to be replenished by blood CCR2+CD14+Mo attracted in skin and are gradually transformed in LC. At inflammation, the most part of DDC pool is replenished by blood DC and, probably, from blood Mo attracted in skin that can be transformed in DDC (Bogunovic 2006, Ginhoux 2007, Ginhoux 2006). DDC are more active in presentation of antigens and make most part of traffic in regional lymph nodes. LC play the leading role in formation of tolerance of the skin immune system in relation to skin commensals. DDC provide adaptive response against bacteria and viruses during trauma or dermal infection (Baker 2006c). In addition about role of dermal Mo, DC and MF in NLS and PLS (Peslyak 2012b, p.8, insert font 9, further k9).

6.2. Phases of psoriatic plaque development

For detailed description of YN-model, all events, both previous and concurrent with development of one plaque, should be divided on processes and phases.

YN-model in the form of the scheme of interaction of local processes is represented in Fig.7.

The most important causal dependencies are represented by color arrows. The color of an arrow depends on the color of a causative process. For simplification of schemes, some dependencies are not designated. Table 2 including all causal dependencies between processes and subprocesses is given.

Table 1 contains processes and phases of plaque development during constant action of SPPN. Each phase is characterized by occurring (sub)processes (+ or *) during its duration, and also by their intensity. For each phase, some marker characterizing processes are is chosen.

Within YN-model there appeared new subprocesses, and content of some processes changed, compared to Y-model. For this reason the name of all local processes was simplified (LX instead of LPX, where X means number), and subprocesses received alphabetic numbering instead of digital one (e.g. LXa instead of LPX.1) (Table A11).

It is supposed that Y-priming of skin has already occurred and, consequently, phase N0 is absent. More information about phase N0 and Y-priming is given in Supplement A9.

Supplements contain illustrations of interacting processes during pinpoint plaque development for each phase of L2(DEMP) case - dermal expansion of commensal microbiome with PsB (Fig.A9, Fig.A10, Fig.A11, Fig.A12, Fig.A13, Fig.A16), as well as during growth of existing plaque (Fig.A14, Fig.A15, Fig.A16). In illustrations used symbols from (Fig.1). In following section the detailed description of each local process is given.

6.3. Process L1. Attraction of immunocytes from blood flow.

Renewal of pool of dermal immunocytes of non-resident origin is constant process occurring in the absence of local inflammation as well (Fig.A9). Process L1 occurs during any of phases (Table 1). After L2 start, process L1 is intensified.

Renewal of this pool takes place due to action of chemokines, as well as AMP (antimicrobial proteins) and some cytokines possessing chemokine properties. All of them are produced by various skin cells, and their assortment and quantity depend on skin condition. Ligands of chemokines are certain chemokine receptors expressed by blood immunocytes (Supplement A12).

Subprocess L1a. Attraction of phagocytes Neu, Neu-Y, Mo, DC, and PDC, NK, etc.

Quantitative characteristics of blood phagocytes from HP and PP are only slightly different. The main differences are found in psoriatic skin. In healthy skin almost all phagocytes are of resident origin, i.e. they come from precursors of monocytes and dendritic cells – resident dermal stem cells. A similar situation occurs in prepsoriatic skin during phase N2, when immune response takes place mainly with participation of cells of resident origin. As development of psoriatic inflammation progresses (starting with phase N3), attraction of blood phagocytes begins. In result in moderate-severe psoriasis (phases N5 or N8) the situation is different – up to 80% of phagocytes have non-resident origin, i.e. they are either attracted from bloodstream or derived from cells attracted from blood flow (Fig.A7).

These are all neutrophils and up to 70% of monocytes-macrophages and dendritic cells. As calculations show, their concentration in the top 0.5-mm skin layer reaches ~41000 cells/mm^3. About 45% of phagocytes are constituted by neutrophils, about 35% - by monocytes (macrophages) and up to 20% - by dendritic cells. The proportion between phagocyte types in psoriatic skin is determined by the increase in average lifetime of macrophages and especially dendritic cells compared to the same values for blood phagocytes (Gaspari 2017, Kabashima 2016, Kabashima 2019).

Attraction of neutrophils (Neu, Neu-Y)

Neutrophils constitute the greatest part of blood phagocytes (> 85%) and are responsible for endocytosis of most bacterial products (Mayadas 2014).

In healthy skin, neutrophils are virtually absent (Di Meglio 2017, Kabashima 2016, Kabashima 2019, Lin 2011). They are attracted into skin at the earliest stage of psoriatic plaque initiation (even before visible skin change). They are especially numerous in primary pinpoint psoriatic plaques (Christophers 2014, Van de Kerkhof 2007).

Their essential part can be grouped in the top layers of epidermis, forming Munro's abscesses (Ozawa 2005, fig.1; Reich 2015, fig.3). In chronic psoriatic plaque, neutrophils constitute the greatest part of skin phagocytes (up to 45% at moderate-severe psoriasis), and nearly all of them have non-resident origin (Fig.A7, Fuentes-Duculan 2010, Gottlieb 2005, Zaba 2009).

Prepsoriatic skin adjacent to active plaques and early plaques, is characterized by the presence of CD15+Neu (Albanesi 2009, Albanesi 2010).

The supposition that attraction of blood neutrophils to psoriatic skin under the influence of CXCL8 (IL8) chemokine, and subsequent secretion of the same chemokine by neutrophils, are links of the vicious cycle, was made long ago (Gilliet 2008, Terui 2000). In other models of pathogenesis (Guttman-Yassky 2011, Perera 2012, Tonel 2009), analyzed in detail in (Peslyak 2012b), neutrophil attraction to psoriatic skin was not included into the vicious cycles. LL37 secretion by neutrophils was regarded as link of the vicious cycle, though.

After the discovery that part of neutrophils in psoriatic skin undergo netosis (Hu 2016, fig.4; Lin 2011, fig.3 and 6; Skrzeczynska-Moncznik 2012), it was discussed by the authors of GK-model (Hawkes 2017, fig.1; Lowes 2014, fig.4; Laboratory for Investigative Dermatology, The Rockefeller University, New York, USA), but netosis was not included in their pathogenesis model. The scheme of GKH-model is simplistic, compared to GK-model scheme. An even stricter approach is chosen by the authors of a detailed review devoted to psoriasis pathogenesis (Benhadou 2018, fig.1): they do not only leave out netosis, but also neutrophils from their pathogenesis model. The BMM-model is virtually a simplified GK-model.

Attraction of neutrophils into skin and their netosis have recently been included in the vicious cycle by authors of the following pathogenesis models FM-model, Fig.A2, Delgado-Rizo 2017),

(SE-model, Fig.A3, Schon 2018), (WG-model, Fig.A4, Shao 2019), (CH-model, Chiang 2019). (Table 5).

In (Herster 2020) hRNA-LL37 complexes take on the role of self-strengthening processes of neutrophil attraction into psoriatic skin, of chemokines and cytokine secretion and, basically, of netosis.

Recently carried out in vitro researches demonstrate netosis influence on T-lymphocytes and on their secretion of IL17 (Lambert 2019). Blood cells were taken from healthy donors, but the main objective was to show that such influence is possible in psoriatic skin.

It is their chemokine receptors and certainly their agonists, which are responsible for neutrophil attraction to skin: chemokines and proteins with chemokine properties. Detailed information on chemokine receptors of neutrophils and their agonists is collected and analyzed (Supplement A12**).**

Neutrophils are attracted actively into skin within subprocess L1a along with other non-lymphocytic blood immunocytes. This attraction begins actively in phase N3, when L3 - innate response begins, and after initiation of PLS-inflammation it is supported within vicious cycle B (Fig.7).

During SPPN, a certain part of senescent neutrophils of blood (along with other neutrophils) is constantly attracted into inflamed psoriatic skin instead of bone marrow. This occurs due to constant CCR1 expression and apparently due to replacing CXCR4 expression by CCR2 expression (Uhl 2016, Ortmann 2018).

Attraction of Mo and DC

The nomenclature of blood monocytes and dendritic cells (Ziegler-Heitbrock 2010) is based on results of many previous studies including (Piccioli 2007, Serbina 2008, Tacke 2006).

According nomenclature population of blood Mo consists of three fractions: Classical CD14++CD16(-)Mo (in the normal state - to 90%, everywhere further they are designated as CD14++Mo), intermediate CD14+CD16+Mo (in the norm - to 10%) and nonclassical CD14(low)CD16+Mo (in the norm to 5%). So far monocytes from two last fractions together taken are considered, they can be is designated as CD16+Mo.

According to this nomenclature, the population of blood myeloid DC consists of two fractions: BDCA-1+DC and BDCA-3+DC. However, the fraction of CD14(-)CD16+BDCA-1(-)slanDC does not match this nomenclature completely, as they express CD16, and expression of BDCA-3 is not obligatory for cells of this fraction (Hansel 2011, Schakel 2006). Therefore, authors of reports devoted to slanDC divide the population of blood myeloid dendritic cells in two fractions: BDCA-1+DC (smaller) and BDCA-1(-)DC (bigger). They include slanDC subfraction in BDCA-1(-)DC fraction. Such divergence in classification can be explained by affinity of characteristics of slanDC to characteristics of CD14(-)CD16+Mo (Schakel 2006). Some authors believe that slanDC should be considered as monocytes, namely a part of the fraction of nonclassical CD14(low)CD16+Mo (Teunissen 2011).

The role of chemokines and AMP, determining traffic of Mo and DC is analysed in some works (Bachmann 2006, Diamond 2009, Gautier 2009, Sozzani 2005). Attraction of Mo and DC from blood flow into dermis takes place due to interaction of their chemokine receptors and chemokines expressed by endothelial cells and secreted in dermis.

In PLS-dermis abrupt (more than 30 times) growth of BCDA-1(-)TipDC number can be seen (Zaba 2009).

Attraction of these cells from blood flow occurs first due to chemokine CX3CL1 (fractalkine) secreted by keratinocytes KC (Sugaya 2003) and DDC (Raychaudhuri 2001) in PLS, and, additionally, CCL2, HBD2 and HBD3, abundantly secreted in PLS-dermis.

CD163+MF in PLS-dermis are classically activated (Fuentes-Duculan 2010), it is probable that their part originates from CD14++Mo.

As it is known, at intensive inflammation the part of LC is formed from Mo and-or DC attracted from blood (Angel 2006, Ginhoux 2007, Ginhoux 2010). In PLS-epidermis the quantity of LC is not increased in comparison with the norm (Jariwala 2007, Sabat 2007).

At inflammation, CCL2 secretion (ligand of CCR2) essentially increases, therefore attraction of CD14++Mo, CD14+CD16+Mo, as well as parts of DC and PDC increases too. It has been established that HBD2 and HBD3 are ligands of CCR2 and support attraction of immunocytes as

well as CCL2 (Rohrl 2010). At inflammation, secretion of CX3CL1 (ligand of CX3CR1) increases, which promotes CD16+Mo attraction. At inflammation, secretion of CCL20 (ligand of CCR6) increases, which strengthens attraction of CCR6+DC. At inflammation, chemerin secretion (ligand of ChemR23) increases, which strengthens attraction of PDC, as well as parts of DC and CD16+Mo (Wang 2020).

Attraction of PDC and NK

Plasmacytoid dendritic cells PDC play an important part in initiating adaptive response, which determines their importance in nearly all models of psoriasis pathogenesis (specifically in YN-model) (Reizis 2019, Wang 2020).

Their homeostatic attraction occurs in the absence of local inflammation as well. This attraction is intensified during local inflammation. PDC play key role in process L4. Mass secretion of IFN-alpha by PDC precedes plaque development (Nestle 2005a). Attraction of PDC in NLS-dermis takes place due to the receptor ChemR23 - ligand of chemerin (Albanesi 2010, Nakajima 2010, Skrzeczynska-Moncznik 2009b). In PLS, chemerin is secreted both in epidermis and in dermal fibroblasts, while in NLS and in the norm - mainly in epidermis. NLS surrounding active and early PLS, is characterized by strong expression of chemerin in dermis and presence of CD15+Neu and CD123+BDCA-2+ChemR23+PDC (Albanesi 2009). PDC traffic at homeostasis and inflammation in skin, besides receptor ChemR23, is also provided by receptors CXCR3 (ligand of CXCL10) and CXCR4 (ligand of CXCL12) (Sozzani 2010).

PDC attraction through their receptors FPR1, FPR2 can also take place due to bacterial product FMLP, possessing chemokine properties.

The role of natural natural killers NK and NKT (TL with properties of killers) is important also. Their distribution in NLS and PLS studied in (Cameron 2002). In one study (Gilhar 2002) it is shown that at injection of NK in NLS-transplant replaced to SCID-mice, PLS-plaque develops, which proves NK role in psoriasis pathogenesis. Later, the same researchers have made an attempt to define this role more precisely (Gilhar 2006). The observational study (Peternel 2009) is devoted to NKT role at psoriasis. Attraction of NK is carried out due to receptors CCR5, CXCR1, CXCR3, CX3CR1, ChemR23.

L1a depends on SPPN. A share of Neu-Y and share of activated (prenetotic) Neu among attracted blood depends on SPPN severity.

L1a depends on L2a(DEMP). Among substances formed due to secretion and degradation of bacteria from commensal microbiome, there are substances possessing chemokine properties. These include, for instance, PSM and FMPL (Supplement A10, Supplement A11).

Subprocess L1b. Attraction of T-lymphocytes (TL).

Homeostatic attraction of T-lymphocytes (TL) also occurs in absence of local inflammation. This attraction is intensified during local inflammation. This is necessary for adaptive response L8.

Attraction of TL from blood flow is carried out with the help of CCR4, CCR6, CCR10 and CXCR3 expressed by various TL fractions in various combinations (Teraki 2004, Kagami 2010). CCR6 is considered as a key receptor on attraction of Th1 and Th17 in PLS (Hedrick 2010).

L1b depends on L7b. TL-Y attraction from regional lymphnodes takes place after their clonal proliferation.

L1 depends on L3. This is true for all phases. During phases N2, N3 and N4 (i.e. at the prepsoriasis stage), the spectrum of secreted chemokines and antimicrobial proteins with chemokine properties is determined exclusively by L2.

Starting with phase N5, this range expands due to L8 start. Thus, range of immunocytes attracted to place of inflammation is determined.

At L3(DEMP), there occurs active sectretion of CCL2, CCL20, CXCL8, CXCL1, LL37, HBD2, HBD3, HNP1, HNP3, S100A7, S100A8, S100A9, chemerin, etc. (for more detail see L3 description). At L3(IN), there occurs active sectretion of CCL2 and CX3CL1, as well as of antimicrobic proteins LL37, HBD2 and HBD3. At L3(HPV), active secretion of CCL2, HBD2 and HBD3 takes place (Supplement A10).

L1 depends on L8. After phase N5 start (i.e. after L8 start) the spectrum of dermal chemokines and AMP extends, and their secretion increases. For example, HBD2 and HBD3 are secreted in large amounts

(De Jongh 2005, Gambichler 2008). Thereby, the rate of attraction of all blood immunocytes (in comparison with previous phases) is amplified.

6.4. Process L2. Initiating and aggravating process.

L2 is specific local inflammatory process in skin, at which conditions for initiation (and, maybe, support) of process L8 - adaptive response against (real and) imaginary dermal expansion of PsB can be created. It can occur, if L3 (innate response) will be insufficient for suppression and elimination of L2. In this case, L4 switches (phase N4 begins) and then L8 begins (phase N5 begins).

With L2 start - phase N2 begins, with L2 end - phase N5 terminates (Table 1, Fig.8, A).

If L2 exists for long time after L8 initiation (phase N5), it aggravates L8 through L3 as intensive functioning of vicious cycles B and C is maintained. There are two local vicious cycles B = {L1a > L3 > L6b > L8 > L1} and C = {L6b > L7b > L1b > L8 > L6b} (Fig.7). These vicious cycles are also amplified by interference between L3 and L8. If vicious cycle B has begun acting, L2 end may not render an influence on functioning of this cycle. If vicious cycles B and C (with SPPN support) after L2 end appear to be self-sufficient, phase N8 begins.

L2 role may be played by any of the following influences and-or processes:

Most probable (within YN-model) are:

- L2(DEMP) = dermal expansion of commensal microbiome with sufficient PsB representation (for more detail see the next subsection as well as on (Fig.A9, Fig.A10, Fig.A11, Fig.A12, Fig.A13, Fig.A16, Fig.A19);
- L2(DEM) = dermal expansion of commensal microbiome with insufficient representation or absence of PsB;

Described in detail (within Y-model):

- L2(IN) = open trauma of dermis Y-model, LP2(IN), Peslyak 2012b, fig. 2-9; fig. 2-10; fig. 2-11; fig. 2-14; fig. 2-15; fig. 2-16; fig. 2-17)
- L2(HPV) = HPV-carriage of KC (Y-model, LP2(HPV), Peslyak 2012b, fig. 2-18; fig. 2-19; fig. 2-11; fig. 2-21; fig. 2-22; fig. 2-23; fig. 2-17)
- And others
- L2(PsB-p) = skin PsB-infection, when PsB is skin pathogen (Str.pyogenes, Str.agalactiae, etc.)
- Skin infections caused by pathogens other than PsB: S.aureus (hereinafter SA), Malassezia species (hereinafter MS), Candida Albicans (hereinafter CA), etc. (Fry 2007b)
- Combustion, contact dermatitis (Fry 2007b)

The trauma L2(IN) are only initiating process since, as a rule, at the very initial stage of PLS-plaque they are usually eliminated (rapid transition to phase N8 takes place).

Bacterial or virus L2 can persist in PLS-epidermis (phase N5). Diffusion of L2 outside PLS-plaque on surrounding NLS can promote expansion of this plaque. Diffusion of L2 on remote NLS provokes appearance of new PLS-plaques.

Microbiome in normal skin and PLS-microbiome was investigated and compared several times. It is well-known that SA, MS and CA in PLS-plaques are found more often than in the norm and, as a rule, aggravate such plaques (Supplement A7).

Y-model was specified and illustrated at L2(IN) - trauma and at L2(HPV) - HPV-carriage of KC (Peslyak 2012b).

In this study, YN-model is concretized and illustrated at L2(DEMP) - dermal expansion of commensal microbiome with sufficient PsB representation, as well as at L2(DEM) - dermal expansion of commensal microbiome with insufficient representation or absence of PsB.

Subprocess L2(DEMP). Dermal expansion of commensal microbiome with PsB.

A brief review of studies devoted to skin microbiome at norm and psoriasis is given in Supplement A7. Information on Staphylococcus and Streptococcus genera representation is collected (Table A10). Each of these two genera contains commensal species, whereas Streptococcus genus also includes PsB - species presumed psoriagenic (Table 6). Notably Staphylococcus genus is well presented on virtually all localizations of healthy, prepsoriatic and psoriatic skin, both in epidermis

and in dermis. The role of skin commensal Staph.epidermidis in immune response formation is well known (Nguyen 2017, Sabate 2017, Stacy 2019).

(Nakatsuji 2013) and (Bay 2020) estimate concentration and composition of dermal microbiome at norm. YN-model presupposes that one of possible initiating and aggravating processes is L2(DEMP) - dermal expansion of commensal microbiome with sufficient PsB representation.

Sufficient PsB representation in commensal microbiome during its dermal expansion is dictated by the fact that TL-Y are formed and become attracted to dermis from lymphnodes in sufficient amounts at phase N5 start. When this occurs, phase N0 (preliminary Y-priming of prepsoriatic skin) can be absent. At L2(DEM), phase N0 is obligatory.

The series of figures (Fig.A9, Fig.A10, Fig.A11, Fig.A12, Fig.A13, Fig.A16, Fig.A19) illustrating psoriatic plaque development demonstrates two groups of commensal bacteria: PsB (yellow ovals and their fragments, particularly from Streptococcus genus) as well as other than PsB (blue ovals and their fragments, particularly from Staphylococcus genus).

It is well known that expansion of commensal microbiome is permanently controlled by skin immune system. This control provides constantly secreted antimicrobial proteins (AMP). They are secreted by virtually all skin cells. Control of commensal microbiome expansion is also facilitated by resident phagocytes: in epidermis - epidermal dendritic cells (Langerhans cells), in dermis - monocytes, macrophages and dermal dendritic cells (Kabashima 2016, Kabashima 2019).

The main AMP significant for psoriatic inflammation are listed (Supplement A10). For each AMP secreting cells are specified. If AMP is chemokine at the same time, cells which can be attracted are listed. Information on AMP secretion intensity depending on localization (epidermis, dermis) and skin condition (norm, prepsoriasis, psoriasis) is also provided. For more detail see description of subprocess L3a.

If L3r - innate response with primary participation of cells of resident origin is insufficient for eliminating (controlling) L2(DEMP), L3 intensification occurs. As a result, blood immunocytes, particularly neutrophils (which are virtually absent at norm), are attracted into skin. Then subprocess L3b - netosis of part of neutrophils in dermis and epidermis - becomes possible.

Subprocess L2a(DEMP). Secretion and degradation of commensal microbiome. Formation of bacterial products of resident origin.

Bacteria of commensal microbiome constantly produce bacterial products. This occurs owing to their secretion, constant self-renewal (decomposition products) as well as due to their degradation under influence of skin immune system. Besides LPS, PG, PG-Y and bacDNA, among bacterial products there are substances with chemokine properties, also serving as netosis factors. These substances are secreted by live bacteria and are present in their decomposition or degradation products (Supplement A10, Supplement A11).

These are PSM-gamma (Cogen 2010) and GroE (Dapunt 2016, Meyle 2012)L, secreted by Staph.epidermidis. This is H_2O_2 - hydrogen peroxide, secreted by oral streptococci, particularly by Str.mitis, Str.oralis, Str.sanguinis and Str.gordonii (Okahashi 2014, Sumioka 2017, Xu 2014). This is FMLP, secreted by a number of bacteria (Hasler 2016, Lipp 2017) (Table 3).

At L2a(DEM), the range of bacterial products of resident origin does not include PG-Y, whereas among netosis provoking substances apparently there is no hydrogen peroxide H_2O_2, secreted by oral streptococci. Admittedly, it can also be secreted by other commensal bacteria.

Cases of L2(IN)=LP2(IN) and L2(HPV)=LP2(HPV) are in detail considered in (Peslyak 2012b, p.16).

L2 is suppressed by L3.

L2 is suppressed by L8b. Not represented in schemes. At L2(DEMP) and L2(DEM), hyperproliferation of keratinocytes is accompanied by decrease of epidermal commensal microbiome concentration, while AMP hypersecretion reduces its concentration both in epidermis and in dermis.

6.5. Process L3. Innate response.

L3 includes seven subprocesses (Table 1, Table 2, Fig.7):

- L3a (L3ar). Secretion of chemokines and AMP.
- L3b. Netosis of neutrophils in skin.

- L3c (L3cr). Formation of NA-complexes with LL37. (NA – nucleic acids)
- L3d (L3dr). Endocytosis of non-host biomaterial. Including bacterial products resident (at DEMP or DEM) and non-resident (from L3b) origin. Formation of DC-Y, Mo-Y, MF-Y (in phase N2 at DEMP only).
- L3e (L3er). Influence of kPAMP. Resident (at DEMP or DEM) and non-resident (from L3b) origin on TLR and NOD receptors.
- L3f. Loss of tolerance to kPAMP at DC-Y, Mo-Y and MoDC-Y of non-resident origin, which have brought Y-antigen from blood (in tables and in figures is absent as is not obligatory).
- L3g (L3gr). Formation of MF, MoDC from Mo, and also formation of MF-Y, MoDC-Y from Mo-Y.

The content of subprocesses L3a, L3b, L3c and L3e is determined by L2; the content of subprocesses L3d, L3f, L3g does not depend on L2.

During L3, subprocess L1 is always intensified. Within YN-model start of innate response is divided. It is assumed that during phase N2 innate response occurs primarily involving cells of resident origin (designated as L3r). If L3r proves insufficient for eliminating (controlling) L2, phase N3 begins, during which innate response is fulfilled with participation of cells of resident and non-resident origin (designated as L3).

If even this proves insufficient for eliminating (controlling) L2, then L4 (phase N4) starts, which stimulates start of L6, L7 and L8.

Within L3, there occurs involvement of PDC from blood, without which L4 is impossible. Other immunocytes, whose range depends on particular L2, are also attracted from blood.

L3r (L3ar, L3dr, L3er and L3gr) occurs during homeostasis (phase N1) as well as during phase N2. During phase N2 at L2(DEM) and L2(DEMP), subprocess L3cr acts as well.

L3 begins to work fully during phase N3 and continues during phases N4, N5 and N8 (Table 1).

Cases L3(IN)=LP3(IN) and L3(HPV)=LP3(HPV) are in detail considered in (Peslyak 2012b, p.18).

Further on, there is a detailed description of all subprocesses of L3(DEMP) - innate response after dermal expansion of commensal microbiome with PsB.

For subprocesses, differences between L3(DEM) and L3(DEMP) are also specified if present.

Subprocess L3a. Secretion of chemokines and AMP.

Chemokine and AMP secretion occurs in all phases of psoriatic plaque development. The differences consist in intensity and range of secretion (Bierkarre 2016, Gilliet 2015, Patra 2018).

During phases N1 and N2, innate response occurs mainly with participation of cells of resident origin. This means that secretion of chemokines and AMP with chemokine properties, which are ligands of chemokine receptors of blood immunocytes (particularly blood neutrophils) is minimal. It is due to this that attraction of blood neutrophils into skin during homeostasis (phase N1) as well as during phase N2 is insignificant (therefore they are not represented in Fig.A9 and Fig.A10).

Commensal bacteria (as well as their bacterial products) and blood neutrophils are assumed to be the key element of psoriatic plaque initiation and development in YN-model at L2(DEMP) or L2(DEM). Therefore, Supplements contain detailed information on all bacterial products and AMP with chemokine properties involved in traffic of neutrophils (and other immunocytes) at psoriasis (Supplement A10).

All known ligands of bacterial products and AMP with chemokine properties are also listed there. (Supplement A11). These ligands are chemokine receptors involved in traffic of neutrophils and PDC at psoriasis. The table also contains information on values of maximum affinity between agonists.

Another table (with comments) contains detailed information on chemokines and their ligands - chemokine receptors involved in traffic of neutrophils at psoriasis (Supplement A12).

During homeostasis (phase N1 - common for all L2, Fig.A9), in response to usual concentration of skin commensal microbiome (both in epidermis and in dermis) there occurs weak secretion of chemokines (CCL2, etc.), AMP (lysozyme and RNAse7) as well as AMP with chemokine properties (LCN2, LL37, HBD2, HBD3, chemerin, S100A7, S100A8, S100A9). Secretion occurs mainly by

keratinocytes and fibroblasts. Intensity and range of AMP secretion as well as influence of resident phagocytes control dermal expansion of commensal microbiome. Dermal expansion attempts also depend on microbiome composition and its bacteria's invasiveness. If such homeostasis is disrupted, there is a transition to phase N2. One of reasons for this can be insufficient bactericidity of AMP and AMP with chemokine properties against commensal microbiome, e.g. against Streptococcus genus (Ouhara 2005).

During initial skin reaction to L2(DEMP) (phase N2, Fig.A10) there occurs intensification of secretion of the above listed chemokines and AMP. This intensification originally occurs within L3r(DEMP) - innate response, mainly with participation of cells of resident origin (L3ar, L3dr and L3gr).

AMP influence on bacteria of commensal microbiome causes their degradation and, more specifically, bacterial products LPS, PG, PG-Y, bacDNA, FMLP, PSM are formed (subprocess L2a(DEMP)).

With L3r(DEMP) being insufficient for controlling and terminating L2(DEMP), there is a transition to phase N3. This means L3r(DEMP) passes into L3(DEMP) - innate response with participation of cells of both resident and non-resident origin. This occurs due to intensive secretion of AMP with chemokine properties as well as to formation of FMLP, PSM - bacterial products with chemokine properties, primarily ligandic to CCR2, CCR6, FPR1, FPR2, RAGE - neutrophil receptors (Supplement A11).

During phase N3 there occurs range extension and intensification of secretion of chemokines CCL2, CCL20, CXCL8, CX3CL1, etc. (Fig.A11), as well as intensive secretion of other chemokines, ligandic to neutrophil's receptors CCR1, CCR2, CCR5, CCR6, CXCR1, CXCR2, CXCR4, CXCR6 (Supplement A12).

AMP (lysozyme and RNAse7) as well as AMP with chemokine properties (LCN2, LL37, HBD2, HBD3, chemerin, S100A7, S100A8, S100A9) continue to be actively secreted.

As a result of bacteria degradation, bacterial products continue to be formed, including FMLP and PSM with chemokine properties.

In the course of L2(DEMP) suppression (phases N4 and N5), there occurs reduction of resultant bacterial products (Fig.A12, Fig.A13). Their formation almost completely stops at L2(DEMP) completion during phases N6, N7 and N8 (Fig.A14, Fig.A15, Fig.A16).

During phases N3, N4, N5 and N8, active secretion of chemokines and AMP with chemokine properties is also performed by immunocytes, including those attracted from blood. Thus, self-amplification of their traffic takes place. Similar secretion is performed by keratinocytes (Furue 2020), primarily under influence of IL17A.

Chemokines and AMP with chemokine properties in high concentration are present in prepsoriatic and psoriatic skin and also get into blood. It is due to this that blood immunocytes, including blood neutrophils, become attracted to the place of inflammation (prepsoriatic and later psoriatic).

Intensive AMP secretion can be genetically preconditioned. It is demonstrated, for example, that probability of psoriasis display is higher if copy number of gene responsible for HBD2 secretion exceeds 2 (this number can reach 7) (Hollox 2008, Machado 2015, Singh 2019, Stuart 2012).

Information sources on secretion of chemokines and AMP as well as on its intensity at norm, at prepsoriatic and psoriatic skin are listed in footnotes and comments to tables (Supplement A10, Supplement A11, Supplement A12). Information on localization (epidermis, dermis) of AMP secretion and its intensity is mainly confirmed by sources (Supplement A10, Bierkarre 2016, Chimenti 2016, Fuentes-Duculan 2017, Gudjonsson 2009, Harder 2010, Kim 2014, Lande 2015, Ong 2002, Park 2009, Patra 2018), but is partly hypothetical.

Subprocess L3a begins within L3(DEMP) - innate response, and after initiation of PLS-inflammation is sustained in vicious cycle B (Fig.7, Fig.8).

L3a depends on L2a(DEMP) or L2(DEM). The range and concentration of chemokines and AMP secreted by skin cells are determined by range and concentration of bacterial products.

L3a depends on L3e. Interaction with PAMP leads to intensive secretion of chemokines and AMP.

Subprocess L3b. Netosis of neutrophils in skin.

After being attracted into skin, neutrophils can undergo apoptosis, and apoptotic bodies are endocyted by other phagocytes (Greenlee-Wacker 2016, Soehnlein 2010). Neutrophils' tendency to

apoptosis is, among other factors, determined by concentration of TNF-alpha, IFN-gamma and GM-CSF (van den Berg 2001, Soehnlein 2010). How exactly neutrophils in skin will terminate their existence (by apoptosis or netosis) depends on inflammatory process development. Predominant apoptosis and subsequent endocytosis (efferocytosis) of apoptosis products by other phagocytes, as a rule, means completion of inflammatory process (Malachowa 2016, Soehnlein 2010, Schuster 2013). Macrophages performing endocytosis of apoptosis products secrete anti-inflammatory cytokines TGF-beta, IL-10, and PGE-2 (Wang 2014). Dendritic cells performing endocytosis of apoptosis products stop their maturing, i.e. their ability to transform into maDC and to present antigens (Schuster 2013). Chemokine receptor CCR5 is expressed only on apoptotic bodies of neutrophils. One of the aims of such expression is attraction and binding of chemokines CCL2, CCL3 and CCL5, which contributes to decrease of new neutrophil attraction to inflammation site and to the completion of inflammatory process (Soehnlein 2010).

Netosis, in its turn, occurs mainly in inflammatory environment and netotic products contribute to intensification of inflammatory process (Sangaletti 2012). It may be assumed that in psoriatic plaque, either stable or growing, neutrophils mainly end their existence by netosis. Only in case of plaque remission they end their existence mainly by apoptosis. Remission of psoriatic plaque and its transformation into normal skin leads to almost total neutrophil disappearance in it, since those which earlier arrived from blood have undergone netosis or apoptosis, whereas income of new neutrophils from blood nearly stops.

In active psoriatic plaque many neutrophils undergo netosis, and netotic products actively influence skin immune system (Hu 2016, fig.4; Lin 2011, fig.3; Pinegin 2015, Skrzeczynska-Moncznik 2012). Authors of two models of pathogenesis included netosis in the vicious cycle (FM-model, Fig.A2, Delgado-Rizo 2017), (SE-model, Fig.A3, Schon 2018) and (WG-model, Fig.A4, Shao 2019), (CH-model, Chiang 2019) (Table 5).

WG-model presupposes that pathogenesis of psoriasis occurs only within innate response. The authors have demonstrated, firstly, that psoriatic blood neutrophils are activated (are in prenetotic state). Secondly, it has been demonstrated that netotic products (formed owing to netosis of psoriatic blood neutrophils) stimulate keratinocytes, which subsequently secrete inflammatory cytokines and chemokines, including LCN2, IL36gamma, CXCL8 and CXCL1. IL36gamma cytokine, in its turn, (through IL36R receptor) induces increased expression of TLR4 in keratinocytes (Madonna 2019). The authors of WG-model have demonstrated that netotic products of psoriatic blood neutrophils collectively affect keratinocytes through TLR4 receptor, which causes through MyD88 and NF-kappaB activation and induces production and secretion of LCN2 and IL36gamma. Eventually, increased LCN2 level is conductive to attraction of new blood neutrophils and to their netosis, thus creating vicious circle (Shao 2016, Shao 2019).

Applying Nano-LC/MALDI-MS equipment (Capitalbio Technology Corporation) enabled to determine the range of netotic proteins formed at netosis of psoriatic blood neutrophils (Shao 2019, supplemental table 1). Then they tested the impact on keratinocytes of proteins S100A9, S100A8, LCN2, HSP70 on TLR4 receptor, firstly, found with high coverage in this range, and secondly, since in several sources their impact on TLR4 was found. However, none of these proteins manifested any impact on LCN2 and IL36gamma secretion, comparable to the one demonstrated by netotic products in general (Shao 2019, fig.3C and fig.3D).

Note should be taken that in the range of netotic proteins discovered, there is no LL37 (MW 4.5 kDa), NE (MW 28.5 kDa) or SLPI (MW 11.7 kDa), which means its incompleteness. Furthermore, there is no LPS (MW ~ 10 kDa) and lipid A (MW ~ 1.8 kDa) in it, which can be found among netotic products, according to YN-model and to the results of studies (Garaeva 2005, Garaeva 2007). Apparently, in course of pre-preparation of netotic products for determining the range, free hDNA, hRNA and LPS connected all LL37 (as well as NE and SLPI) and formed complexes (Scott 2011, Skrzeczynska-Moncznik 2012), which were not identified?

The fact that netotic products of psoriatic blood neutrophils actively influence keratinocytes through TLR4 receptor, in its turn, can be regarded as proof of LPS presence in these netotic products and/or its TLR4-active fragments, endocyted by neutrophils in blood flow (SPN8).

The most detailed analysis of the possible role of netosis in psoriatic inflammation is given in a survey (Pinegin 2015). Firstly, this is participation of netotic products (LL37, NE - neutrophil elastasa, etc.) in forming complexes with hDNA (influence PDC through TLR9) and RNA (influence DC through TLR7 and TLR8). Secondly, it is stimulation of pro-inflammatory cytokine secretion (IL17, etc.) and, thirdly, it is formation of netotic products which can become autoantigens.

In (Herster 2020) hRNA-LL37 complexes have the role of self-amplification of the following processes: neutrophil attraction into psoriatic skin, secretion of chemokines and cytokines and, basically, netosis. For the first time it is demonstrated that netotic products contain hRNA. It is also demonstrated that LL37, which is, firstly, actively secreted by neutrophils and, secondly, contained in netotic products, forms complexes with hRNA lost during netosis. Besides, it is demonstrated that only these complexes (but not hRNA or LL37 separately) can influence neutrophils through endosomal receptor TLR8. Colocalization of NE (neutrophil elastasa), hRNA and LL37 in psoriatic skin is also shown. The authors of the work assume that netosis can pose a self-amplification factor of psoriatic plaque.

The role of netosis in pathogenesis of various diseases (systemic lupus erythematosus, rheumatoid arthritis, ANCA vasculitis, arterial and venous thrombosis, pulmonary fibrosis, psoriasis, gout) is systematized in (Mitsios 2017, fig.1 and fig.2). It proposes a two-factor scheme of netosis role in pathogenesis of these diseases. The first factor (hit trigger) is the conditions under which proteins provoking a particular disease appear (are formed) in neutrophils; the second factor (hit trigger) is the conditions under which netosis takes place, accompanied by ejection of these proteins. The authors of this study suggested a new term "netopathy" to denote diseases in whose pathogenesis netosis plays the key role.

Within YN-model netosis of neutrophils in skin is conditioned, firstly, by chronic kPAMP-load on these neutrophils in blood before their attraction into psoriatic skin. This load makes some of them kPAMP-carriers and brings them into activated (prenetotic) state. As this occurs, part of neutrophils undergoes netosis directly in blood (Hu 2016, fig.1 and 3; Lin 2011, fig.4; Shao 2019, fig.1; Teague 2019). Secondly, netosis in skin is determined by those conditions in which blood neutrophils (some of which are already in prenetotic state) find themselves in prepsoriatic and psoriatic skin (Table 3).

Netosis of part of neutrophils in skin begins during phase N3 (Fig.A11) and proceeds intensively during subsequent phases N4, N5, N8 (Fig.A12, Fig.A13, Fig.A16, Table 1).

At L2(DEMP) and L2(DEM), the main cause of netosis during phases N3 and N4 are substances secreted by bacteria of commensal microbiome. These are PSM-gamma (Cogen 2010) and GroEL, (Dapunt 2016, Meyle 2012), secreted by Staph.epidermidis. This is H_2O_2, hydrogen peroxide, secreted by oral streptococci, particularly by Str.mitis, Str.oralis, Str.sanguinis and Str.gordonii (Okahashi 2014, Sumioka 2017, Xu 2014) (at L2(DEMP)). This is FMLP, secreted by a number of bacteria (Hasler 2016, Lipp 2017).

While bacteria of commensal microbiome are degraded, in extracellular space there appear LPS and PG, which can also provoke netosis.

Bacterial products provoke netosis in inflamed dermis until dermal expansion of commensal microbiome takes place. In process of suppression of this expansion (due to growth of AMP and phagocyte concentration), the role of bacterial products of resident origin as provokers of netosis in dermis diminishes. Notably during phase N8 (when process L2 has completely stopped), netosis will mainly be caused by other factors.

These are cytokines CXCL8, IL18, IL1beta (Delgado-Rizo 2017, Grayson 2016, Hasler 2016, Ortmann 2018), hRNA-LL37 complexes (Herster 2020), and platelets (Grayson 2016, Herster 2019, Papayannopoulos 2018, Pinegin 2015, Schon 2018). A detailed list of netosis factors (real and presumed) as well as information on their presence in prepsoriatic and psoriatic skin is given in (Table 3).

During netosis of Neu and Neu-Y, netotic products NET, including non-degraded kPAMP (LPS, PG, PG-Y and bacDNA) of non-resident origin, are ejected into extracellular space. These proteins (along with other substances) are endocyted by phagocytes (subprocess L3d).

Subprocess L3b begins within L3, and, after initiation of PLS inflammation, is sustained in vicious cycle B (Fig.7).

Neu and Neu-Y, being in pro-inflammatory environment, secrete cytokines of TNF-alpha, IL17 and IL22 (Lin 2011, Pinegin 2015, Reich 2015, Schon 2018). Such secretion occurs irrespective of netosis. These cytokines, however, can also be found in netotic products.

L3b depends on SPPN. If SPPN is interrupted, then, firstly, blood neutrophils will not be in prenetotic state, and secondly, they will not contain kPAMP endocyted in blood, including PG-Y.

L3b depends on L1a. If there is no sufficient neutrophil attraction from blood into skin, their smaller part will undergo netosis.

L3b depends on L2a(DEMP) or L2a(DEM). Netosis intensity is determined by bacterial products, acting as netosis factors.

L3b depends on L3a. Some of chemokines and/or AMP (e.g. CXCL8, LCN2, LL37, etc.) are factors provoking netosis (Table 3).

L3b depends on L3c. (Herster 2020) suggests a pathogenesis model, in which hRNA-LL37 complexes act as netosis factors, thus contributing to its self-amplification. Other sources do not mention such an option. This dependence is hypothetical.

Subprocess L3c. Formation of NA-complexes with LL37.

LL37 is a unique protein, possessing pleyotropic properties (Chieosilapatham 2018, Kahlenberg 2013). Apart from the fact that LL37 is AMP with chemokine ability to facilitate netosis (Neumann 2014), connect LPS and prevent its impact on TLR4 receptor (Chieosilapatham 2018, Scott 2011), it can also connect nucleic acids (NA) and form complexes with them, particularly with bacDNA (Duan 2018), as well as with hDNA and hRNA (Ganguly 2009, Lande 2015, Pinegin 2015).

Starting with phase N2, secretion of LL37 by keratinocytes takes place. As a result, at L2(DEMP) or L2(DEM) during phase N2 there appear bacDNA-LL37 complexes, whose components have resident origin.

Starting with phase N3, secretion of LL37 by neutrophils is added (Fuentes-Duculan 2017), and owing to netosis of some neutrophils (L3b), in extracellular space there appear LL37, hDNA and hRNA. As LL37 interacts with hDNA and hRNA, complexes hDNA-LL37 and hRNA-LL37 are formed.

Among netotic products, kPAMP is present, earlier endocyted in blood, particularly bacDNA. As a result, starting with phase N3, bacDNA-LL37 complexes are formed, whose component has non-resident origin.

It is in the form of NA-complexes with LL37 (bacDNA-LL37, hDNA-LL37, hRNA-LL37) that plasmacytoid dendritic cells PDC endocyte and deliver bacDNA, hDNA or hRNA to endosomal TLR9 for interaction (Panda 2017).

Note should also be taken that such AMP as HBD2, HBD3 and lysozyme facilitate formation of complexes with hDNA-LL37 and participate in stimulating PDC to IFN-alpha secretion (Lande 2015).

Process L4 (phase N4) begins when PDC endocyte NA-complexes with LL37 (interacting with endosomal TLR9) and begin to actively secrete IFN-alpha.

hRNA-LL37 complexes also facilitate maturing of DC (L6b) (Ganguly 2009).

In the early models of pathogenesis – N-model (Perera 2012), GK-model (Guttman-Yassky 2011) and GKH-model (Lowes 2014, Hawkes 2017), TC-model (Tonel 2009), GL-model (Ganguly 2009, Gilliet 2008, Gilliet 2015), AL-model (Albanesi 2018) – the main source of hDNA and hRNA were keratinocytes damaged as a consequence of trauma.

In Y-model, damaged keratinocytes were also one of two possible sources of hDNA and hRNA (L3c(IN)=LP3.1(IN), Peslyak 2012b, p.19).

However, in newer models of pathogenesis – FM-model (Delgado-Rizo 2017) and GLD-model (Di Domizio 2019)– neutrophils undergoing netosis are regarded as the main source of hDNA and hRNA in prepsoriatic and psoriatic skin (Table 5).

In YN-model, neutrophils undergoing netosis (L3b) are regarded as one of the main sources of hDNA and hRNA, which does not exclude additional sources of hDNA and hRNA (e.g. from mast cells undergoing self-damage (Lin 2011) or from damaged keratinocytes).

It is due to this that, at L3(DEMP) and L3(DEM), subprocess L3c intensifies starting with phase N3, i.e. from the moment of neutrophil attraction into skin and netosis of some of them.

At L2(IN) and L2(HPV) (trauma and HPV-carriage of KC), damaged keratinocytes act as the source of hDNA and hRNA. At L2(HPV), in its turn, at virus degradation, CpG is formed, and CpG-LL37 complexes with similar influence on PDC are additionally formed.

Cases L2(IN) and L3c(IN) = LP3.1(IN) as well as L2(HPV) and L3c(HPV) = LP3.1(HPV) are discussed in (Peslyak 2012b, p.19).

L3c depends on L2a(DEMP) or L2(DEM). As bacDNA is formed at degradation of commensal microbiome. It is this that determines possibility of subprocess L3cr during phase N2.

L3c depends on L3a. Intensity of complex formation depends on intensity of LL37 secretion.

L3c depends on L3b. Intensity of complex formation depends on intensity of netosis, during which hDNA and hRNA appear in extracellular space.

Subprocess L3d. Endocytosis of non-host biomaterial. Including bacterial products of resident (at DEMP or DEM) and non-resident (from L3b) origin. Formation of DC-Y, Mo-Y, MF-Y.

During phase N1 (homeostasis), endocytosis of non-host biomaterial, including bacterial products in small amounts, takes place in dermis.

At L2(DEMP) or L2(DEM), starting with phase N2, there begins intensive endocytosis of bacterial products of resident origin, including non-degraded LPS, PG, PG-Y (at DEMP) and bacDNA.

Netotic products NET, including bacterial products of non-resident origin (and specifically non-degraded LPS, PG, PG-Y and bacDNA) appear starting with phase N3.

At L2(DEMP), formation of DC-Y, Mo-Y and MF-Y takes place starting with phase N2 (Table 1). During this phase, Y-antigen has only resident origin.

Starting with phase N3, there occurs endocytosis of bacterial products of both resident origin (at DEMP or DEM) and non-resident (from L3b) origin.

Fig.A18 shows a conditional concentrations of endocyted Y-antigens of resident origin (yellow line) and of non-resident origin (red line) during phased development of psoriatic plaque at L3d(DEMP).

Starting with phase N2, the main source of Y-antigen is PG-Y, which is formed during PsB degradation (subprocess L2a(DEMP)). Starting with phase N3, there appears an additional source of Y-antigen – non-degraded netotic products of Neu-Y. As suppression of L2(DEMP) progresses, concentration of Y-antigen of resident origin decreases, and during phase N8 is practically reduced to zero. Meanwhile, concentration of Y-antigen of non-resident origin grows, as attraction of blood neutrophils increases, and some of them (including Neu-Y) constantly undergo netosis.

Netotic products NET actively influence other cells, but are also endocyted by skin phagocytes (Grayson 2016, Schuster 2013, Soehnlein 2010, Wang 2014). Endocytosis is effected by other neutrophils, macrophages, monocytes and dendritic cells of skin. When endocytosis is effected by monocytes Mo (having potential to be transformed into dendritic cells MoDC) and by dendritic cells DC, and if non-degraded antigens (particularly PG-Y) are retained in endocyted material, Mo-Y and DC-Y are formed.

Next, transformation of Mo-Y into MoDC-Y (L3g), and then transformation of DC-Y and MoDC-Y into mature dendritic cells maDC-Y (L6b) is possible. As a result, presentation of Y-antigens to effector lymphocytes TL-Y becomes possible (Fig.6, Fig.7).

Phagocytes (monocytes and dendritic cells), which endocyted apoptosis products of neutrophils, can entrap even live intracellular bacteria lost by neutrophils (Karaji 2017, McCracken 2014, Schuster 2013) and thus to become infected.

Interaction of dendritic cells with apoptosis products has been studied for a long time. It has been demonstrated that they are able to effect processing and presenting antigens which were endocyted together with apoptosis products (Nauseef 2013, Schuster 2013).

Comparison of these processes has been made on the example of ANCA vasculites, when autoantibodies are formed to proteins PR3 or MPO, which are products of apoptosis and netosis of neutrophils. It has been demonstrated that these proteins to a much greater extent retain their autoantigenic properties during netosis. Formation of autoantibodies takes place with the active participation of dendritic cells which endocyte netotic products and then process and present autoantigens contained in them (Sangaletti 2012, video of endocytosis).

Taking into account the above-mentioned information, endocytosis of non-degraded bacterial products lost during netosis in psoriatic skin by monocytes and dendritic cells seems quite possible.

And subsequent processing and presentation of Y-antigens contained in them are their direct responsibility (monocytes Mo-Y perform it after transformation into dendritic cells MoDC-Y).

Subprocess L3dr takes place at homeostasis, intensifies due to start of L3r (innate response with participation of cells primarily of resident origin), and after initialization of PLS-inflammation (as L3d) is sustained in vicious cycle B (Fig.7).

At L2(DEM), Y-antigen is not present among bacterial products of resident origin. Therefore, formation of DC-Y, Mo-Y and MF-Y begins only with phase N3, and all Y-antigen has non-resident origin. This is the main difference of L3d(DEM) from L3d(DEMP).

L3d depends on L2(DEMP) or L2(DEM). Endocytosis of non-host biomaterial depends on intensity of dermal expansion of commensal microbiome.

L3d depends on L3b. Intensity of endocytosis of netotic products depends on netosis intensity.

L3d depends on L3e. Endocytosis is stimulated by interaction with kPAMP. For intracellular receptors, such as TLR9 and NOD2, endocytosis of kPAMP precedes this interaction.

Subprocess L3e. Influence of kPAMP.

kPAMP within YN-model are LPS, PG (incl. PG-Y) and bacDNA.

bacDNA is present in healthy, prepsoriatic and psoriatic skin both in epidermis and dermis (Supplement A7). Since commensal microbiome contains both Gram(-) and Gram(+) bacteria, LPS and PG are constantly formed at their degradation (Baker 2006a, Baker 2006b).

Due to this, during phase N1 (homeostasis) kPAMP of resident origin is always present in skin (mainly in epidermis). During dermal expansion of commensal microbiome (L2(DEMP) or L2(DEM)), intensive formation of kPAMP begins, not only in epidermis, but also in dermis (phase N2 and further), i.e. during phases N1 and N2, kPAMP only of resident origin affect TLR and NOD receptors of skin cells. Netotic products NET including kPAMP of non-resident origin appear starting with phase N3. Thereby, starting with phase N3, TLR and NOD receptors are affected by kPAMP both of resident origin (at DEMP or DEM) and of non-resident (from L3b) origin. After elimination of L2(DEMP) or L2(DEM), phase N5 is completed and, as a consequence, kPAMP of resident origin practically disappear from dermis, i.e. during phase N8, TLR and NOD receptors of dermal cells are affected by kPAMP only of non-resident (from L3b) origin.

The main receptor for LPS is TLR4 (membrane and endosomal). (Shao 2019) has recently demonstrated that netotic products of psoriatic blood neutrophils actively interact with TLR4 receptor of keratinocytes, which serves as indirect confirmation of presence of non-degraded LPS fragments among netotic products.

The main receptors for PG are TLR2 (membrane and endosomal) as well as intracellular NOD1 (for DAP) and intracellular NOD2 (for MDP) (Fukui 2016a, Kim 2010, Pashenkov 2018). For bacDNA and CpG, the main receptor is endosomal TLR9. Expression of all these receptors increases as concentration of corresponding kPAMP continues to grow. Thus, it is possible to indirectly estimate their concentration.

(Baker 2003) examined expression of TLR1, TLR2 and TLR5 at norm and psoriasis. Considerable excess of expression over norm was found only for TLR2 (mainly in epidermis). (Begon 2007) studied expression of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6 and TLR9 at norm and psoriasis. Considerable excess of expression over norm was found only for TLR2 (mainly in epidermis. (Okhlopkov 2012) examined expression of TLR2 and TLR4 at norm and psoriasis. It was demonstrated that their expression takes place only in epidermis. (Tervaniemi 2016) studied NOD2 expression at norm (HS), NLS and PLS. Increased expression (PLS > NLS > HS) was discovered both in epidermis (mainly in keratinocytes) and in dermis. (Morizane 2012b) examined TLR9 expression at norm and at psoriasis. It was demonstrated that intracellular expression of TLR9 in keratinocytes increases under LL37 influence. (Stepanenko 2015) studied TLR9 expression at norm and psoriasis. It was demonstrated that the maximum endosomal TLR9 expression takes place at psoriasis in basal and spinosum layer of epidermis as well as at dermal monocytes and macrophages. The survey in (Sun 2019) gives a detailed description of alarm mechanisms and skin cell reaction at PAMP impact on TLR receptors, specifically at atopic dermatitis and psoriasis. It enumerates possibilities of therapeutic impact on expression of TLR receptors (particularly of TLR2, TLR4 and TLR9) for remission achievement.

L3e depends on L3b. kPAMP concentration in skin depends, in particular, on intensity of netosis, in course of which kPAMP of non-resident origin appear in extracellular space.

Subprocess L3f. Loss of tolerance to kPAMP at DC-Y, Mo-Y and MoDC-Y of non-resident origin, which brought Y-antigen from blood.

In YN-model, this subprocess is possible, but not obligatory. It is described in detail in Y-model (as LP6.1).

Subprocess L3g. Formation of MF, MoDC from Mo, and also formation of MF-Y, MoDC-Y from Mo-Y.

During this subprocess, transformation of Mo in MF and MoDC (in all phases), as well as Mo-Y in MF-Y and MoDC-Y takes place (at L2(DEMP) from phase N2, in others cases – from phase N3).

Formation of MF occurs constantly - with low intensity during phases N1 and N2, with average intensity during phase N3 and with high intensity during phases N4, N5 and N8 (Table 1).

Active formation of MoDC begins during phase N4, under the influence of IFN-alpha and TNF-alpha secreted by PDC during L4. Presence of PAMP (outside or inside) of Mo activates their transformation in MoDC. Activity of these formations in all subsequent phases N5 and N8 depends on L8 intensity.

Mo (MF) endocytose and-or contact with L2-content, activate and secrete TNF-alpha, IL1beta, IL12 and IL20 (Clark 2006b, Fuentes-Duculan 2010, Wang 2006).

L3g depends on L2a(DEMP). Intensity of MF-Y and MoDC-Y formation depends on PG-Y concentration in bacterial products.

L3g depends on L3b. MF-Y and MoDC-Y formation depends on intensity of netosis, in course of which Y-antigen of non-resident origin appears in extracellular space.

L3g depends on L3e. Interaction with kPAMP stimulates MF and MoDC formation.

L3 depends on L1a. Starting with phase N3, L3 intensity is determined by non-resident immunocytes. The more Neu and Neu-Y get into skin, the more netotic products are formed. The more Mo and DC get into skin, the more of them can participate in endocytosis of netotic products and in subsequent transformations. At inflammation, most dermal MF, Mo and DC are derived from Mo and DC attracted from blood.

L3 as a whole is initiated and supported by L2.

L3 depends on L8. Innate and adaptive responses amplify each other.

6.6. Process L4. Trigger of adaptive response.

Active peak-like secretion of IFN-alpha by PDC, is a signal formed only in result of innate response L3, which couldn't eliminate L2. This trigger signal provides active start of adaptive response (Chiricozzi 2018, Di Meglio 2017, Lande 2010, McKenna 2005, Seo 2010, Reizis 2019, Tang 2010, Wang 2020, Zhang 2005).

This trigger starts working if intensity of process L2 is combined with insufficiency of process L3.

Process L4 start determines phase N3 end and short-term phase N4 start. This short-term phase N4 terminates at phase N5 start, namely with L8 begin.

The major role for transition to phase N4 belongs to those proteins which are formed (FMLP) or are secreted (chemerin) in NLS-dermis and are chemokines for PDC (Supplement A10) and LL37, with which NA-complexes (L3c) are formed.

L4 has limited duration, initiates and supports L6 until this support is provided by L8 (Fig.7, dot-and-dash line). Notably, intensive L8 supresses L4 (Table 1, Fig.7, Fig.8).

PDC produce and secrete considerable amount of IFN-alpha approximately 7 days prior to appearance of pinpoint psoriatic plaque. For the first time it has been proved at carrying out experiments with NLS-transplants transferred to AGR129-mice (Nestle 2005a).

The majority of models of pathogenesis of psoriasis include dermal PDC as obligatory components, which under influence of hDNA-LL37 complexes transitively and actively secrete IFN-alpha before plaque appearance (Table 5).

When plaque has already started to develop, the level of IFN-alpha gradually decreases to the norm (LP4 calms down). Therefore, only in acute (but not chronic) plaques high level of MxA protein (which is a marker of previously high level of IFN-alpha) is detected (Nestle 2005a).

PDC continue to be involved into PLS-dermis and appear there in increased amount, however they lose their ability to intensive secretion of IFN-alpha (despite increased level of hDNA-LL37 complexes). It occurs under the influence of suppressive activity of high level of TNF-alpha (being secreted during L8) on PDC (Mylonas 2018, Palucka 2005, Schon 2019).

On external border of growing psoriatic plaque, however, PDC keep intensively secreting IFN-alpha, which facilitates its expansion (Nestle 2005a) (phase N7, Fig.A15).

In more detail in (Peslyak 2012b, p.20).

KC can act as an additional source of IFN-alpha. KC carry out secretion of IFN-alpha under influence of hDNA-LL37 complexes on intracellular receptor TLR9. Notably, LL37 facilitates an increase in TLR9 expression in KC. This additional source of IFN-alpha can be crucial at insufficient PDC concentration, particularly in epidermis (Morizane 2012a, Morizane 2012b).

Content of L4 at L2(IN) and L2(HPV) are in detail considered in (Peslyak 2012b, p.21).

L4 depends on L1a. Increased level of PDC coming from blood in the place of future plaque provides intensity of subsequent L4.

L4 depends on L2. This dependence is at work only at L2(IN) and L2(HPV).

L4 depends on L3. The more intensive LL37 secretion (L3a), netosis (L3b) and formation of hDNA-LL37 complexes are, the more intensively PDC secrete IFN-alpha. This dependence is suppressed by L8.

L4 is suppressed by L8. This occurs due to TNF-alpha, whose increased level is formed during L8.

6.7. Process L5. Adaptive response against L2.

In YN-model this process is possible, but is not obligatory.
It is in detail described in Y-model (as LP5).

6.8. Process L6. Mature dendritic cells formation.

L6 begins due to L4, under influence of (IFN-alpha + TNF-alpha), and intensifies while L8 is at work (phases N5 and N8) under cumulative influence of IFN-gamma, TNF-alpha, IL12, IL1beta (Chiricozzi 2018, Delgado-Rizo 2017, Di Meglio 2017, Hawkes 2017). Additional impact on DC maturing is made by active neutrophils and netotic products (Schuster 2013).

If L3 and L8 in interaction fully eliminate L2, and if there is enough L8 for sustaining L3 and L6b, phase N8 begins.

In addition about DDC in (Peslyak 2012b, p.24, k9).

Subprocess L6a. maDC-Z formation.

In YN-model this subprocess is possible, but is not obligatory. It is in detail described in Y-model (as LP6.3).

Subprocess L6b. maDC-Y formation.

The subprocess begins during phase N4 (or N7) and proceeds with high intensity during phases N5 and N8 (Table 1).

DC-Y and MoDC-Y secrete TNF-alpha, IL12 and IL23. Under the influence of IL12 and IL23 acceleration of their maturation (self-activation) takes place. Their maturation is also positively influenced by the combination of IFN-gamma and IL1beta. IFN-alpha and GM-CSF support maturation of MoDC-Y (Farkas 2011). DC-Y and MoDC-Y process bacterial products (containing kPAMP and PG-Y), form complexes of MHC class II with Y-antigen and transport them to the cell wall.

At fagosomal (endosomal) PG-Y degradation, MDP is always formed, which is NOD2 ligand. This gives Y-antigen an advantage in processing. Potential presence of other kPAMP (apart from PG-Y) in these very phagosomas (endosomes) enhances this advantage (Iwasaki 2010).

After that, maDC-Y appear to be ready to begin Y-antigen presentation (Delgado-Rizo 2017, Sabat 2007).

DC-Y and MoDC-Y having insufficient PG-Y content are incapable of transformation into maDC-Y. Such cells will show the activity as more as they content kPAMP.

Y-antigen presentation to effector TL-Y occurs during subprocess L8a. Final maturation of maDC-Y occurs during interaction with TL-Y, i.e. subprocesses L6a and L8a are interrelated.

Additionally about maDC in (Peslyak 2012b, p.26, k9).

L6b depends on L3e. kPAMP support maturation of DC and MoDC.

L6b depends on L3g. As more formation of MoDC-Y, as more formation of maDC-Y.

L6 depends on L3c. hRNA-LL37 complexes formed during L3c cause activation of DC. It occurs through endosomal TLR8 and leads to secretion of TNF-alpha and IL6 and maturation of DC in maDC. hRNA-LL37 complexes are found in PLS-dermis and colocalizated with maDC. Their quantity correlates with CD208+maDC quantity. (Ganguly 2009, fig.8).

L6 depends on L4. Under the influence of IFN-alpha, Mo and DC increase expression of PAMP-receptors. IFN-alpha promotes formation of MoDC (Farkas 2011). And cooperation of IFN-alpha with TNF-alpha accelerates this formation. IFN-alpha also accelerates maturation of DC, which, at that, secrete IL12 more actively (Piccioli 2007). After PDC have executed their role in L4, they can be transformed into maDC (Zhang 2005).

L6 depends on L8. Intensity of secreted TNF-alpha, IL1beta, IL6 and IFN-gamma (at interaction of maDC-Y with TL-Y or mediated by FB and KC), determines the degree of transformation intensity of all Mo and DC. In particular, maDC-Y finally mature during interaction with TL-Y.

6.9. Process L7. Lymphnodes. Clonal proliferation.

This process is well-known and can occur during adaptive response. Subprocess L7a happens during L5 (i.e. within YN-model is not obligatory). Subprocess L7b happens along with L8 and, therefore, it takes place during phases N5 and N8 (Table 1, Fig.7, Fig.8).

Subprocess L7a. TL-Z formation.

In YN-model this subprocess is possible, but is not obligatory. It is in detail described in Y-model (as LP7.1).

Subprocess L7b. TL-Y formation.

Through afferent lymphovessels, maDC-Y get from inflammation place to the nearest regional lymphnodes. In consequence of maDC-Y interaction with naive nTL (at primary response) or with Tcm-Y (at secondary response), a number of new TL-Y appear, i.e. effector Tem-Y and central Tcm-Y. Such reproduction of T-lymphocytes is called ‘clonal proliferation’.

Then Tem-Y enter blood flow through the efferent lymph vessel. The expression of homing-receptors on Tem-Y (in particular, CLA) provides their migration to postarterial venules, on which ligandic adhesive molecules (in particular E-selectin and ICAM-1) are expressed. In areas of inflammation this expression is promoted, in particular, by TNF-alpha. Migration of Tem-Y occurs mainly to the inflammation areas, from where maDC-Y have come to lymphnodes (Delgado-Rizo 2017, Gudjonsson 2004).

Part of Tcm-Y enters blood flow similarly, but go to farther regional lymphnodes to proliferate there and differentiate in Tem-Y, which then enter other regional tissues (Fig.A17).

On the endothelium of postarterial venules, due to interaction of Tem receptors and ligandic adhesive molecules, infiltration of Tem from blood flow into dermis, and then, their movement inside dermis and epidermis takes place under the influence of chemokines.

Mostly (> 90%), in the absence of inflammation, Tem are constantly present in skin. The rest of Tem (<10%) circulate in blood flow. Skin Tem do not express CCR7 and L-selectin, which makes impossible their moving into lymphnodes. The total amount of Tem reaches 1 million per cm^2 of skin (among them specific to all antigens, in respond to which SIS (skin immune system) earlier have formed adaptive response). Such location of Tem provides the fastest and effective secondary adaptive response formed by SIS at repeated contact with antigens (Clark 2010).

At primary response, L7b start precedes dermal interaction of maDC-Y with Tem-Y. It is possible only at primary PLS-plaque and only in case if SIS has never earlier formed adaptive response against PsB.

At secondary response, Tem-Y is already present in skin, and Tcm-Y in lymphnodes. In this case, interaction of maDC-Y with Tem-Y (L8a) begins at once, and fast activation of subprocess L7b occurs later if in the inflammation area deficiency of Tem-Y develops.

It happens at any nonprime plaque, and, of course, on the external border of extending plaque (Vissers 2004).

It happens both at primary plaque if SIS has previously formed adaptive response, for example, against external PsB-infection or dermal expansion of PsB.

Additional places for clonal proliferation are formed directly in psoriatic dermis in form of iSALT (indusible skin-associated lymphoid tissue). maDC-Y in them also present Y-antigen to effector Tem-Y, and their proliferation may take place (Egawa 2020, Kabashima 2019, Kim 2014, Kim 2015).

Irrespective of the order of events, we consider that with L8 and-or L7b start phase N5 begins.

L7b depends on L6b. The more dermal maDC-Y is formed, the greater possibility that the amount of dermal Tem-Y (cooperating with maDC-Y) will be insufficient, and the more uninvolved maDC-Y will enter to lymphnodes.

6.10. Process L8. Adaptive response on (real and) imaginary dermal expansion of PsB.

Mature dendritic cells maDC-Y process PG-Y fragments contained in them, and after processing present Y-antigen to TL-Y, both resident and involved from blood flow. The skin immune system SIS receives a false target – an imaginary dermal expansion of PsB, regarded by SIS by presented Y-antigens.

This process occurs at any initiating and aggravating processes L2, in particular at L2(DEMP), L2(DEM), L2(IN) and L2(HPV).

The vicious cycle B = {L1a > L3 > L6b > L8 > L1} is initiated at L2 activation (through L3 and L4) (Fig.7). This cycle represents:

- Income phagocytes (including Neu-Y) from blood to the area of developing inflammation (L1a).
- Netosis of some Neu-Y. In extracellular space there are netotic products, including Y-antigens (L3b).
- Endocytosis of non-host biomaterial, netotic products, including PG-Y. Formation of DC-Y, Mo-Y (L3d).
- Formation of MoDC-Y from Mo-Y (L3g).
- Formation of maDC-Y from DC-Y and MoDC-Y (L6b).
- Interaction of maDC-Y with TL-Y (L8a), which, in its turn, supports L1.

The vicious cycle B amplifies by the vicious cycle C = { L6b > L7b > L1b > L8 > L6b}. At excess of maDC-Y and shortage of TL-Y movement of maDC-Y appears in the inflammation area into regional lymphnodes, where clonal proliferation of Tem-Y takes place (L7b). Due to homing, TL-Y arrive through blood flow to the inflammation area and adjacent areas (L1b), which causes intensification and expansion of plaque (L8).

Additional places for clonal proliferation are formed directly in psoriatic dermis in form of iSALT (indusible skin-associated lymphoid tissue). In them there is also presentation (Egawa 2020, Kabashima 2019, Kim 2014, Kim 2015).

Process L8 influences process L3 through secreted cytokines (Fig.7).

For L8 functioning, L1, L6 and L7b actively supported by L8 (Fig.A16), can be sufficient. It means that process L2 (and together with it potentially possible L6a and L7a) can come to the end, and L8 will proceed (PLS will pass into phase N8).

If L2 is preserved, or some secondary infections develop, PLS remains in phase N5.

The vicious cycle B can be interrupted in case of breach of SIS work, which can be realized for a while by application of biological drugs. However, the unique long-term decision eliminating the original cause of psoriasis is weakening or termination of SPPN.

Within L8 limits, KC hyperproliferation begins (physical protection of skin). At L2(DEMP) and L2(DEM), this reduces concentration of epidermal commensal microbiome and, consequently, intensity of its dermal expansion. At L2(IN) it accelerates trauma healing. At L2(HPV) it complicates possibility of the complete replicative cycle of virus. Thereby, process L3 is being assisted.

Within L8, there occurs active secretion of IL26, possessing, apart from antimicrobic properties, an ability to connect NA and to form bacDNA-IL26 and hDNA-IL26 complexes (subprocess L8c) (Chiricozzi 2018, Larochette 2019, Meller 2015).

Subprocess L8a. Y-antigen presentation by maDC-Y to effector TL-Y.

Due fast maturation (L6b) maDC-Y process PG-Y and present Y (fragments of interpeptide bridges) to effector TL-Y.

TL-Y are activated, proliferate and secrete TNF-alpha, IFN-gamma, IL17, IL22, IL26. Cytokine IFN-gamma is mainly secreted by Th1-Y. Cytokine IL17 (IL17A and IL17F) is mainly secreted by Th17-Y. Cytokine IL22 is mainly secreted by Th22-Y (Guttman-Yassky 2011, Nestle 2009a, Nestle 2009b, Tonel 2009).

The role of IL17A cytokine in psoriatic plaque development is undeniable (Furue 2020, Li 2020). This fact is taken into account in nearly all models of pathogenesis (Chiricozzi 2018, Delgado-Rizo 2017, Di Meglio 2017, Hawkes 2017).

IL23 secreted by MF and maDC plays important role in effector TL stimulation for secretion of all these cytokines. Genetic deviations in the condition of receptors for IL12 and-or IL23, can influence TL-reaction intensity (Gudjonsson 2009).

Under the influence of TNF-alpha, expression of adhesive molecules on endotelial cells of postarterial venules increases, with the subsequent increase of permeability of endothelium (it influences L1).

Events occur variously, it depends on whether there are resident TL-Y in skin or not, i.e. whether Y-priming have taken place (Clark 2010, Sabat 2007, Sabat 2011). If Y-priming has taken place, TL-Y is present in dermis. It means that the patient either already has psoriasis, or he\she has (or had) some skin, tonsillar (SP6) or generalized PsB-infections (Fig.A8).

In this case, maDC-Y, having executed PG-Y processing, presents Y to resident TL-Y. L8 begins quickly, at that, the threshold level of (PG-Y)-carriage by blood phagocytes for its initiation can be lower.

TL-Y amount in skin is enough to provide the active beginning and support of adaptive response in case of interaction with maDC-Y. At that, the need in clonal proliferation of TL-Y in lympnodes (subprocess L7b) increases later, when maDC-Y amount starts to exceed TL-Y amount essentially.

Y-priming (not because of psoriasis) increases probability of primary psoriasis and lowers the middle age of its occurrence. Such priming explains fast development (flash) in some patients of abundant primary plaques.

If Y-priming was absent, TL-Y in dermis is absent, i.e. the patient did not and does not have psoriasis, as well as skin, tonsillar or generalized PsB-infections. In this case, maDC-Y at the absence of TL-Y, express CCR7 and begin chemotactic movement through afferent lymph vessels into nearest lymphnodes. In lympnodes clonal proliferation of Tem-Y takes place, then they get to blood flow through the efferent lymph vessels (supprocess L7b).

If such beginning of psoriasis is possible at L2(PsB), L2(DEMP) and L2(IN) with PsB.

In detail about phases of development of psoriatic plaque (Supplement A9).

L2, initiating primary plaques, should be more intensive, than L2, initiating secondary plaques (when skin priming has already occurred).

L8a depends on L1b. L8a intensity depends on income of TL-Y from blood flow.

L8a depends on L3e. kPAMP are adjuvant promoting antigen presentation.

Subprocess L8b. KC hyperproliferation. Change of skin architecture. Growth of basal membrane area and vascularity increase.

This subprocess is a consequence of subprocess L8a and develops in time of its intensification. KC hyperproliferation begins at once in basal layers of epidermis at a skin site, where L8a has begun.

However, visible pinpoint plaque appears on the surface of skin with a several-day delay. This natural delay is necessary for displacement of normal KC of the overbasal layers by incompletely differentiated KC, quickly rising from the basal layers. Thus, changes of architecture of skin begin, being definitively formed in process of expansion and aggravation of plaque. These changes cover epidermis and lower dermis and are accompanied by the growth of basal membrane area and vascularity increase.

IFN-gamma, IL17, IL20, IL22 and TNF-alpha influence KC and cause their hyperproliferation (Chiricozzi 2018, Delgado-Rizo 2017, Di Meglio 2017, Hawkes 2017). Thus, IL20 is secreted by KC, and then both IL20 (in the autocrine way) and IL22 promote much more intensive hyperproliferation (Guttman-Yassky 2011, Sabat 2011). TNF-alpha and IL17 is synergic influence on KC (Chiricozzi 2010).

The hyperproliferation is realized by

- increase of the volume of the basal layer because of increase of the basal membrane area;
- increase of the fraction of growth (a part of proliferating KC in the basal layer) from 10-30% to 100%;
- increase of the amount of cycles of TA-keratinocytes division (TA - Transit Amplifying), which proceeds after their lifting to the overbasal layers.

In PLS, simultaneous increase of dermal papillas height and reduction of thickness of the layer above the papillas takes place (Fig.A16). At that, epidermis thickness as a whole is enlarged. These changes are a consequence of accelerated proliferation (basal and overbasal layers), forwarded and incomplete differentiation (spinous and granular layers) and accelerated desquamation (cornual layer) of keratinocytes.

Within the limits of YN-model, the accelerated desquamation of KC realizes physical protection of SIS against an imaginary dermal expansion of PsB.

KC in PLS secrete cytokines TNF-alpha, IL1beta, IL6, IL18, IL36gamma, TGF-beta, etc.

KC in PLS secrete chemokines (CCL2, CCL20, CX3CL1, CXCL1, CXCL3, CXCL5, CXCL8, CXCL9, CXCL10, CXCL11, etc.) and AMP (LL37, HBD1, HBD2, S100A7, S100A8, S100A9, etc.). It occurs under the influence of IFN-gamma, IL17, IL20, IL22 and TNF-alpha. In particular, IL17 and IL22 are capable of synergic influence on KC providing active secretion of HBD2.

It is the way of VEGF secretion causing angiogenesis. At early stages of inflammation, CCL2, HBD2 are more actively secreted, and, as a consequence, blood CCR2+phagocytes are mostly involved. At intensification of PLS-inflammation, KC secrete CCL20 more actively, and, as a consequence, blood CCR6+DC, CCR6+Tem are involved.

Secretion of chemokines and AMP, increase of vascularity and the basal membrane area, provides more intensive income of immunocytes in dermis from blood flow (L1) per unit of skin surface (Nestle 2009a, Nestle 2009b, Tonel 2009).

L8b depends on L8a. This occurs due to secreted cytokines.

Subprocess L8c. Formation of NA-complexes with IL26.

Affected by IL1beta and other cytokines, Th17 actively secrete IL26 (Weiss 2019). This cytokine possesses pleiotropic properties, and specifically it is able (similar to LL37) to connect NA and to form bacDNA-IL26 and hDNA-IL26 complexes (Chiricozzi 2018, Larochette 2019, Meller 2015).

NA-complexes with IL26 do not affect PDC present in psoriatic plaque, as high TNF-alpha concentration prevents this. Nevertheless, along with NA-complexes with LL37, they can affect PDC in prepsoriatic skin, adjoining the existing plaque (process L4).

Thus, prepsoriatic skin around the existing psoriatic plaque is in phase N6 (Fig.A14), and can pass into phase N7 (Fig.A15) and subsequently into phase N8. This means that psoriatic plaque can expand without any trigger process L2 (Fig.A18, B; Fig.A19, f-h).

L8c depends on L8a. The amount of secreted IL26 depends on Tem-Y concentration and on intensity of their activation during Y-antigen presentation.

L8 depends on L3. L8 is supported by L3 process, in course of which pro-inflammatory cytokines are secreted.

L8 depends on L6b. Without preliminary and sufficient formation of maDC-Y, L8a start is impossible, as well as its support without constant formation of new.

It is shown that L8 does not depend directly on L4 (Bissonnette 2010). Process L4 is transitory and necessarily preceding to development of new plaque, but not participating in its support. Due to L4, subprocess L6b is initiated. And then subprocess L6b is supported by L8.

6.11. Discussion

YN-model can be presented in the most simplified form (Fig.6).

The left part of the scheme shows the main components of systemic psoriatic process SPPN: Small intestine hyperpermeability for bacterial products with PAMP (including LPS, PG, bacDNA) and SP2 - SIBO with PsB-bacteria. SP1 and SP2 result in chronically increased concentration of PAMP (including PG-Y) in blood and to increased kPAMP- and (PG-Y)-load on blood neutrophils. As a result, a number of blood neutrophils become kPAMP- and (PG-Y)-carriers and pass into prenetotic state (subprocesses SPN4 and SPN8).

The main local processes are represented in the right part of the scheme.

In healthy skin, neutrophils are virtually absent. They are attracted from blood flow at the earliest stage of emergence of psoriatic plaque (even before visible changes of skin). One of possible causes of their attraction are L2(DEMP) and L2(DEM) - dermal expansion of commensal microbiome (with PsB and without PsB, respectively). Neutrophil attraction continues as long as plaque exists. Due to pro-inflammatory environment, in a stable or growing plaque neutrophils end their existence mainly by netosis (and at plaque remission – by apoptosis). In prepsoriatic skin, netosis is caused mainly by bacterial products and in psoriatic skin – by pro-inflammatory cytokines (subprocess L3b).

In netotic products, there appear non-degraded kPAMP (including PG-Y) brought by neutrophils from blood flow. They are endocyted by skin phagocytes and particularly by dendritic cells (subprocess L3d). Dendritic cells process PG-Y and present Y-antigen (contained in PG-Y) to effector T-lymphocytes. Other kPAMP act as adjuvants. Adaptive response of skin immune system to imaginary dermal expansion of PsB is formed (process L8).

Psoriatic plaques emerge and grow while **systemic psoriatic process** is at work, i.e. while attracted blood neutrophils contain kPAMP and PG-Y.

YN-model of pathogenesis of psoriasis is based on three factors: one systemic and two local:

Systemic necessary factor

- SPPN severity. It is estimated by unit Y-carriage of blood phagocytes (quantity of Y-antigens in phagocytes in 1 ml of blood). It is defined by a set of the interconnected subprocesses:
    - Small intestine permeability for bacterial products (SP1)
    - Specific small intestine dysbiosis (SP2)
    - Disorder of production and-or circulation of bile acids (SP3).
    - Overload and-or disorder of detoxicating systems (SP5)
    - Chronic PAMP-nemia (SPN4)

Local factors in specific skin site

- Intensity and duration of L2-inflammation.
- Y-priming level. It is estimated by concentration of TL-Y (Tem-Y - in dermis, Tcm-Y - in lymphnodes);

If combination of these factors for specific NLS site appears critical, it is transformed to PLS-plaque. The role of any of these factors (processes and subprocesses) can be strengthened by genetic (Gudjonsson 2009, Hollox 2008) and-or functional deviations.

Any PLS-plaque is caused by constant income in dermis of blood phagocytes (neutrophils, first of all) containing endocytosed kPAMP (including PG-Y) (L1a). At L2 and/or PLS-inflammation, this subprocess is intensified.

Process L2 can be any of triggers: DEMP, DEM, trauma, HPV, S.aureus, Malassezia sp., Candida albicans, skin PsB-infection, etc. Processes L2 can be different in different skin sites.

Owing to processes L3, L6b and L8, the level of cytokines IFN-gamma, GM-CSF, IL1beta, IL12, IL17, IL20, IL22, IL23, IL26, IL36gamma, TNF-alpha secreted in PLS increases.

Under their influence, KC and FB actively secrete chemokines and AMP: CCL2, CCL20, CX3CL1, LL37, HBD2, HBD3, chemerin, S100A7, S100A8, S100A9, lysozyme, RNAse7, etc.

Chemokines and AMP get to blood flow, and even more blood phagocytes and TL-Y are attracted to the inflammation site.

Because of the increasing income from blood of (PG-Y)+ phagocytes (inluding Neu-Y), more maDC-Y, cooperating with effector TL-Y are formed.

TL-Y are activated, proliferate and secrete cytokines promoting hyperproliferation of KC, which is an attempt of skin to eliminate imaginary dermal expansion of PsB through intensive renewal.

If SPPN severity and-or intensity and duration of L2-inflammation are insufficient, L8 will not be able to begin. Or L8 will begin, but at L2 end it will terminate at once, as L8 will not be able to become self-sufficient.

This alternative (beginning or impossibility of PLS-plaque beginning) also depends on the level of Y-priming in the site of L2-inflammation.

If in some NLS-site L2 is accompanied by L3 only (for example at latent HPV-carriage) L8 might not begin or begin with delay. The reasons of delayed initiation of L8 can be: delayed activation of L3 with cells of non-resident origin and-or increasing SPPN severity and-or increasing level of Y-priming (for example because of tonsillar PsB-infection).

If an increase of SPPN severity is temporary, plaques can be temporary, this exactly occurs at temporary guttate psoriasis.

During phase N5 (L2-inflammation and PLS-inflammation), each L2-activation aggravates and-or promotes plaque expansion. For this reason, process L2 is called initiating and aggravating.

Similarly, secondary infections act (other than initiating L2) that can join to already existing plaque.

If L8 has already begun, the further existence of initiating LP2 in this plaque can appear unessential, i.e. phase N5 can go to phase N8. During phase N8, plaque severity and its expansion rate are defined by SPPN severity (Fig.7, vicious cycles B and C) and by Y-priming level in the site surrounding this plaque.

Y-priming level (resident placing Tem-Y - in skin, Tcm-Y - in lymphnodes), increases during any PsB-infection (tonsillar, skin or systemic) (Fig.A8).

High SPPN severity causes formation of psoriatic plaques even at weak Y-priming and also at weak L2(PsB), L2(DEMP) and L2(IN). On skin sites with increased level of Y-priming and at intensive L2, the primary plaque can begin at lower SPPN severity.

Psoriasis, once having begun, provides constant increased Y-priming of areas adjacent to plaques, as well as the whole skin surface. Hence, for expansion of primary and initializations of subsequent plaques, lower SPPN severity is enough, than that for primary plaques initialization.

After plaque remission, an invisible NLS-spot with increased level of Y-priming remains on its place, which leads to increased probability of new PLS-plaque occurrence in the future in the same site (Clark 2011).

Primary guttate psoriasis approximately in 30% of cases completely resolves spontaneously, but in 70% it turns into chronic plaques immediately or after remission (Baker 2000, Baker 2006b). Guttate plaques is often preceded by intensive tonsillar PsB-infection when Y-priming of skin takes place and temporary, but intensive SPPN occurs. Temporary plaques appear and then spontaneously disappearing at SPPN end.

PLS-plaque is a reaction of SIS (skin immune system) caused by blood neutrophils Neu-Y that, which getting into dermis undergo netosis therefore in extracellular space there are non-degraded Y-antigens. Then Y-antigens are endocyted by phagocytes and a part of them are transformed in maDC-Y and present Y-antigen to effector ThN-Y.

This reaction includes epidermal hyperproliferation, as one of mechanisms of false adaptive response of SIS on imaginary dermal expansion of PsB.

PLS-plaque initiation can happen only during L2-inflammation including L3 (innate response with phagocytes and bacterial products not only resident, but also non-resident origin).

In particular it is possible at L2(DEMP) and L2(DEM) - dermal expansion of commensal microbiome (with PsB and without PsB, respectively), at L2(IN) - open trauma of dermis and at L2(HPV) – HPV-carriage of KC.

Existence and severity of PLS-plaque is defined by intensity of income into dermis of Y-antigen brought blood phagocytes.

Severity of PLS-plaque is aggravated by intensity of income into dermis of kPAMP brought by blood phagocytes.

These incomes are conditioned by SPPN severity.

Severity of PLS-plaque is aggravated by intensity of L2-inflammation if it continue to develop during PLS-inflammation.

SPPN it is necessary for initialization and support of any PLS-plaque. SPPN severity defines total severity of PLS-plaques as a whole. At decrease of SPPN severity, remission of separate plaques takes place, up to total disappearance of all PLS-plaques.

6.12. Conclusions

In YN-model (as well as in other models) it is admitted that genetic deviations can define the severity and the form of psoriasis manifestation, but they are not the reason of initialization or support of PLS-plaques.

Systemic psoriatic process (SPPN) has been included in YN-model as a necessary factor for initialization and support of plaques. Comparison of YN-model with other models shows that the majority of local processes included in YN-model have been earlier formulated in one or several models. However, as a whole, YN-model is principally new.

Concepts not borrowed from other models and formulated for the first time are collected in the block «YN-model novelty».

The systemic approach allows closer coming to construction of the model of pathogenesis of psoriatic arthritis as joint manifestation of SPPN, and then to the model of pathogenesis of psoriatic disease as a whole. The new YN-model requires check up. Although numerous facts from practice of researches and treatment confirm and-or do not contradict YN-model, yet does not mean its validity. The results of future researches will allow investigators to confirm and-or specify YN-model, define more precisely the role of intestine PsB, quantitative parameters of dependencies between processes (both systemic and local) (Peslyak & Korotky 2019).

The role of netosis in YN-model is congruent with the scheme offered in (Mitsios 2017), and if YN-model proves correct, psoriasis should be classified as netopathy.

We hope that this work will stimulate joint researches of the dermatologists, rheumatologists, gastroenterologists and microbiologists and approximate complete solution of the riddle of psoriatic disease.

In the future, treatment of psoriatic disease will be directed not to cosmetic and-or anti-inflammatory correction of local manifestations, rather elimination and-or decrease of action of original causes, i.e. in most cases, to the treatment of GIT dysfunctions (SP1, SP2). The efficiency of such treatment will depend on the patient, his/her desire and possibility to control the way of life and diet (De Santis 2015, Madden 2020). As consequence, remission will be prolonged (or life-long!), probably supported by regular or periodic intake of medicines (bacteriophages, pre - and probiotics).

YN-model novelty

- systemic psoriatic process SPPN - as the main necessary factor
- Y-antigen is defined and the mechanism of its appearance in dermal maDC-Y is suggested.
- role of Neu-Y and their netosis in derm as a necessary link of vicious cycle B
- L2(DEMP) and L2(DEM) as an initiating processes
- mechanism of initialization of PLS-inflammation during L2-inflammation (Koebner effect) is suggested.
- Y-priming role
- PLS-inflammation as a reaction of SIS to an imaginary dermal expansion of PsB

7. Supplements

Psoriasis as netopathy. Model of pathogenesis with unique netosis role. Supplements. e1.2
DOI: 10.5281/zenodo.4310107

Parts

Supplement A1. Small intestine permeability at psoriasis.

Supplement A2. Small intestine microbiome at healthy persons, SIBO (without psoriasis) and psoriasis.

Supplement A3. Bile acids role at psoriasis. Study results.

Supplement A4. PAMP-nemia and other changes in blood at psoriasis.

Supplement A5. Definition of concept of PAMP-loads on phagocytes.

Supplement A6. Pharynx microbiome at psoriasis. Study results.

Supplement A7. Bacterial metagenome of skin.

Supplement A8. Comparison Y-model and YN-model.

Supplement A9. Development phases of psoriatic plaque.

Supplement A10. Bacterial products with chemokine properties and AMP.

Supplement A11. Bacterial products and AMP with chemokine properties, and also their ligands - chemokine receptors, involved in traffic of neutrophils and PDC.

Supplement A12. Chemokines and their ligands - chemokine receptors, involved in traffic of neutrophils.

Supplement A13. Cytokines which are actively secreted by immunocytes in dermis.

Supplement A14. Figures in Supplements.

Supplement A15. Bibliography in Supplements.

Tables in Supplements

Table A1. Luminal microbiome of small intestine at patients with SIBO (without psoriasis) and at healthy persons.

Table A2**.** Luminal microbiome of proximal department of small intestine at PP and HP.

Table A3**.** Small intestine microbiome of psoriatic patients in zone of Treitz ligament**.**

Table A4. Composition of mucosal and luminal duodenal metagenome at HP.

Table A5. Composition of duodenal metagenome (16S-tests).

Table A6. Risk factors of initiation and support of SIBO.

Table A7. Average serum bile acids level (mkg/ml) in PP (in aggravation period).

Table A8. Average serum bile acids level (mkg/ml) in HP, patients with chronic hepatitis and PP before and after hepatotropic therapy.

Table A9. Biochemical structure and indicators of lithogenicity gallbladder (B) and hepatic (C) bile at HP and PP.

Table A10. Staphylococcus and Streptococcus representation in skin metagenomes at PP and HP.

Table A11. Y-model and YN-model. Processes and subprocesses.

Table A12. Y-model and YN-model. Hypotheses.

Table A13. Abbreviations and terms.

Figures in Supplements

Fig.A1. BF-model of pathogenesis (Baker 2006b, Fry 2007a).

Fig.A2. FM-model of pathogenesis of psoriasis with NET and MCET (Delgado-Rizo 2017)

Fig.A3. SE-model of pathogenesis of psoriasis with NET (Schon 2018)

Fig.A4. WG-model of pathogenesis of psoriasis with NET (Shao 2019)

Fig.A5. SIBO at psoriasis

Fig.A6. PAMP-income and PAMP-consumption.

Fig.A7. Attraction of blood phagocytes in skin at moderate-severe psoriasis (phase N5 and N8).

Fig.A8. Skin priming. Transition all skin from phase N0 to phase N1.

Fig.A9. Phase N1. Prepsoriasis. Marker - homeostatic L1.

Fig.A10. Phase N2. Prepsoriasis at L2(DEMP) - dermal expansion of commensal microbiome with PsB. Markers - L2(DEMP) and L3r(DEMP).

Fig.A11. Phase N3. Prepsoriasis at L2(DEMP) - dermal expansion of commensal microbiome with PsB. Markers - L2(DEMP) and L3(DEMP).

Fig.A12. Phase N4. Prepsoriasis at L2(DEMP) - dermal expansion of commensal microbiome with PsB. Markers - L2(DEMP), L3(DEMP) and L4.

Fig.A13. Phase N5. Psoriasis at L2(DEMP) - dermal expansion of commensal microbiome with PsB. Markers - L2(DEMP), L3(DEMP) and L8.

Fig.A14. Phase N6. Prepsoriasis. External border of existing plaque. Marker - L3. There is no L2 process.

Fig.A15. Phase N7. Prepsoriasis. External border of existing plaque. Markers - L3 and L4. There is no L2 process.

Fig.A16. Phase N8. Psoriasis. Markers - L3 and self-sufficient L8. There is no L2 process.

Fig.A17. Process L7b. Lymph node. Primary and secondary responses. TL-Y formation, i.e. Tem-Y and Tcm-Y.

Fig.A18. Conditional concentration of endocyted Y-antigen.

Fig.A19. Psoriatic plaque development at L2(DEMP) - dermal expansion of commensal microbiome with PsB.

8. Figures

Symbols

PG	PG – any peptidoglycan (in particular PG-Y)		EC - endothelial cells, that form vascular walls	Mo	Mo - monocytes
Y-antigen	Y-antigen = part(s) of interpeptide bridge IB-Y	KC	KC - keratinocytes	DC	DC – dendritic cells
PG-Y	PG-Y = peptidoglycan with interpeptide bridges IB-Y	TL	T-lymphocytes	MoDP	MoDP – resident stem cells - precursors of MF and MoDC in skin
PsB	PsB = psoriagenic bacteria = Gram+ bacteria with peptidoglycan PG-Y. - small variant.	TL-Y	Y-specific T-lymphocytes	MoDC	DC derived from Mo or from MoDP
LPS	LPS = lipopolysaccharide, free and bound in complexes	Tem-Y	Tem-Y = Y-specific Tem	MF	Macrophages derived from Mo or from MoDP
	Gram(-) TLR4-active bacteria	Tcm-Y	Tcm-Y = Y-specific Tcm	Mo-Y	Mo-Y = PG-Y(+)Mo
	Gram+ and Gram(-) bacteria - intestine commensals	Neu	Neu - neutrophils	DC-Y	DC-Y = PG-Y(+)DC
	bacDNA – bacterial DNA	Neu-Y	Neu-Y = PG-Y(+)Neu	MoDC-Y	MoDC-Y = PG-Y(+)MoDC
	Bacteria – skin commensal (different from PsB).	NET	NET – netotic products from Neu and Neu-Y	MF-Y	MF-Y = PG-Y(+)MF
	Enterocytes - epithelial cells of small intestine	PDC	PDC - plasmacytoid dendritic cells	maDC-Y	maDC-Y = mature dendritic cells, presenting Y-antigen

Fig.1. Symbols.

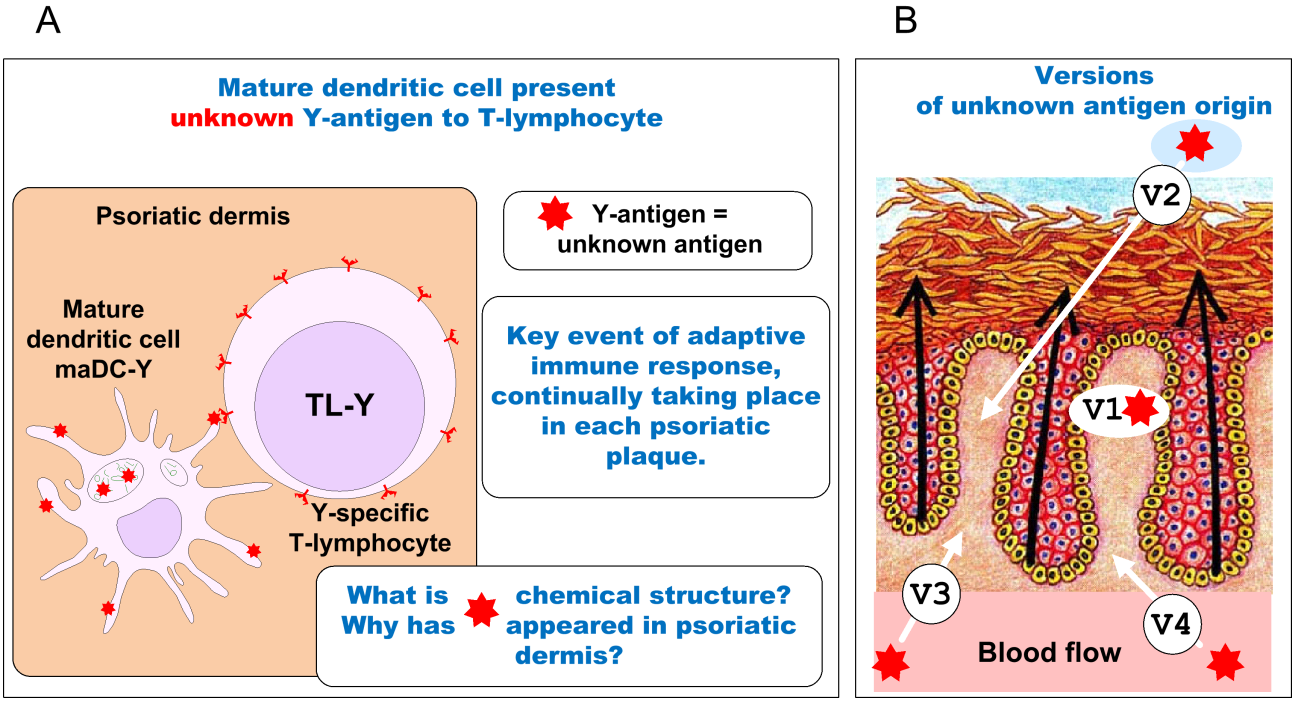


Fig.2. Versions of unknown antigen origin.

A) The key event of adaptive response which is taking place in each psoriatic plaque.

B) Versions of unknown antigen origin.

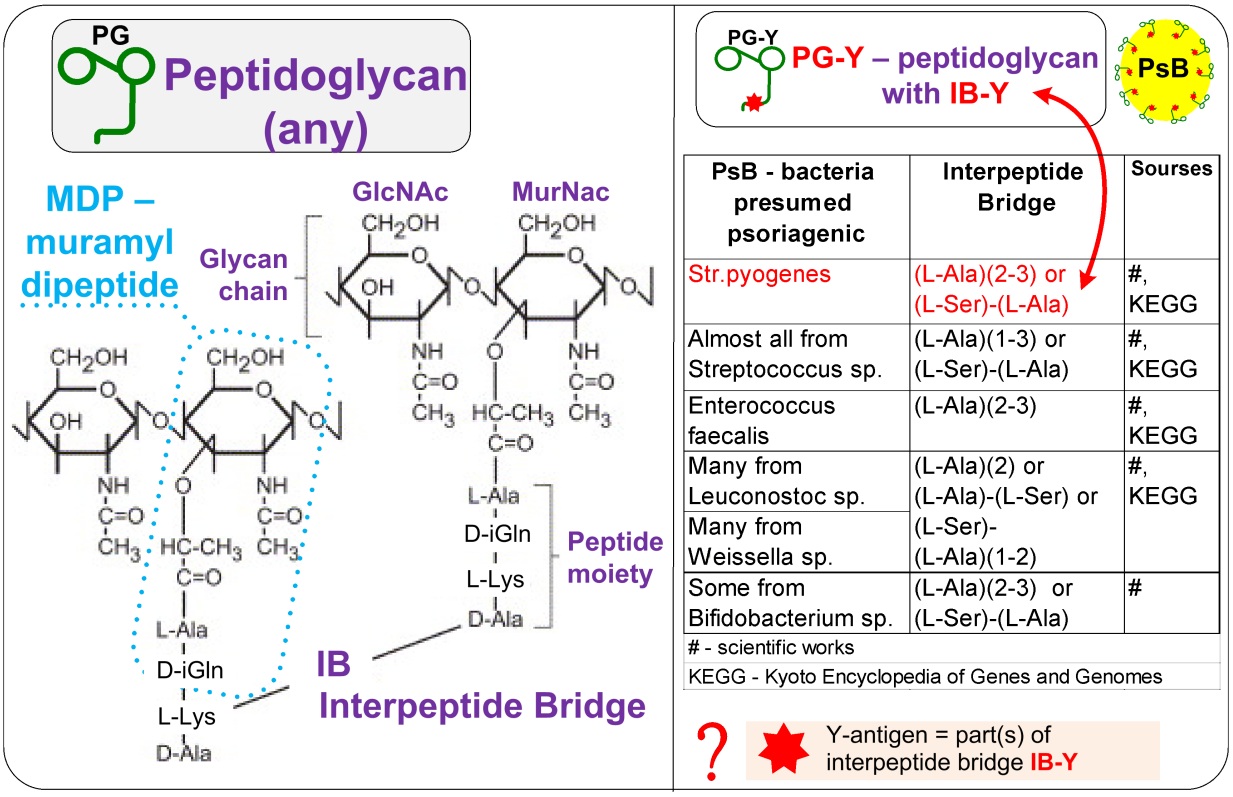
V1. Origin is resident and host.

V2. Origin is non-resident of external environment (of course, non-host).

V3. Origin is non-resident from within (for example, from blood flow) and non-host.

V4. Origin non-resident from within (for example, from blood flow) and host..

Peptidoglycan (PG) structure and PsB



PsB - bacteria presumed psoriagenic	Interpeptide Bridge	Sourses
Str.pyogenes	(L-Ala)(2-3) or (L-Ser)-(L-Ala)	#, KEGG
Almost all from Streptococcus sp.	(L-Ala)(1-3) or (L-Ser)-(L-Ala)	#, KEGG
Enterococcus faecalis	(L-Ala)(2-3)	#, KEGG
Many from Leuconostoc sp.	(L-Ala)(2) or (L-Ala)-(L-Ser) or (L-Ser)-(L-Ala)(1-2)	#, KEGG
Many from Weissella sp.		
Some from Bifidobacterium sp.	(L-Ala)(2-3) or (L-Ser)-(L-Ala)	#

- scientific works

KEGG - Kyoto Encyclopedia of Genes and Genomes

? Y-antigen = part(s) of interpeptide bridge IB-Y

Fig.3. Peptidoglycan structure and PsB

A) Peptidoglycan of A3alpha type.

B) Presumed psoriagenic bacteria have peptidoglycan similar Str.pyogenes.

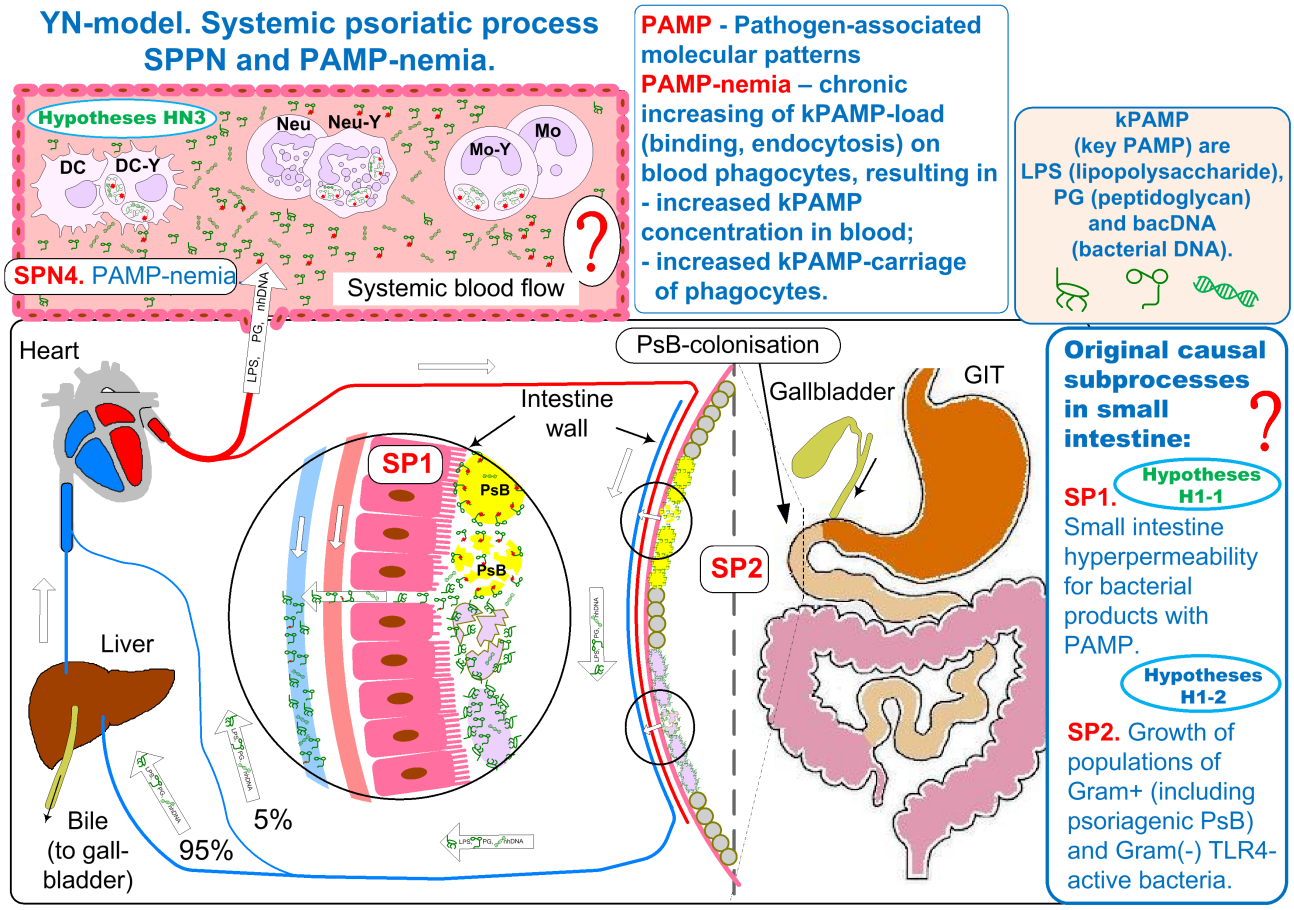


Fig.4. YN-model. Systemic psoriatic process SPPN and PAMP-nemia.

Subprocess SP1. Small intestine hyperpermeability for bacterial products with PAMP (i.e. LPS, PG, bacDNA). Subprocess SP2. SIBO with PsB-bacteria. Subprocesses SP1 and SP2 support PAMP-nemia (subprocess SPN4): chronically increased kPAMP and PG-Y concentration in blood and kPAMP-and (PG-Y)-load on blood phagocytes. As a result many blood neutrophils become kPAMP- and (PG-Y)-carriers and pass into prenetotic state. Hypotheses (Table A12).

YN-model. Systemic psoriatic process SPPN.

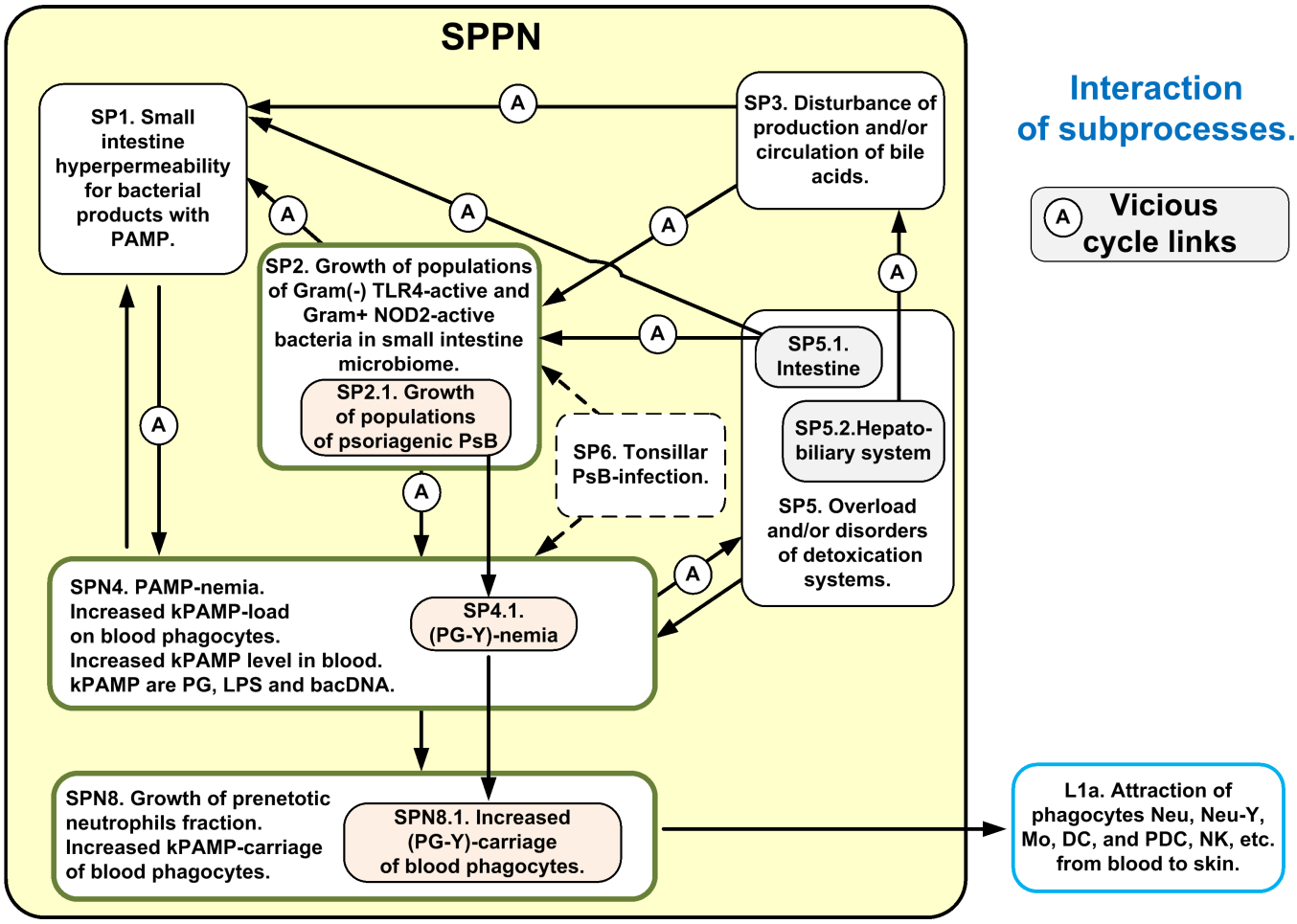


Fig.5. YN-model. Systemic psoriatic process SPPN. Interference of subprocesses.

Letter A - vicious cycle. Subprocesses SP2.1, SP4.1 and SPN8.1 are basis for attraction (PG-Y)-carriers of blood phagocytes in skin (subprocess L1a).

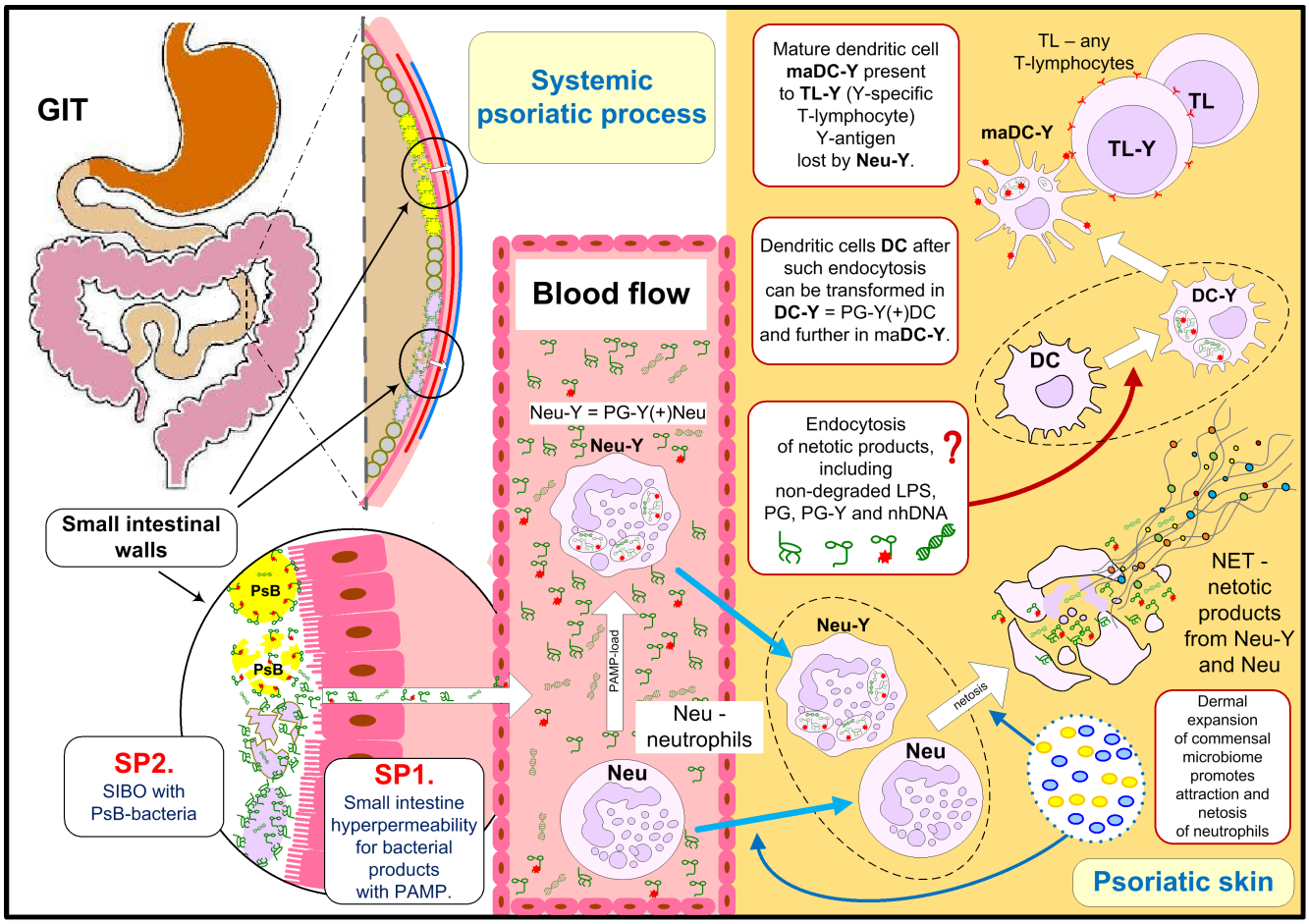


Fig.6. YN-model of pathogenesis - is simplified (systemic and local processes together).
Subprocesses SP1 and SP2 support PAMP-nemia: chronically increased concentration of kPAMP (including PG-Y) in blood and kPAMP- and (PG-Y)-load on blood neutrophils. Some of them pass into prenetotic state and become kPAMP-carriers (particularly (PG-Y)-carriers - Neu-Y). Neu and Neu-Y from blood flow are attracted into psoriatic skin. Affected by prenetotic condition and by presence of netosis factors, some of attracted neutrophils undergo netosis. At the same time, in extracellular space there also appear non-degraded kPAMP (including PG-Y). Netotic products, including non-degraded kPAMP, are endocyted by skin phagocytes, specifically dendritic cells DC. As a result, some of them become (PG-Y)-carriers DC-Y. After maturing DC-Y to mature dendritic cells maDC-Y, presentation of Y-antigen to Y-specific T-lymphocytes becomes possible.

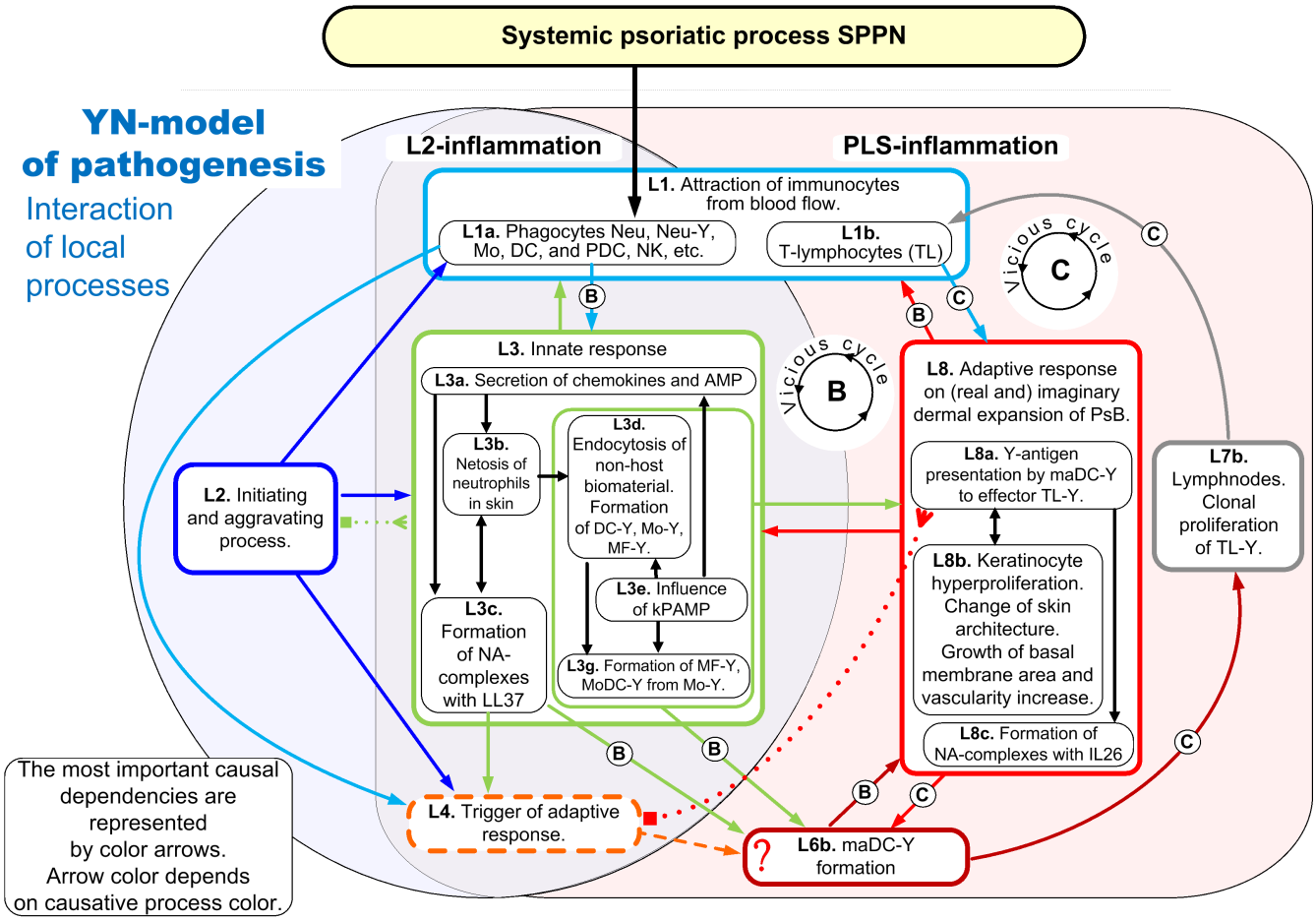


Fig.7. YN-model of pathogenesis. Interaction of local processes.

Dashed lines - transit process L4 and influences connected to it. Dotted arrows with small squares - suppression.

Letters B and C – vicious cycles.

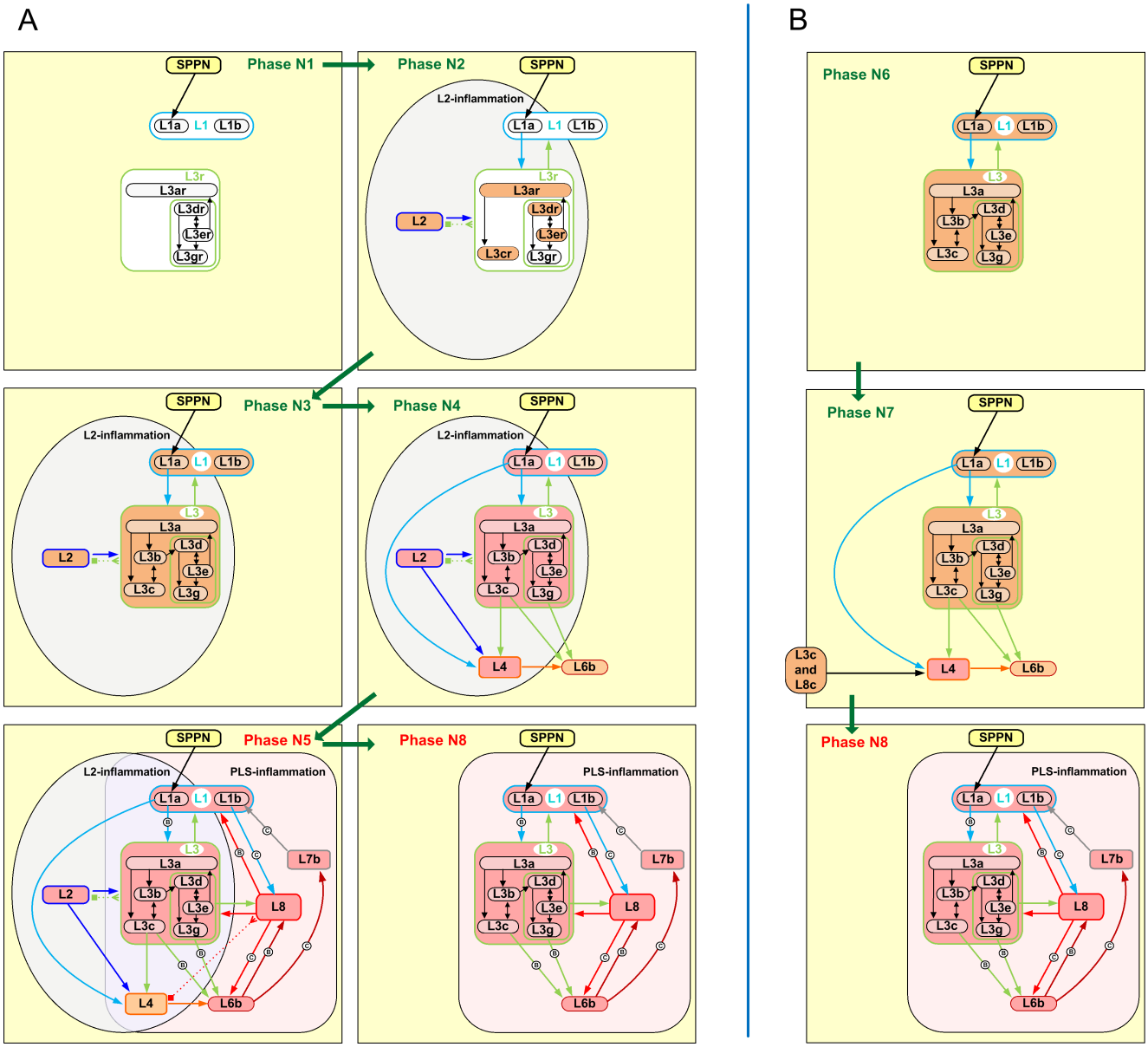


Fig.8. YN-model of pathogenesis (L2 is not concretized). Phased development of psoriatic plaque.

A) Development of new pinpoint plaque. B) Enlargement of existing plaque.
Vicious cycles are designated by letters B and C.
Phases N5 and N8 correspond to psoriatic plaque, other phases correspond to prepsoriatic condition of skin..

9. Tables

Table 1. Processes and phases of psoriatic plaque development.

			Prepsoriasis						Psoriasis	
Phases in YN-model		Development of pinpoint	N1	N2	N3	N4			N5	N8
		Enlagment of existing					N6	N7		N8
Phases N2, N3, N4, N5 at L2(DEMP) only			Fig.A9	Fig.A10	Fig.A11	Fig.A12	Fig.A14	Fig.A15	Fig.A13	Fig.A16
Phases in Y-model			1	2	2	3	-	-	5	6
Comment				L2 start	L3 start	L4 start	L3 start	L4 start	L8 start	
Marker processes / (Sub)process			Homeo static L1	L2, L3r	L2, L3	L2, L3, L4	L3	L3, L4	L2, L3 L8	L3 and self-suffi-cient L8
	SPPN	Systemic psoriatic process	*	*	*	*	*	*	*	*
	L1	Attraction from blood flow								
	L1a	Non-lymphocytic immunocytes: Neu, Neu-Y, Mo, DC, PDC, NK, etc.	+	+	++	+++	++	++	+++	+++
	L1b	T-lymphocytes (TL)	+	+	++	+++	++	++	+++	+++
	L2	Initiating and aggravating process		+++	++	++			++	
	L3 (L3r)	Innate response								
	L3a (L3ar)	Secretion of chemokines and AMP	+r	++r	++	+++	++	++	+++	+++
	L3b	Netosis of neutrophils in skin			++	+++	++	++	+++	+++
	L3c (L3cr)	Formation of NA-complexes with LL37		+r	++	+++	++	++	+++	+++
	L3d (L3dr)	Endocytosis of non-host biomaterial.	+r	++r	++	+++	++	++	+++	+++
		Including bacterial products of resident origin (at DEMP or DEM)		++r	++	+++			++	
		Including bacterial products of non-resident origin (from L3b).			++	+++	++	++	+++	+++
		DC-Y, Mo-Y, MF-Y formation (in phase N2 at DEMP only).		++r	++	+++	++	++	+++	+++

	L3e (L3er)	Influence of kPAMP (LPS, PG and bcDNA) on TLR and NOD receptors.	+r	++r	++	+++	++	++	+++	+++
		Including kPAMP of resident origin (in particular at DEMP or DEM).	+r	++r	++	+++			++	
		Including kPAMP of non-resident origin (from L3b).			++	+++	++	++	+++	+++
	L3g (L3gr)	Formation of MF, MoDC from Mo.	+r	+r	++	+++	++	++	+++	+++
		Formation of MF-Y, MoDC-Y from Mo-Y (in phase N2 at DEMP only).		+r	++	+++	++	++	+++	+++
	L4	Trigger of adaptive response				+++		+++	+	+
	L6b	maDC-Y formation				++		++	+++	+++
	L7b	Lymphnodes. Clonal proliferation of TL-Y							+++	+++
	L8	Adaptive response on (real and) imaginary dermal expansion of PsB.								
	L8a	Y-antigen presentation by maDC-Y to effector TL-Y.							+++	+++
	L8b	KC hyperproliferation. Change of skin architecture. Growth of basal membrane area and vascularity increase.							+++	+++
	L8c	Formation of NA-complexes with IL26							+++	+++

Notes.

Color in the first column (here and everywhere further) is used for highlighting of particular process and its subprocesses. An empty table cell means that (sub)process does not occur.

SPPN activity mark with the symbol *. SPPN occurs constantly with intensity not depending on local processes. During phases N1 and N2, SPPN intensity is practically immaterial, as intensity of phagocyte attraction is weak, and neutrophil attraction is scarcely present. However, from phase N3 initiation and support of any PLS-plaque depends on SPPN intensity.

Local (sub)process:

+ (white) - occurs with weak intensity;

++ (beige) - inflammatory, average intensity;

+++ (pink) - inflammatory, high intensity;

+r or ++r - means that process (subprocess) is fulfilled mainly with participation of cells of resident origin.

In YN-model, numbering and content of phases differ from Y-model. Content of phases N1, N5 and N8 generally corresponds to phases 1, 5 and 6. Phases N2 and N3 partly correspond to phase 2, phase N4 partly corresponds to phase 3, and nothing corresponds to phase 4 in YN-model as process L5 is not obligatory. Phases N6 and N7 are new (compared to Y-model), they are only present at expansion of existing psoriatic plaque (Supplement A9).

Table 2. Causative dependencies between processes and subprocesses.

Effect			Cause: SPPN	L1: L1a	L1: L1b	L2	L3: L3a	L3: L3b	L3: L3c	L3: L3d	L3: L3e	L3: L3g	L4	L6b	L7b	L8: L8a	L8: L9b	L8: L8c
		SPPN																
	L1	L1a	+			+	+									+B		
		L1b													+C			
	L2						#			#						#		
	L3	L3a									+							
		L3b	+	+B			+		+(?)		+							
		L3c				+	+	+								+		
		L3d	+	+B				+B			+							
		L3e						+										
		L3g	+							+	+		+					
	L4			+		+			+							#		
	L6b		+						+B				+			+C		
	L7b		+											+C				
	L8	L8a	+		+C					+				+B			+	
		L8b														+		
		L8c						+								+		

Notes:
The table is made according to YN-model of pathogenesis (Fig.7).
Non-obligatory processes and sub-processes (L3f, L5, L6a, and L7a) are not included.
Colors are used to highlight (sub)process.
+ - positive influence; +B or +C - vicious cycles; # - negative influence (suppression);
Empty table cells mean that connections are either absent or insignificant.

Table 3. Real and presumed factors of netosis at psoriasis.

Factor	Sources	Systemic blood flow during SPPN	NLS - prepsoriatic skin	PLS - psoriatic skin
	Netosis is confirmed	Lin 2011, Hu 2016	no	Lin 2011, Hu 2016
Platelets	Grayson 2016, Schon 2018, With LPS: Pinegin 2015, Papayannopoulos 2018	In complexes with Neu: Vorobjeva 2014, Herster 2019, Teague 2019	Herster 2019 (in complexes with Neu)	
ANCA (anti-neutrophil cytoplasmic antibody)	Grayson 2016, Hasler 2016, Delgado-Rizo 2017	?	?	?
ACPA (anti-citrullinated peptide antibody)	Hasler 2016, Delgado-Rizo 2017	?	?	?
CXCL8 (IL8), self-amplification (?)	Grayson 2016, Hasler 2016, Ortmann 2018	yes	yes	
LCN2, self-amplification (?)	Shao 2016, Shao 2019	yes	yes	
LL37, self-amplification (?)	Neumann 2014, Chieosilapatham 2018	yes	yes	
hRNA-LL37 complexes, self-amplification (?)	Herster 2020	?	?	yes
IL18	Grayson 2016, Hasler 2016	yes	Yes, in epidermis during trauma (LP2(IN), Peslyak 2012b)	yes, in epidermis
IL1beta	Grayson 2016, Hasler 2016, Delgado-Rizo 2017	secretion by blood monocytes is possible	Yes, in the presence of HPV (LP2(HPV), Peslyak 2012b)	yes, it is actively secreted
Bacteria, fungi	Delgado-Rizo 2017, Hoppenbrouwers 2017, Kenny 2017, Papayannopoulos 2018	only at bacterial or fungal infection (sepsis)	pathogens at infection, commensals at expansion	
Staphylococcus sp., incl.		at infection only (sepsis)		
Staph.aureus by Leukotoxin GH and Panton–Valentine leucocidin	Delgado-Rizo 2017, Papayannopoulos 2018		pathogen – at infection	
Staph.epidermidis by PSM-gamma (=delta-toxin)	Cogen 2010		commensal – at expansion, PSM-gamma is chemokine for Neu and PDC also (receptors FPR1 and FPR2 are ligands)	
Staph.epidermidis by GroEL	Dapunt 2016, Meyle 2012		commensals at expansion	
Streptococcus sp., including		at infection only (sepsis)		
Streptococcus sp. of group A and B	Kenny 2017, Papayannopoulos 2018		pathogen – at infection	
Str.pneumoniae by EndA and α-enolase	Delgado-Rizo 2017, Papayannopoulos 2018		pathogen – at infection	
Str.pneumoniae by hydrogen peroxide (H_2O_2)	Kaldor 2019		pathogen – at infection	
Viridans group streptococci (VGS)	Holder 2019		pathogens at infection, commensals at expansion	
Oral streptococci, including Str.mitis, Str.oralis Str.sanguinis, Str.gordonii by hydrogen peroxide (H_2O_2)	Xu 2014, Okahashi 2014, Sumioka 2017		commensals at expansion	

Factor	Sources	Systemic blood flow during SPPN	NLS - prepsoriatic skin	PLS - psoriatic skin
Candida albicans	Delgado-Rizo 2017, Hoppenbrouwers 2017, Kenny 2017		pathogen – at infection	
Viruses	Schonrich 2016 Delgado-Rizo 2017, Papayannopoulos 2018	only at virus infection	Yes, in epidermis in the presence of HPV (see LP2(HPV), Peslyak 2012b) or of other virus skin infections	
Protozoan parasites	Grayson 2016, Hasler 2016, Papayannopoulos 2018	only at protozoan infection	no	
M1 protein (group A streptococci) + fibrinogen complex	Oehmcke 2009, Vorobjeva 2014	yes, at streptococcal infection (e.g. tonsillar infection)	no	
LPS	Chiang 2019, Hasler 2016, Pieterse 2016, Delgado-Rizo 2017, Lipp 2017, Papayannopoulos 2018, Ortmann 2018	yes (Garaeva 2007)	yes	
PG	Hasler 2016, Alyami 2018, Alyami 2019	possible	yes	
H_2O_2 (hydrogen peroxide)	Fuchs 2007, Hoppenbrouwers 2017, Sumioka 2017	?	yes	
FMLP (N-Formylmethionyl-leucyl-phenylalanine) (synthesized by bacteria)	Hasler 2016, Lipp 2017	?	yes, FMLP is chemokine for Neu and PDC also (receptors FPR1 and FPR2 are ligands)	
Ionomycin and ionophore (synthesized by Streptomyces sp.)	Delgado-Rizo 2017, Kenny 2017	?	Yes, in case of using topical drugs which contain them	

Table 4. Roles of neutrophils at psoriasis: known and presumed.

	Roles	Locali-zation	Status	Notes
1	Endocytosis of any non-host products contained in blood	Systemic blood flow	proved	Well-known
2	Netosis, ejection of netotic products into extracellular space.	Systemic blood flow	proved	Lin 2011, Skrzeczynska-Moncznik 2012, Hu 2016.
3	Attraction from systemic blood flow into prepsoriatic and psoriatic skin		proved	van de Kerkhof 2007, Christophers 2014, Gilliet 2008 (GL-model), Perera 2012 (N-model), Peslyak 2012b (Y-model), (Lin 2011, suppl. fig.4), (Ozawa 2005, fig.1), (Reich 2015, fig.3), YN-model
4	Netosis, ejection of netotic products into extracellular space.	Psoriatic skin	proved	Lin 2011 (KB-scheme), Skrzeczynska-Moncznik 2012, Lowes 2014, Hu 2016, Schon 2017, Schon 2018 (SE-model),YN-model
4.1	LL37 - active secretion, as well as ejection during netosis	Psoriatic skin	proved	Secretion only: Gilliet 2008, Ganguly 2009 (GL-model), Guttman-Yassky 2011 (GK-model), Perera 2012 (N-model), Peslyak 2012b (Y-model). Lowes 2014, Hawkes 2017 (GKH-model), Secretion and ejection during netosis: Lin 2011 (KB-scheme), Pinegin 2015, Delgado-Rizo 2017 (FM-model), Schon 2018 (SE-model), YN-model
4.2	Active secretion of IL-17			Lin 2011 (KB-scheme), Pinegin 2015, Schon 2018 (SE-model), YN-model
4.3	Active secretion of TNF-alpha, IL-22			Schon 2018 (SE-model), YN-model
4.4	Ejection of hDNA during netosis			Lin 2011 (KB-scheme), Pinegin 2015, Delgado-Rizo 2017 (FM-model), YN-model
4.5	Ejection of hRNA during netosis			Herster 2020
4.6	Ejection of MPO (myeloperoxidase) during netosis			Schon 2018 (SE-model).
5	Impact on plasmacytoid dendritic cells PDC, contributing to active secretion of IFN-alpha, through hDNA-LL37 complexes.	Psoriatic dermis	proved	hDNA source - damaged keratinocytes: Gilliet 2008, Ganguly 2009 (GL-model), Tonel 2009 (TC-model), Guttman-Yassky 2011 (GK-model), Perera 2012 (N-model), Peslyak 2012b (Y-model). hDNA source - netotic products: Lin 2011 (KB-scheme), Skrzeczynska-Moncznik 2012, Delgado-Rizo 2017 (FM-model) Schon 2018 (SE-model). Panda 2017 (review of PDC property), YN-model
6	Impact on dendritic cells DC, contributing to their maturing, through hRNA-LL37 complexes.	Psoriatic dermis	proved	hRNA source - damaged keratinocytes: Gilliet 2008, Ganguly 2009 (GL-model). hRNA source - netotic products: Herster 2020
7	Netotic products may contain non-degraded non-host products, earlier endocyted in blood (particularly Y-antigen).	Psoriatic skin	possible	Hypothesis H12 (Table A12). YN-model
8	Neutrophils Neu-Y can independently present Y-antigen to specific TL-Y-lymphocytes.	Psoriatic skin	possible	Davey 2014, Lin 2017. Under the influence of GM-CSF, IFN-gamma, IL-4 and TNF-alpha, as well as when interacting with memory CD4+ T-lymphocytes, neutrophils can perform the functions of antigen-presenting cells. Not assumed in YN-model.

Table 5. Models of psoriasis pathogenesis, neutrophils and LL37.

Patho-genesis model	Sources	Neutrophils in systemic blood flow	Neutrophils in psoriatic skin	Netosis in psoriatic skin	hDNA-LL37 complexes affecting PDC and/or hRNA-LL37 affecting DC	Notes
BF-model	Baker 2006b	no	no	no	no	Systemic. Presumed antigen - peptidoglycan fragment.
GL-model	Gilliet 2008, Ganguly 2009, Gilliet 2015	no	LL37 secretion	no	hDNA and hRNA from damaged keratinocytes	Vicious cycle.
GLD-model	Di Domizio 2019	no	LL37 secretion	Yes. Ejection of hDNA, LL37.	hDNA from netosis. hDNA-LL37 complexes affect on Mo and DC only.	Simplification of GL-model. The putative antigen is LL37. PDC is not mentioned in this model.
TC-model	Tonel 2009	no	no	no	LL37 and hDNA from damaged keratinocytes	
N-model	Di Meglio 2011, Perera 2012, Di Meglio 2017	no	yes	no	LL37 and hDNA from damaged keratinocytes	Unknown antigen (keratin?).
GK-model	Guttman-Yassky 2011	no	LL37 secretion	no	hDNA from damaged keratinocytes	Unknown antigen (keratin?). Vicious cycle.
GKH-model	Lowes 2014, Kim 2015, Hawkes 2017	no	LL37 secretion	no	LL37, hDNA and hRNA from damaged keratinocytes	Specification of GK-model. Potential antigens - keratins, streptococcal proteins, ADAMTSL5. Presentation takes place in iSALT - indusible skin-associated lymphoid tissue in dermis. Vicious cycle.
KB-scheme	Lin 2011	no	LL37 and IL-17 secretion	Yes. Ejection of hDNA, LL37.	hDNA from netosis	Vicious cycle (includes netosis). Netosis is taken into account for the first time.
Y-model	Peslyak 2012a, Peslyak 2012b	Bone marrow transformation Mo and DC with apoptotic neutrophil participation.	LL37 secretion	no	hDNA and hRNA from damaged keratinocytes	Systemic. Presumed Y-antigen - peptidoglycan fragment. Includes the proved links of models BF, N, GK, GL and TC. Compatible with YN-model. Two vicious cycles.
FM-model	Delgado-Rizo 2017	no	LL37 secretion	Yes. Ejection of hDNA, LL37.	hDNA from netosis	Unknown antigen (only in the scheme). Vicious cycle (includes netosis). Extension of KB-scheme.
AL-model	Albanesi 2018	no	yes	no	hDNA and hRNA from damaged keratinocytes	Potential antigens – LL37, lipid antigens, ADAMTSL5. Vicious cycle.
SE-model	Schon 2018, Schon 2019	no	Secretion of LL37, IL-17, TNF-alpha, IL-22	Yes. Ejection of LL37, IL-17, MPO	hDNA from netosis	Potential antigens - keratin 17, streptococcal protein M1, LL37, ADAMTSL5. Vicious cycle.
BMM-model	Benhadou 2018	no	no	no	Not present (mentioned in the text but absent on schemes)	Potential antigens - LL37, ADAMTSL5. Vicious cycle.

Patho-genesis model	Sources	Neutrophils in systemic blood flow	Neutrophils in psoriatic skin	Netosis in psoriatic skin	hDNA-LL37 complexes affecting PDC and/or hRNA-LL37 affecting DC	Notes
WG-model	Shao 2019	preactivated	no	yes	no	Model suggests a vicious cycle based only on innate response.
CH-model	Chaing 2019	no	Secretion of proteinase 3, elastase, cathepsin G, LL37, MPO, LCN2	Yes, ROS (reactive oxygen species) release.	hDNA from netosis	The description of this model in work differs markedly from the semantic content of figure (Chaing 2019, fig. 6). In particular, there is no description of sequential phases (trigger, initiation, support) shown in scheme Vicious cycle.
YN-model	Peslyak & Korotky 2019; Korotky & Peslyak 2020, this work	Endocytosis of kPAMP, including that of Y-antigen.	Secretion of AMP (LL37, HBD2, etc.) TNF-alpha, IL17, IL22.	Yes. Ejection of hDNA, hRNA, LL37. Ejection of non-degraded kPAMP, including that of Y-antigen.	LL37, hDNA and hRNA at chronicity, primarily from netosis	Systemic. Presumed Y-antigen - peptidoglycan fragment. Includes the proved links of BF, N, GK, GL, TC, FM, SE models. Compatible with Y-model. Two vicious cycles: the first one includes netosis.

Table 6. PsB – presumed psoriagenic bacteria species.

Streptococcus sp.		From other genera
Streptococcus agalactiae	Streptococcus sanguinis	Enterococcus faecalis
Streptococcus anginosus	Streptococcus sobrinus	Enterococcus silesiacus
Streptococcus constellatus	Streptococcus suis	Eubacterium sulci
Streptococcus cristatus	Streptococcus thermophilus	Lactococcus garvieae
Streptococcus dysgalactiae	Streptococcus uberis	Lactococcus piscium
Streptococcus equi	Streptococcus vestibularis	Lactococcus raffinolactis
Streptococcus equinus		Leuconostoc carnosum
Streptococcus gallolyticus		Leuconostoc citreum
Streptococcus gordonii		Leuconostoc garlicum
Streptococcus infantarius		Leuconostoc gelidum
Streptococcus iniae		Leuconostoc kimchii
Streptococcus intermedius		Leuconostoc lactis
Streptococcus lutetiensis		Leuconostoc mesenteroides
Streptococcus macedonicus		Leuconostoc pseudomesenteroides
Streptococcus mitis		Melissococcus plutonius
Streptococcus mutans		Oenococcus oeni
Streptococcus pantholopis		Oenococcus sicerae
Streptococcus parasanguinis		Weissella ceti
Streptococcus parauberis		Weissella cibaria
Streptococcus pasteurianus		Weissella hellenica
Streptococcus pneumoniae		Weissella jogaejeotgali
Streptococcus pseudopneumoniae		Weissella koreensis
Streptococcus pyogenes		Weissella paramesenteroides
Streptococcus salivarius		Weissella soli

Notes.

IB-Y = (L-Ala)-(L-Ala) or (L-Ser)-(L-Ala)
Information from data base KEGG.

Table 7. Abbreviations and terms

	Description
AMP	Antimicrobial proteins (peptides)
bacDNA	Bacterial DNA
DC	Dendritic cells
DC-Y	(PG-Y)+DC = Dendritic cells repleted by PG-Y
IB-Y	Interpeptide bridges of peptidoglycan Str.pyogenes: (L-Ala)-(L-Ala) or (L-Ser)-(L-Ala).
IN	Open injury of dermis
hDNA	Host DNA (in this work human DNA)
hRNA	Host RNA (in this work human RNA)
HPV	Human Papilloma Virus
KC	Keratinocytes
kPAMP	LPS, PG and (in YN-model) bacDNA.
LBP	Lipopolysaccharide binding protein
LDG (=LDN)	Low density granulocytes (neutrophils)
LPS	Lipopolysaccharide
maDC	Mature DC
maDC-Y	Mature DC presenting Y-antigen, derived from Y-model: DC-R or MoDC-R, YN-model: DC-Y or MoDC-Y
maDC-Z	Mature DC, presenting Z-antigen
MDP	Muramyl dipeptide - component Gram+ and Gram(-) PG, ligand of NOD2
MF	Macrophages, derived from Mo or from MoDP
Mo	Monocytes
Mo-Y	(PG-Y)+Mo = Monocytes repleted by PG-Y
MoDP	Skin resident stem cells - precursors of part of MoDC and MF
MoDC	DC, derived from Mo or from MoDP
MoDC-Y	(PG-Y)+MoDC = MoDC repleted by PG-Y
Neu	Neutrophils
Neu-Y	(PG-Y)+Neu = Neutrophils repleted by PG-Y
NET	Neutrophil extracellular traps (= netosis products) - are formed at netosis
NLS	Non-lesional (prepsoriatic, uninvolved) skin – psoriatic skin without symptoms
NOD1	Intracellular receptor - ligand to DAP (Pashenkov 2018)
NOD2	Intracellular receptor - ligand to MDP (Pashenkov 2018)
nTL	Naive TL
PAMP	Pathogen-associated molecular patterns (in particular LPS, PG, bacDNA and (1,3)-beta-D-glucan) (Fukui 2016a)
PAMP-nemia	Definition in YN-model: Chronic increase kPAMP-load (binding, endocytosis) on blood phagocytes resulting - increasing of kPAMP concentration in blood; - increased kPAMP-carriage of phagocytes. kPAMP are LPS, PG and bacDNA.
PASI	Psoriasis Area and Severity Index
PDC	Plasmacytoid dendritic cells
PG	Peptidoglycan. Any (including PG-Y)
PG-Y	Peptidoglycan A3alpha with interpeptide bridges IB-Y (but can contain and others also)
Pla	Platelets
PLS	Psoriatic lesional skin
PP	PP - Psoriatic patient
PsB	Psoriagenic bacteria - species of bacteria presumed psoriagenic (with PG-Y peptidoglycan)
PsB-p	Skin pathogenic PsB
SIBO	Small intestine bacterial overgrowth. Excess of total bacteria concentration over norm and/or pathogens presence in biomaterial. As biomaterial there can be smears, scrapes from mucous or aspirate.
SIS	Skin immune system
SPP	Systemic psoriatic process (basis of Y-model of pathogenesis) (Peslyak 2012a)
SPPN	Systemic psoriatic process in YN-model - differs from SPP
Tcm	Central memory TL

	Description
Tcm-Y	Y-specific Tcm
Tem	Effector memory TL
Tem-Y	Y-specific Tem
Th1	CD4+Tem, characterized by secretion: IFN-gamma(+)IL17(-)IL22(-)
Th17	CD4+Tem characterized by secretion: IFN-gamma(-)IL17(+)IL22(-)
Th22	CD4+Tem, characterized by secretion: IFN-gamma(-)IL17(-)IL22(+)
TL	T-lymphocytes
TL-Y	Y-specific TL (they have receptors ligandic to Y-antigen epitopes). They are Tem-Y and Tcm-Y. In skin – Tem-Y.
TL-Z	Y-specific Tem or Tcm
TLR2	Membranous receptor - ligand to PG-fragments LTA, BLP
TLR4	Membranous receptor - ligand to LPS
TLR7	Endosomal receptor – ligand to ssRNA, bacRNA, but also and to hRNA-LL37 complexes.
TLR8	Endosomal receptor – ligand to ssRNA, bacRNA, but also and to hRNA-LL37 complexes.
TLR9	Receptor - ligand to CpG - fragment of bacterial or virus DNA. As a rule, intracellular (endosomal), but at neutrophils it expressed on membrane also (Lindau 2013).
Y-antigen	part(s) of interpeptide bridge IB-Y (SP2.1 part)
Y-model	model of pathogenesis of psoriasis offered in (Peslyak 2012a, Peslyak 2012b)
YN-model	model of pathogenesis of psoriasis offered in this work

The words in bold denote common abbreviations.

10. Bibliography

Akiba Y, Maruta K, Takajo T, Narimatsu K, Said H, Kato I, et al. (2020). Lipopolysaccharides transport during fat absorption in rodent small intestine. Am J Physiol Gastrointest Liver Physiol. 318:G1070-G1087. doi:10.1152/ajpgi.00079.2020

Albanesi C, Madonna S, Gisondi P, Girolomoni G. (2018). The Interplay Between Keratinocytes and Immune Cells in the Pathogenesis of Psoriasis. Front Immunol. 9:1549. doi:10.3389/fimmu.2018.01549

Albanesi C, Scarponi C, Bosisio D, Sozzani S, Girolomoni G. (2010). Immune functions and recruitment of plasmacytoid dendritic cells in psoriasis. Autoimmunity. 2010 Apr;43(3):215-9. Autoimmunity. 43:215-9. doi:10.3109/08916930903510906.

Albanesi C, Scarponi C, Pallotta S, Daniele R, Bosisio D, Madonna S, et al. (2009). Chemerin expression marks early psoriatic skin lesions and correlates with plasmacytoid dendritic cell recruitment. J Exp Med.206:249-58. doi:10.1084/jem.20080129.

Albareda M, Ravella A, Castelló M, Saborit S, Peramiquel L, Vila L. (2014). Metabolic syndrome and its components in patients with psoriasis. Springerplus. 3:612. doi:10.1186/2193-1801-3-612

Alyami H. (2018). NOD1/NOD2 Upregulation in Fusobacterium Nucleatum Induced NETosis. Dental Teses. 29. https://repository.upenn.edu/dental_theses/29

Alyami HM, Finoti LS, Teixeira HS, Aljefri A, Kinane DF, Benakanakere MR (2019). Role of NOD1/NOD2 receptors in Fusobacterium nucleatum mediated NETosis. Microb Pathog. 131:53-64. doi:10.1016/j.micpath.2019.03.036

Arakawa A, Siewert K, Stohr J, Besgen P, Kim SM, Rühl G, et al. (2015). Melanocyte antigen triggers autoimmunity in human psoriasis. J Exp Med. 212:2203-12. doi:10.1084/jem.20151093

Assimakopoulos SF, Scopa CD, Vagianos CE. (2007). Pathophysiology of increased intestinal permeability in obstructive jaundice. World J Gastroenterol. 48:6458-64. doi:10.3748/wjg.v13.i48.6458

Awosika O, Eleryan MG, Rengifo-Pardo M, Doherty L, Martin LW, Ehrlich A. (2018). A Case-control Study to Evaluate the Prevalence of Nonalcoholic Fatty Liver Disease Among Patients with Moderate-to-severe Psoriasis J Clin Aesthet Dermatol. 11:33-37. link.

Baker BS. (2000). Recent Advances in PSORIASIS: The Role of the Immune System. ICP Imperial College Press,180 p. ISBN 1860941206.

Baker BS, Ovigne JM, Powles AV, Corcoran S, Fry L. (2003). Normal keratinocytes express Toll-like receptors (TLRs) 1, 2 and 5: modulation of TLR expression in chronic plaque psoriasis. Br J Dermatol. 148:670-9. doi:10.1046/j.1365-2133.2003.05287.x

a Baker BS, Laman JD, Powles A. van der Fits L, Voerman JSA, Melief M-J, Fry L. (2006). Peptidoglycan and peptidoglycan-specific Th1 cells in psoriatic skin lesions. J Pathol. 209:174-81. doi:10.1002/path.1954.

b Baker BS, Powles A, Fry L. (2006). Peptidoglycan: a major aetiological factor for psoriasis? Trends Immunol. 27:545-51. doi:10.1016/j.it.2006.10.001.

c Baker BS.(2006). Skin Immune Mechanisms in Health and Disease, Garner Press, 328 p. ISBN 0955160308.

Baker BS.(2008). From Arsenic To Biologicals: A 200 Year History Of Psoriasis, Garner Press, 128 p. ISBN 978-0955160325.

Baltabaev MK, Khamidov SA, Valikhanov UA, Khamidov FS. Psoriasis and bile acids metabolism, Vestn Dermatol Venerol 2005;(4):25-28. (rus), elib.

Bartenjev I, Rogl Butina M, Potocnik M. (2000). Subclinical microbial infection in patients with chronic plaque psoriasis. Acta Derm Venereol Suppl (Stockh). (211):17-8. doi:10.1080/00015550050500068

Bay L, Barnes CJ, Fritz BG, Thorsen J, Restrup MEM, Rasmussen L, et al. (2020). Universal Dermal Microbiome in Human Skin. mBio.11. pii: e02945-19. doi:10.1128/mBio.02945-19

Begley M, Gahan CG, Hill C. (2005). The interaction between bacteria and bile. FEMS Microbiol Rev. 29:625-51. doi:10.1016/j.femsre.2004.09.003

Begon E, Michel L, Flageul B, Beaudoin I, Jean-Louis F, Bachelez H, et al. (2007). Expression, subcellular localization and cytokinic modulation of Toll-like receptors (TLRs) in normal human keratinocytes: TLR2 up-regulation in psoriatic skin. European Journal of Dermatology. 17: 497-506. doi:10.1684/ejd.2007.0264

Benhadou F, Mintoff D, del Marmol V (2018). Psoriasis: Keratinocytes or Immune Cells – Which Is the Trigger? Dermatology 235:91-100. doi:10.1159/000495291.

Berthelot JM. (2003). Psoriatic arthritis as a mountain, Reumatismo, 55:6-15. doi:10.4081/reumatismo.2003.6

Bissonnette R, Papp K, Maari C, Yao Y, Robbie G, White WI, Le C, White B. (2010). A randomized, double-blind, placebo-controlled, phase I study of MEDI-545, an anti-interferon-alfa monoclonal antibody, in subjects with chronic psoriasis. J Am Acad Dermatol. 62:427-36. doi:10.1016/j.jaad.2009.05.042

Bierkarre H, Harder J, Cuthbert R, Emery P, Leuschner I, Mrowietz U, et al. (2016). Differential expression of antimicrobial peptides in psoriasis and psoriatic arthritis as a novel contributory mechanism for skin and joint disease heterogeneity. Scand J Rheumatol. 45:188-96. doi:10.3109/03009742.2015.1091497

Bogunovic M, Ginhoux F, Wagers A, Loubeau M, Isola LM, Lubrano L, et al. (2006). Identification of a radio-resistant and cycling dermal dendritic cell population in mice and men. J Exp Med. 203:2627-38. doi:10.1084/jem.20060667

Bondarenko VM, Matsulevich TV,. Intestine dysbacteriosis as a clinical and laboratory syndrome. Current state of problem. GEOTAR-MEDIA, 2007, 304 p. ISBN: 9785970404300. (rus).

Bouhnik Y, Alain S, Attar A, Flourie B, Raskine L, Sanson-Le Pors MJ, Rambaud JC. (1999). Bacterial populations contaminating the upper gut in patients with small intestinal bacterial overgrowth syndrome. Am J Gastroenterol. 94:1327-31. doi:10.1111/j.1572-0241.1999.01016.x

Bures J, Cyrany J, Kohoutova D, Förstl M, Rejchrt S, Kvetina J, et al. (2010). Small intestinal bacterial overgrowth syndrome. World J Gastroenterol. 24:2978-90. doi:10.3748/wjg.v16.i24.2978

Cai YH, Lu ZY, Shi RF, Xue F, Chen XY, Pan M, et al. (2009). Enhanced Proliferation and Activation of Peripheral Blood Mononuclear Cells in Patients with Psoriasis Vulgaris Mediated by Streptococcal Antigen with Bacterial DNA. J Invest Dermatol. 129:2653-60. doi:10.1038/jid.2009.153

Cameron AL, Kirby B, Fei W, Griffiths CEM. (2002). Natural killer and natural killer-T cells in psoriasis. Arch Dermatol Res. 294:363–369. doi: 10.1007/s00403-002-0349-4

Camilleri M. (2019). Leaky gut: mechanisms, measurement and clinical implications in humans. Gut. 68:1516-1526. doi:10.1136/gutjnl-2019-318427

Capaldo CT, Powell DN, Kalman D. (2017). Layered defense: how mucus and tight junctions seal the intestinal barrier. J Mol Med (Berl).95:927-934. doi:10.1007/s00109-017-1557-x

Cheung KL, Jarrett R, Subramaniam S, Salimi M, Gutowska-Owsiak D, Chen YL, et al. (2016). Psoriatic T cells recognize neolipid antigens generated by mast cell phospholipase delivered by exosomes and presented by CD1a. J Exp Med. 213:2399-2412. doi:10.1084/jem.20160258

Chiang CC, Cheng WJ, Korinek M, Lin CY, Hwang T. (2019). Neutrophils in Psoriasis. Front Immunol. 10:2376. doi:10.3389/fimmu.2019.02376

Chieosilapatham P, Ikeda S, Ogawa H, Niyonsaba F. (2018). Tissue-specific Regulation of Innate Immune Responses by Human Cathelicidin LL-37. Curr Pharm Des. 24:1079-1091. doi:10.2174/1381612824666180327113418

Chin AC, Flynn AN, Fedwick JP, Buret AG. (2006). The role of caspase-3 in lipopolysaccharide-mediated disruption of intestinal epithelial tight junctions. Can J Physiol Pharmacol. 84:1043-50. doi:10.1139/y06-056

Chiricozzi A, Romanelli P, Volpe E, Borsellino G, Romanelli M. (2018). Scanning the Immunopathogenesis of psoriasis. Int J Mol Sci.19. pii: E179. doi:10.3390/ijms19010179

Ciampolini M, Bini S, Orsi A. (1996). Microflora persistence on duodenum-jejunal flat or normal mucosa in time after a meal in children. Physiol Behav. 60:1551-6. doi:10.1016/S0031-9384(96)00312-5

Clark RA. (2010). Skin-resident T cells: the ups and downs of on site immunity. J Invest Dermatol.130:362-70. doi:10.1038/jid.2009.247

Clark RA. (2011). Gone but not forgotten: lesional memory in psoriatic skin. J Invest Dermatol. 131:283-5. doi:10.1038/jid.2010.374

Chimenti MS, Triggianese P, Botti E, Narcisi A, Conigliaro P, Giunta A, Teoli M, Perricone R, Costanzo A. (2016). S100A8/A9 in psoriatic plaques from patients with psoriatic arthritis. J Int Med Res. 44:33-37. doi:10.1177/0300060515598900

Christophers E, Metzler G, Röcken M. (2014). Bimodal immune activation in psoriasis. Br J Dermatol. 170:59-65. doi:10.1111/bjd.12631

Cogen AL, Yamasaki K, Muto J, Sanchez KM, Crotty Alexander L, et al. (2010). Staphylococcus epidermidis antimicrobial delta-toxin (phenol-soluble modulin-gamma) cooperates with host antimicrobial peptides to kill group A Streptococcus. PLoS One. 5:e8557 doi:10.1371/journal.pone.0008557

Coll RC, O'Neill LA. (2010). New insights into the regulation of signalling by toll-like receptors and nod-like receptors. J Innate Immun. 2:406-21. doi:10.1159/000315469

Dalpke A, Frank J, Peter M, Heeg K. (2006). Activation of Toll-Like Receptor 9 by DNA from different bacterial species. Infect Immun. 74:940-6. doi:10.1128/IAI.74.2.940-946.2006

Dapunt U, Gaida MM, Meyle E, Prior B, Hänsch GM. (2016). Activation of phagocytic cells by Staphylococcus epidermidis biofilms: effects of extracellular matrix proteins and the bacterial stress protein GroEL on netosis and MRP-14 release. Pathog Dis. 74. pii: ftw035. doi:10.1093/femspd/ftw035

Davey MS, Morgan MP, Liuzzi AR, Tyler CJ, Khan MW, Szakmany T, et al. (2014). Microbe-specific unconventional T cells induce human neutrophil differentiation into antigen cross-presenting cells. J Immunol. 193:3704-16. doi:10.4049/jimmunol.1401018

De Jesús-Gil C, Ruiz-Romeu E, Ferran M, Chiriac A, Deza G, Hóllo P, et al. (2018). CLA+ T Cell Response to Microbes in Psoriasis. Front Immunol. 9:1488. doi:10.3389/fimmu.2018.01488

De Jongh GJ, Zeeuwen PL, Kucharekova M, Pfundt R, van der Valk PG, Blokx W, et al., (2005). High expression levels of keratinocyte antimicrobial proteins in psoriasis compared with atopic dermatitis. J Invest Dermatol. 125:1163-73. doi:10.1111/j.0022-202X.2005.23935.x

De Santis S, Cavalcanti E, Mastronardi M, Jirillo E, Chieppa M. (2015). Nutritional Keys for Intestinal Barrier Modulation. Front Immunol. 6:612. doi:10.3389/fimmu.2015.00612

Delgado-Rizo V, Martínez-Guzmán MA, Iñiguez-Gutierrez L, García-Orozco A, Alvarado-Navarro A, Fafutis-Morris M. (2017). Neutrophil Extracellular Traps and Its Implications in Inflammation. Front Immunol. 8:81. doi:10.3389/fimmu.2017.00081

Dhotre S, Jahagirdar V, Suryawanshi N, Davane M, Patil R, Nagoba B. (2018). Assessment of periodontitis and its role in viridans streptococcal bacteremia and infective endocarditis. Indian Heart J. 70:225-232 doi:10.1016/j.ihj.2017.06.019

Di Domizio J, Gilliet M. (2019). Psoriasis caught in the NET. J Invest Dermatol. 139:1426-1429. doi:10.1016/j.jid.2019.04.020.

Di Meglio P, Nestle FO. (2017). Immunopathogenesis of Psoriasis. Chapter 21 from “Clinical and Basic Immunodermatology”. Springer 2017, ISBN 9783319297859 doi:10.1007/978-3-319-29785-9_21

Di Meglio P, Perera GK, Nestle FO. (2011). The multitasking organ: recent insights into skin immune function. Immunity.35:857-69. doi:10.1016/j.immuni.2011.12.003

Doger FK, Dikicioglu E, Ergin F, Unal E, Sendur N, Uslu M. (2007). Nature of cell kinetics in psoriatic epidermis. J Cutan Pathol. 34:257-63. doi:10.1111/j.1600-0560.2006.00719.x

Duan Z, Fang Y, Sun Y, Luan N, Chen X, Chen M, et al. (2018). Antimicrobial peptide LL-37 forms complex with bacterial DNA to facilitate blood translocation of bacterial DNA and aggravate ulcerative colitis. Science Bulletin. 63:1364-1375 doi:10.1016/j.scib.2018.09.014

Egawa G, Kabashima K. (2020). Role of Lymphoid Structure in Skin Immunity. Curr Top Microbiol Immunol. 426:65-82. doi:10.1007/82_2020_206

Elgharib I, Khashaba SA, Elsaid HH, Sharaf MM. (2019). Serum elafin as a potential inflammatory marker in psoriasis. Int J Dermatol. 58:205-209. doi:10.1111/ijd.14217

El-Rachkidy RG, Hales JM, Freestone PP, Young HS, Griffiths CE, Camp RD. (2007). Increased Blood Levels of IgG Reactive with Secreted Streptococcus pyogenes Proteins in Chronic Plaque Psoriasis. J Invest Dermatol. 127:1337-42. doi:10.1038/sj.jid.5700744

Ely PH. (2018). Is psoriasis a bowel disease? Successful treatment with bile acids and bioflavonoids suggest it is. Clin Dermatol. 36:376-389. doi:10.1016/j.clindermatol.2018.03.011

Farkas A, Kemény L. (2011). Interferon-alpha in the generation of monocyte-derived dendritic cells: Recent advances and implications for dermatology. Br J Dermatol. 165:247-54. doi:10.1111/j.1365-2133.2011.10301.x

Fasano A, Nataro JP. (2004). Intestinal epithelial tight junctions as targets for enteric bacteria-derived toxins. Adv Drug Deliv Rev. 56:795-807. doi:10.1016/j.addr.2003.10.045

Ferran M, Galván AB, Rincón C, Romeu ER, Sacrista M, Barboza E, et al. (2013). Streptococcus induces circulating CLA(+) memory T-cell-dependent epidermal cell activation in psoriasis. J Invest Dermatol. 133:999-1007. doi:10.1038/jid.2012.418

Filipe SR, Severina E, Tomasz A. (2001). Functional analysis of Streptococcus pneumoniae MurM reveals the region responsible for its specificity in the synthesis of branched cell wall peptides. J Biol Chem. 276:39618-28. doi:10.1074/jbc.M106425200

Fiser A, Filipe SR, Tomasz A. (2003). Cell wall branches, penicillin resistance and the secrets of the MurM protein. Trends Microbiol. 11:547-53. doi:10.1016/j.tim.2003.10.003

Fitting C, Parlato M, Adib-Conquy M, Memain N, Philippart F, Misset B, et al. (2012). DNAemia detection by multiplex PCR and biomarkers for infection in systemic inflammatory response syndrome patients. PLoS One. 7:e38916. doi:10.1371/journal.pone.0038916

Frasca L, Palazzo R, Chimenti MS, Alivernini S, Tolusso B, Bui L, et al. (2019). Anti-LL37 Antibodies Are Present in Psoriatic Arthritis (PsA) Patients: New Biomarkers in PsA. Front Immunol. 9:1936 doi:10.3389/fimmu.2018.01936

Fry L, Baker BS, Powles AV. (2007). Psoriasis - A possible candidate for vaccination. Autoimmun Rev. 6:286-9. doi:10.1016/j.autrev.2006.09.007

Fry L, Baker BS. (2007). Triggering psoriasis: the role of infections and medications. Clin Dermatol. 25:606-15. doi:10.1016/j.clindermatol.2007.08.015

Fuchs TA, Abed U, Goosmann C, Hurwitz R, Schulze I, Wahn V, et al. (2007). Novel Cell Death Program Leads to Neutrophil Extracellular Traps. J Cell Biol.176:231-41. doi:10.1083/jcb.200606027

Fuentes-Duculan J, Suárez-Fariñas M, Zaba LC, Nograles KE, Pierson KC, Mitsui H, et al. (2010). A Subpopulation of CD163-Positive Macrophages Is Classically Activated in Psoriasis. Journal of Investigative Dermatology 130:2412-2422. doi:10.1038/jid.2010.165

Fuentes-Duculan J, Bonifacio KM, Hawkes JE, et al. (2017). Autoantigens ADAMTSL5 and LL37 are significantly upregulated in active Psoriasis and localized with keratinocytes, dendritic cells and other leukocytes. Exp Dermatol. 26:1075-1082. doi:10.1111/exd.13378.

a Fukui H. (2016). Endotoxin and Other Microbial Translocation Markers in the Blood: A Clue to Understand Leaky Gut Syndrome. Cell Mol Med, 2:3. link.

b Fukui H. (2016). Increased Intestinal Permeability and Decreased Barrier Function: Does It Really Influence the Risk of Inflammation? Inflamm Intest Dis. 3:135-145. doi:10.1159/000447252

Furue M, Furue K, Tsuji G, Nakahara T. (2020). Interleukin-17A and Keratinocytes in Psoriasis. Int J Mol Sci. 21:1275 doi:10.3390/ijms21041275

Gambichler T, Skrygan M, Tomi NS, Othlinghaus N, Brockmeyer NH, Altmeyer P, Kreuter A. (2008). Differential mRNA Expression of Antimicrobial Peptides and Proteins in Atopic Dermatitis as Compared to Psoriasis Vulgaris and Healthy Skin. Int Arch Allergy Immunol. 147:17-24. doi:10.1159/000128582

Ganguly D, Chamilos G, Lande R, Gregorio J, Meller S, Facchinetti V, et al. (2009). Self-RNA-antimicrobial peptide complexes activate human dendritic cells through TLR7 and TLR8. J Exp Med. 206:1983-94. doi:10.1084/jem.20090480

Garaeva ZS. Clinical significance of levels of antiendotoxic and antibacterial immunity in psoriatics. Dissertation, Kazan, 2005, 142 p. (rus).

Garaeva ZS, Safina NA, Tiurin IA, Kuklin VT, Zinkevich OD. Intesitnal dysbiosis as the cause of systemic endotoxemia in psoriatic patients. Vestn Dermatol Venerol, 2007;(1): 23-27. (rus). elib.

Garcia-Rodriguez S, Arias-Santiago S, Perandrés-López R, Castellote L, Zumaquero E, Navarro P. et al. (2011). Increased gene expression of Toll-like receptor 4 on peripheral blood mononuclear cells in patients with psoriasis. J Eur Acad Dermatol Venereol. 27:242-50. doi:10.1111/j.1468-3083.2011.04372.x

Gaspari AA, Tyring SK, Kaplan DH. (2017). Clinical and Basic Immunodermatology. Springer, 889 p. ISBN 978-3-319-29785-9.

Gilliet M. (2015). Immunopathogenesis of psoriasis: antimicrobial peptides take centre stage. in Monograph 28. The epidermis of man: co-existing with commensals. Old Herborn University. https://www.old-herborn-university.de/publication/monograph-28/

Gilliet M, Lande R. (2008). Antimicrobial peptides and self-DNA in autoimmune skin inflammation. Curr Opin Immunol. 20:401-7. doi:10.1016/j.coi.2008.06.008

Ginhoux F, Tacke F, Angeli V, Bogunovic M, Loubeau M, Dai XM, et al. (2006). Langerhans cells arise from monocytes in vivo. Nat Immunol. 7:265-73. doi:10.1038/ni1307

Ginhoux F, Collin MP, Bogunovic M, Abel M, Leboeuf M, Helft J, et al. (2007). Blood-derived dermal langerin+ dendritic cells survey the skin in the steady state. J Exp Med. 204:3133-46 doi:10.1084/jem.20071733.

Ginhoux F, Merad M. (2010). Ontogeny and homeostasis of Langerhans cells. Immunol Cell Biol. 88:387-92. doi:10.1038/icb.2010.38

Gisondi P, Targher G, Zoppini G, Girolomoni G. (2009). Non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. J Hepatol. 51:758-64. doi:10.1016/j.jhep.2009.04.020

Glebova NS. Changes of intestine microbiocenosis under the influence of destabilizing action of blastocystic invasion. Bulletin OGU, 2007 (5):155-160. (rus). elib

a Gnauck A, Lentle RG, Kruger MC. (2016). Chasing a ghost? - Issues with the determination of circulating levels of endotoxin in human blood. Crit Rev Clin Lab Sci. 53:197-215. doi:10.3109/10408363.2015.1123215

Gottlieb AB, Chamian F, Masud S, Cardinale I, Abello MV, Lowes MA, et al. (2005). TNF inhibition rapidly down-regulates multiple proinflammatory pathways in psoriasis plaques. J Immunol. 175:2721-9. doi: 10.4049/jimmunol.175.4.2721

Graziani C, Talocco C, De Sire R, Petito V, Lopetuso LR, Gervasoni J, et.al. (2019). Intestinal permeability in physiological and pathological conditions: major determinants and assessment modalities. Eur Rev Med Pharmacol Sci. 23:795-810. doi:10.26355/eurrev_201901_16894

Grayson PC, Kaplan MJ. (2016). At the Bench: Neutrophil extracellular traps (NETs) highlight novel aspects of innate immune system involvement in autoimmune diseases. J Leukoc Biol. 99:253-64. doi:10.1189/jlb.5BT0615-247R

Greenlee-Wacker MC. (2016). Clearance of apoptotic neutrophils and resolution of inflammation. Immunol Rev. 273:357-70. doi:10.1111/imr.12453

Gudjonsson JE, Thorarinsson AM, Sigurgeirsson B, Kristinsson KG, Valdimarsson H. (2003). Streptococcal throat infections and exacerbation of chronic plaque psoriasis: a prospective study. Br J Dermatol. 149:530-4. doi:10.1046/j.1365-2133.2003.05552.x

Gudjonsson JE. Johnston A, Sigmundsdottir H. & Valdimarsson H. (2004). Immunopathogenic mechanisms in psoriasis. Clin Exp Immunol 135: 1-8. doi:10.1111/j.1365-2249.2004.02310.x

Gudjonsson JE, Elder JT. (2007). Psoriasis: epidemiology. Clin Dermatol. 25:535-46. doi:10.1016/j.clindermatol.2007.08.007

Gudjonsson JE, Ding J, Li X, Nair RP, Tejasvi T, Qin ZS, Ghosh D, Aphale A, Gumucio DL, Voorhees JJ, Abecasis GR, Elder JT. (2009). Global Gene Expression Analysis Reveals Evidence for Decreased Lipid Biosynthesis and Increased Innate Immunity in Uninvolved Psoriatic Skin. J Invest Dermatol. 129:2795-804. doi:10.1038/jid.2009.173

Guerville M, Boudry G. (2016). Gastrointestinal and hepatic mechanisms limiting entry and dissemination of lipopolysaccharide into the systemic circulation. Am J Physiol Gastrointest Liver Physiol. 311:G1-G15. doi:10.1152/ajpgi.00098.2016

a Gumayunova NG. Syndrome of small intestine bacterial overgrowth at psoriatic disease against blastocystic invasion. Dissertation, Chelyabinsk, 2009, 169 p, (rus), elib.

b Gumayunova NG, Potaturkina-Nesterova NI, Nesterov AS, Magomedov MA. New approaches to diagnosis intestinal dysbiosis of patients who have psoriatic disease. Bulletin of Russian Peoples Friendship University. Medicine. 2009;(2):93-97. (rus). elib.

c Gumayunova NG. Revealing of small intestine bacterial overgrowth at psoriatic disease. Postgraduate bulletin of Volga region, 2009 (3-4):162-4. (rus). elib.

Gumayunova NG, Nesterov AS, Potaturkina-Nesterova NI. Small intestine bacterial overgrowth syndrome and psoriatic disease. Monograph. Ulyanovsk state university, 2016, 156 p. ISBN 9785888665923. (rus), elib.

Gunn JS. (2000). Mechanisms of bacterial resistance and response to bile. Microbes Infect. 2:907-13. doi:10.1016/s1286-4579(00)00392-0

Guttman-Yassky E, Nograles KE, Krueger JG. (2011). Contrasting pathogenesis of atopic dermatitis and psoriasis-Part II: Immune cell subsets and therapeutic concepts. J Allergy Clin Immunol. 127:1420-32. doi:10.1016/j.jaci.2011.01.054

Gyurcsovics K, Bertok L. (2003). Pathophysiology of psoriasis: coping endotoxins with bile acid therapy. Pathophysiology. 10:57-61. doi:10.1016/j.pathophys.2003.07.001

Harder J, Dressel S, Wittersheim M, Cordes J, Meyer-Hoffert U, Mrowietz U, et al. (2010). Enhanced expression and secretion of antimicrobial peptides in atopic dermatitis and after superficial skin injury. J Invest Dermatol. 130:1355-64. doi:10.1038/jid.2009.432

Harkov EI, Prohorenkov VI, Shiryaeva YuA. Indices of functional activity of small intestine in patients with psoriasis. Siberian Medical Review, 2008;(6):55-58. (rus). elib.

Harkov EI, Shiryaeva YuA, Teryoshina DS. Malabsoption syndrome and psoriasis: the method of correction. Siberian Medical Journal (Irkutsk), 2006;(7):61-63. (rus). elib.

Harkov EI, Shiryaeva YuA. Malabsorption syndrome in psoriasis: clinical-laboratory parallels. Siberian Medical Review, 2005;(2-3):62-64. (rus). elib.

Hasler P, Giaglis S, Hahn S. (2016). Neutrophil extracellular traps in health and disease. Swiss Med Wkly. 146:w14352. doi:10.4414/smw.2016.14352

Hawkes JE, Chan TC, Krueger JG. (2017). Psoriasis pathogenesis and the development of novel targeted immune therapies. J Allergy Clin Immunol. 140:645-653. doi:10.1016/j.jaci.2017.07.004

He C, Deng J, Hu X, Zhou S, Wu J, Xiao D, Darko KO, et al. (2019). Vitamin A inhibits the action of LPS on the intestinal epithelial barrier function and tight junction proteins. Food Funct. 10:1235-1242. doi:10.1039/c8fo01123k

Helander HF, Fändriks L. (2014). Surface area of the digestive tract - revisited. Scand J Gastroentero. 49:681-9. doi:10.3109/00365521.2014.898326

Herster F, Bittner Z, Dickhoefer S, Eisel D, Eigenbrod T, Knorpp T, et al. (2020). Neutrophil Extracellular Trap-Associated RNA and LL37 Enable Self-Amplifying Inflammation in Psoriasis. Nat Commun. 11:105. doi:10.1038/s41467-019-13756-4.

Herster F, Bittner Z, Cordrea MC, Archer N, Heister M, Löffler MW et al. (2019). Platelets Aggregate With Neutrophils and Promote Skin Pathology in Psoriasis. Front Immunol. 10:1867. doi:10.3389/fimmu.2019.01867

Hofmann AF, Eckmann L. (2006). How bile acids confer gut mucosal protection against bacteria. Proc Natl Acad Sci U S A. 103:4333-4. doi:10.1073/pnas.0600780103

Holder MJ, Wright HJ, Couve E, Milward MR, Cooper PR. (2019). Neutrophil Extracellular Traps Exert Potential Cytotoxic and Proinflammatory Effects in the Dental Pulp. J Endod. 45:513-520.e3. doi:10.1016/j.joen.2019.02.014

Hollox EJ, Huffmeier U, Zeeuwen PL, Palla R, Lascorz J, Rodijk-Olthuis D et al. (2008). Psoriasis is associated with increased beta-defensin genomic copy number. Nat Genet. 40:23-5. doi:10.1038/ng.2007.48

Holmannova D, Borsky P, Borska L, Andrys C, Hamakova K, Rehacek V, Svadlakova T, et al. (2020). Metabolic Syndrome, Clusterin and Elafin in Patients with Psoriasis Vulgaris. Int J Mol Sci. 21:E5617 doi:10.3390/ijms21165617

Hoppenbrouwers T, Autar ASA, Sultan AR, Abraham TE, van Cappellen WA, Houtsmuller AB, et al. (2017). In vitro induction of NETosis: Comprehensive live imaging comparison and systematic review. PLoS One. 12:e0176472. doi:10.1371/journal.pone.0176472

Hu SC, Yu HS, Yen FL, Lin CL, Chen GS, Lan CC. (2016). Neutrophil extracellular trap formation is increased in psoriasis and induces human β-defensin-2 production in epidermal keratinocytes. Sci Rep. 6:31119 doi:10.1038/srep31119.

Husebye E. (2005). The pathogenesis of gastrointestinal bacterial overgrowth. Chemotherapy.51 Suppl 1:1-22. doi:10.1159/000081988

Husebye H, Halaas O, Stenmark H, Tunheim G, Sandanger Ø, Bogen B, et al. (2006). Endocytic pathways regulate Toll-like receptor 4 signaling and link innate and adaptive immunity. EMBO J. 25:683-92. doi:10.1038/sj.emboj.7600991

Ibliyaminova AA, Khismatullina ZR, Krukova AJ. Clinical and functional condition of psoriatics biliary tract. Modern questions of dermatovenerology, immunology and medical cosmetology. 2009; 3:39-43. (rus). elib.

Jialal I, Rajamani U. (2014). Endotoxemia of metabolic syndrome: a pivotal mediator of meta-inflammation. Metab Syndr Relat Disord. 12:454-6. doi:10.1089/met.2014.1504

Johnson LR. (2012). Physiology of the Gastrointestinal Tract. Academic Press. 5th edition. 2308 p. eISBN: 9780123820273.

Jozsef L, Khreiss T, Filep JG. (2004). CpG motifs in bacterial DNA delay apoptosis of neutrophil granulocytes. FASEB J. 18:1776-8. doi:10.1096/fj.04-2048fje

Kabashima K. (2016). Immunology of the Skin. Basic and Clinical Sciences in Skin Immune Responses. Springer Japan, 510 p. ISBN 978-4-431-55855-2.

Kabashima K, Honda T, Ginhoux F, Egawa G. (2019). The immunological anatomy of the skin. Nat Rev Immunol. 19:19-30. doi:10.1038/s41577-018-0084-5

Kahlenberg JM, Kaplan MJ. (2013). Little peptide, big effects: the role of LL-37 in inflammation and autoimmune disease. J Immunol. 191:4895-901 doi:10.4049/jimmunol.1302005

Kaldor CD (2019). Oxidant generation by Streptococcus pneumoniae associated with neutrophil extracellular traps. Thesis, Master of Science. University of Otago http://hdl.handle.net/10523/9842

Karaji N, Sattentau QJ. (2017). Efferocytosis of Pathogen-Infected Cells. Front Immunol. 8:1863. doi:10.3389/fimmu.2017.01863

Kenny EF, Herzig A, Krüger R, Muth A, Mondal S, Thompson PR, et al. (2017). Diverse Stimuli engage different Neutrophil Extracellular Trap pathways. Elife. 6. pii: e24437. doi:10.7554/eLife.24437

Khardikova SA, Beloborodova EI, Pesterev PN. Psoriasis, intestinal adsorption. Tomsk, NTL, 2000, 120 p. (rus), ISBN 589503084x. elib

Khardikova CA, Beloborodova EI, Pesterev PN, Nepomniashchikh GI. Morphofunctional changes in gastrointestinal tract in patients with psoriasis accompanied by chronic opisthorchosis, Klin Med (Mosk), 2005;(1):43-46. (rus), elib.

Kim J, Krueger JG. (2015). The Immunopathogenesis of Psoriasis. Dermatol Clin. 33:13-23. doi:10.1016/j.det.2014.09.002

Kim SJ, Jenne CN (2016). Role of platelets in neutrophil extracellular trap (NET) production and tissue injury. Semin Immunol. 28:546-554. doi:10.1016/j.smim.2016.10.013

Kim SK, Park S, Lee ES. (2010). Toll-like receptors and antimicrobial peptides expressions of psoriasis: correlation with serum vitamin D level. J Korean Med Sci. 25:1506-12. doi:10.3346/jkms.2010.25.10.1506

Kim TG, Jee H, Fuentes-Duculan J, Wu WH, Byamba D, Kim DS, et al. (2014). Dermal Clusters of Mature Dendritic Cells and T Cells Are Associated with the CCL20/CCR6 Chemokine System in Chronic Psoriasis. J Invest Dermatol. 134:1462-1465 doi:10.1038/jid.2013.534

Kobayashi T, Tani T, Yokota T, Kodama M. (2000). Detection of peptidoglycan in human plasma using the silkworm larvae plasma test. FEMS Immunol Med Microbiol. 28:49-53. doi:10.1111/j.1574-695X.2000.tb01456.x

Korotky NG, Peslyak MY. Psoriasis as a consequence of incorporation of beta-streptococci into the microbiocenosis of highly permeable intestines (a pathogenic concept), Vestn Dermatol Venerol, 2005;(1): 9-18. (rus), elib

Korotky N, Peslyak M. (2020). Blood metagenome in health and psoriasis. Front. Med. 7:333 doi:10.3389/fmed.2020.00333

Kuranova NYu, Khardikova SA, Beloborodova YeI, Kalyuzhina MI. Influence od dehelmithization on bile lithogenity indices in patients having psoriasis combined with chronic opisthorchiasis. Siberian Medical Journal (Tomsk), 2009;(1):49-52. (rus). elib.

Lambert S, Hambro CA, Johnston A, Stuart PE, Tsoi LC, Nair RP, Elder JT. (2019). Neutrophil Extracellular Traps Induce Human Th17 Cells: Effect of Psoriasis-Associated TRAF3IP2 Genotype. J Invest Dermatol. 139:1245-1253. doi:10.1016/j.jid.2018.11.021

Lande R, Chamilos G, Ganguly D, Demaria O, Frasca L, Durr S, et al. (2015). Cationic antimicrobial peptides in psoriatic skin cooperate to break innate tolerance to self-DNA. Eur J Immunol. 45:203-13. doi:10.1002/eji.201344277

Lande R, Botti E, Jandus C, Dojcinovic D, Fanelli G, Conrad C, et al. (2014). The antimicrobial peptide LL37 is a T-cell autoantigen in psoriasis. Nat Commun. 5:5621. doi:10.1038/ncomms6621

Larochette V, Miot C, Poli C, Beaumont E, Roingeard P, Fickenscher H, et al. (2019). IL-26, a Cytokine With Roles in Extracellular DNA-Induced Inflammation and Microbial Defense. Front Immunol. 10:204. doi:10.3389/fimmu.2019.00204

Leite GGS, Weitsman S, Parodi G, Celly S, Sedighi R, Sanchez M, et al. (2019). Mapping the Segmental Microbiomes in the Human Small Bowel in Comparison with Stool: A REIMAGINE Study Dig Dis Sci. Mar 6. doi:10.1007/s10620-020-06173-x

Leite G, Morales W, Weitsman S, Celly S, Parodi G, Mathur R, et al. (2020). The duodenal microbiome is altered in small intestinal bacterial overgrowth. PLoS One. 15:e0234906. doi:10.1371/journal.pone.0234906

Li B, Huang L, Lv P, Li X, Liu G, Chen Y, et al. (2020). The role of Th17 cells in psoriasis. Immunol Res. Epub Aug 22. doi:10.1007/s12026-020-09149-1

Lin A, Loré K. (2017). Granulocytes: New Members of the Antigen-Presenting Cell Family. Front Immunol. 8:1781. doi:10.3389/fimmu.2017.01781

Lin AM, Rubin CJ, Khandpur R, Wang JY, Riblett M, Yalavarthi S, et al. (2011). Mast Cells and Neutrophils Release IL-17 through Extracellular Trap Formation in Psoriasis. J Immunol. 187:490-500. doi:10.4049/jimmunol.1100123

Lindau D, Mussard J, Wagner BJ, Ribon M, Rönnefarth VM, Quettier M, et al. (2013). Primary blood neutrophils express a functional cell surface Toll-like receptor 9. Eur J Immunol. 43:2101-13. doi:10.1002/eji.201142143

Lipp P, Ruhnau J, Lange A, Vogelgesang A, Dressel A, Heckmann M. (2017). Less Neutrophil Extracellular Trap Formation in Term Newborns than in Adults. Neonatology. 111:182-188. doi:10.1159/000452615

Lowes MA, Suárez-Fariñas M, Krueger JG. (2014). Immunology of psoriasis. Annu Rev Immunol.32:227-55. doi:10.1146/annurev-immunol-032713-120225

Madden SK, Flanagan KL, Jones G. (2020). How lifestyle factors and their associated pathogenetic mechanisms impact psoriasis. Review Clin Nutr. 39:1026-1040 doi:10.1016/j.clnu.2019.05.006

Madonna S, Girolomoni G, Dinarello GA, Albanesi C. (2019). The significance of IL-36 hyperactivation and IL-36R targeting in psoriasis. Int J Mol Sci. 20:3318. doi:10.3390/ijms20133318

Machado LR, Ottolini B. (2015). An evolutionary history of defensins: a role for copy number variation in maximizing host innate and adaptive immune responses. Front Immunol. 6:115. doi:10.3389/fimmu.2015.00115

Malachowa N, Kobayashi SD, Quinn MT, DeLeo FR. (2016). NET Confusion. Front Immunol. 7:259. doi:10.3389/fimmu.2016.00259

Mantovani A, Gisondi P, Lonardo A, Targher G. (2016). Relationship between Non-Alcoholic Fatty Liver Disease and Psoriasis: A Novel Hepato-Dermal Axis? Review Int J Mol Sci. 17:217. doi:10.3390/ijms17020217

Martynov VL. SIBO (surgical treatment and prevention), monograph. SPb: LITEO, 2016, 312 p. ISBN 9785000717202. (rus)

Matusevich SL, Kungurov NV, Filimonkova NN, Gerasimova NM. Psoriasis and opisthorchiasis, Tyumen, 2000, 232 p. (rus). ISBN 5881311337.

Mayadas TN, Cullere X, Lowell CA. (2014). The multifaceted functions of neutrophils. Annu Rev Pathol. 9:181-218. doi:10.1146/annurev-pathol-020712-164023

McCracken JM, Allen LA. (2014). Regulation of Human Neutrophil Apoptosis and Lifespan in Health and Disease. J Cell Death. 7:15-23. doi:10.4137/JCD.S11038

McMichael JW, Roghanian A, Jiang L, Ramage R, SallenaveJM. (2005). The antimicrobial antiproteinase elafin binds to lipopolysaccharide and modulates macrophage responses. Am J Respir Cell Mol Biol. 32:443-52 doi:10.1165/rcmb.2004-0250OC

Meller S, Di Domizio J, Voo KS, Friedrich HC, Chamilos G, Ganguly D, et al. (2015). T(H)17 cells promote microbial killing and innate immune sensing of DNA via interleukin 26. Nat Immunol. 16:970-9. doi:10.1038/ni.3211

Meyer D, Telele S, Zelená A, Gillen AJ, Antonucci A, Neubert E, et al. (2020). Transport and programmed release of nanoscale cargo from cells by using NETosis. Nanoscale, 12: 9104-9115 doi:10.1039/D0NR00864H

Meyle E, Brenner-Weiss G, Obst U, Prior B, Hänsch GM. (2012). Immune defense against S. epidermidis biofilms: components of the extracellular polymeric substance activate distinct bactericidal mechanisms of phagocytic cells. Int J Artif Organs.35:700-12. doi:10.5301/ijao.5000151

Michalek IM, Loring B, John SM. (2017). A systematic review of worldwide epidemiology of psoriasis. J Eur Acad Dermatol Venereol. 31:205-212. doi:10.1111/jdv.13854

Mitsios A, Arampatzioglou A, Arelaki S, Mitroulis I, Ritis K. (2017). NETopathies? Unraveling the Dark Side of Old Diseases through Neutrophils. Front Immunol. 7:678 doi:10.3389/fimmu.2016.00678

a Morizane S, Gallo RL. (2012). Antimicrobial peptides in the pathogenesis of psoriasis. J Dermatol. 39:225-30. doi:10.1111/j.1346-8138.2011.01483.x.

b Morizane S, Yamasaki K, Mühleisen B, Kotol PF, Murakami M, Aoyama Y, et al. (2012). Cathelicidin Antimicrobial Peptide LL-37 in Psoriasis Enables Keratinocyte Reactivity against TLR9 Ligands. J Invest Dermatol. 132:135-43. doi:10.1038/jid.2011.259

Mu Q, Kirby J, Reilly CM, Luo XM. (2017). Leaky Gut As a Danger Signal for Autoimmune Diseases. Front Immunol. 8:598 doi:10.3389/fimmu.2017.00598

Munford RS. (2016). Endotoxemia-menace, marker, or mistake? J Leukoc Biol. 100:687-698. doi:10.1189/jlb.3RU0316-151R

Munz OH, Sela S, Baker BS, Griffiths CE, Powles AV, Fry L. (2010). Evidence for the presence of bacteria in the blood of psoriasis patients. Arch Dermatol Res. 302:495-8. doi:10.1007/s00403-010-1065-0

Myers B, Brownstone N, Reddy V, Chan S, Thibodeaux Q, Truong A, et al. (2019). The Gut Microbiome in Psoriasis and Psoriatic Arthritis. Best Pract Res Clin Rheumatol. 33:101494 doi:10.1016/j.berh.2020.101494

Mylonas A, Conrad C. (2018). Psoriasis: Classical vs. Paradoxical. The Yin-Yang of TNF and Type I Interferon Front Immunol. 9:2746. doi:10.3389/fimmu.2018.02746

Myhre AE, Aasen AO, Thiemermann C, Wang JE. (2006). Peptidoglycan--an endotoxin in its own right? Shock. 25:227-35. doi:10.1097/01.shk.0000191378.55274.37

Nagl M, Kacani L, Müllauer B, Lemberger EM, Stoiber H, Sprinzl GM, et al. (2002). Phagocytosis and Killing of Bacteria by Professional Phagocytes and Dendritic Cells. Clin Diagn Lab Immunol. 9:1165-8. doi:10.1128/cdli.9.6.1165-1168.2002

Nakatsuji T, Chiang HI, Jiang SB, Nagarajan H, Zengler K, Gallo RL. (2013). The microbiome extends to subepidermal compartments of normal skin. Nat Commun. 4:1431. doi:10.1038/ncomms2441

Nauseef WM, Borregaard N. (2014). Neutrophils at work. Nat Immunol. 15:602-11. doi:10.1038/ni.2921

Nesterov AS. Features of pathogenesis and therapy of chronic dermatoses at blastocystic invasion. Dissertation, St.-Petersburg, 2009, 298 p. (rus) elib.

a Nestle F, Conrad C, Tun-Kyi A, Homey B, Gombert M, Boyman O, et al. (2005a). Plasmacytoid predendritic cells initiate psoriasis through interferon--alpha production. J Exp Med. 202:135-43. doi:10.1084/jem.20050500

a Nestle FO, Di Meglio P, Qin JZ, Nickoloff BJ. (2009a). Skin immune sentinels in health and disease. Nat Rev Immunol. 9:679-91. doi:10.1038/nri2622

b Nestle FO, Kaplan DH, Barker J. (2009b). Psoriasis. N Engl J Med. 361:496-509. doi:10.1056/NEJMra0804595

Neumann A, Berends ETM, Nerlich A, Molhoek EM, Gallo RL, Meerloo T, et al. (2014). The antimicrobial peptide LL-37 facilitates the formation of neutrophil extracellular traps. Biochem J. 464:3-11. doi:10.1042/BJ20140778

Nguyen TH1, Park MD1, Otto M1. (2017). Host Response to Staphylococcus epidermidis Colonization and Infections. Front Cell Infect Microbiol. 7:90. doi:10.3389/fcimb.2017.00090

O'Hara JR, Buret AG. (2008). Mechanisms of intestinal tight junctional disruption during infection. Front Biosci. 13:7008-21. PMID 18508712.

Oehmcke S, Mörgelin M, Herwald H. (2009). Activation of the human contact system on neutrophil extracellular traps. J Innate Immun. 1:225-30. doi:10.1159/000203700

Ojetti V, De Simone C, Aguilar Sanchez J, Capizzi R, Migneco A, Guerriero C, et al. (2006). Malabsorption in psoriatic patients: cause or consequence? Scand J Gastroenterol. 41:1267-71. doi:10.1080/00365520600633529

Okahashi N, Sumitomo T, Nakata M, Sakurai A, Kuwata H, Kawabata S. (2014). Hydrogen Peroxide Contributes to the Epithelial Cell Death Induced by the Oral Mitis Group of Streptococci. PLoS One. 9:e88136. doi:10.1371/journal.pone.0088136

Okhlopkov VA, Pravdina OV, Gorodilov RV, Zykova EA. Expression of toll-like receptors 2nd and 4th types in the affected skin of patients with psoriasis. Omsk Scientific Bulletin 2012, 108: 49-52. elib

Ong PY, Ohtake T, Brandt C, Strickland I, Boguniewicz M, Ganz T, et al. (2002). Endogenous antimicrobial peptides and skin infections in atopic dermatitis. Engl J Med. 347:1151-60. doi:10.1056/NEJMoa021481

Ortmann W, Kolaczkowska E. (2018). Age is the work of art? Impact of neutrophil and organism age on neutrophil extracellular trap formation. Cell Tissue Res. 371:473-488. doi:10.1007/s00441-017-2751-4

Ouhara K, Komatsuzawa H, Yamada S, Shiba H, Fujiwara T, Ohara M, et al. (2005). Susceptibilities of periodontopathogenic and cariogenic bacteria to antibacterial peptides, b-defensins and LL37, produced by human epithelial cells. J Antimicrob Chemother. 55:888-96. doi:10.1093/jac/dki103

Ozawa M, Terui T, Tagami H. (2005). Localization of IL-8 and complement components in lesional skin of psoriasis vulgaris and pustulosis palmaris et plantaris. Dermatology. 211:249-55. doi:10.1159/000087019

Pagano J. Healing psoriasis: The natural alternative., 2008, 352 p, ISBN: 9780470267264

Païssé S, Valle C, Servant F, Courtney M, Burcelin R, Amar J, Lelouvier B. (2016). Comprehensive description of blood microbiome from healthy donors assessed by 16S targeted metagenomic sequencing. Transfusion. 56:1138-47. doi:10.1111/trf.13477

Paliogiannis P, Satta R, Deligia G, Farina G, Bassu S, Mangoni AA, et al. (2019). Associations between the neutrophil-to-lymphocyte and the platelet-to-lymphocyte ratios and the presence and severity of psoriasis: a systematic review and meta-analysis Clin Exp Med. 19:37-45. doi:10.1007/s10238-018-0538-x

Palucka AK, Blanck JP, Bennett L, Pascual V, Banchereau J. (2005). Cross-regulation of TNF and IFN-alpha in autoimmune diseases. Proc Natl Acad Sci U S A. 102:3372-7. doi:10.1073/pnas.0408506102

Panda SK, Kolbeck R, Sanjuan MA. (2017). Plasmacytoid dendritic cells in autoimmunity. Curr Opin Immunol. 44:20-25. doi:10.1016/j.coi.2016.10.006

Papayannopoulos V. (2018). Neutrophil extracellular traps in immunity and disease. Nat Rev Immunol. 18:134-147. doi:10.1038/nri.2017.105

Parfenov AI, Mazo VK, Gmoshinskii IV, Safonova SA, Ekisenina NI. Clinical significance of evaluation of ovalbumin blood level after oral load dose of chicken egg proteins, Russian Journal of Gastroenterology, 1999;(2). (rus).

Parisi R, Symmons DP, Griffiths CE, Ashcroft DM; Identification and Management of Psoriasis and Associated ComorbidiTy (IMPACT) project team. (2013). Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol. 133:377-85. doi:10.1038/jid.2012.339

Park CC, Kim KJ, Woo SY, Chun JH, Lee KH. (2009). Comparison of the Expression Profile of JunB, c-Jun, and S100A8 (Calgranulin A) in Psoriasis Vulgaris and Guttate Psoriasis Ann Dermatol. 21:35-8 doi:10.5021/ad.2009.21.1.35

Pashenkov MV, Dagil YA, Pinegin BV. (2018). NOD1 and NOD2: Molecular targets in prevention and treatment of infectious diseases. Int Immunopharmacol. 54:385-400. doi:10.1016/j.intimp.2017.11.036

Patra V, Mayer G, Gruber-Wackernagel A, Horn M, Lembo S, Wolf P. (2018). Unique profile of antimicrobial peptide expression in polymorphic light eruption lesions compared to healthy skin, atopic dermatitis, and psoriasis. Photodermatol Photoimmunol Photomed. 34:137-144. doi:10.1111/phpp.12355

Perera GK, Di Meglio P, Nestle FO. (2012). Psoriasis. Annu. Rev. Pathol. Mech. Dis. 7:385–422 doi:10.1146/annurev-pathol-011811-132448

a Peslyak MY. Model of pathogenesis of psoriasis. Part 1. Systemic psoriatic process, Moscow, MYPE, 2012, 84 p., ISBN 9785905504020, link.

b Peslyak MY. Model of pathogenesis of psoriasis. Part 2. Local processes. Moscow, MYPE, 2012, 110 p., ISBN 9785905504044. link.

c Peslyak MY, Gumayunova NG, Nesterov AS, Potaturkina-Nesterova NI. (2012). Small intestine microflora at psoriasis. Its possible role in pathogenesis, Conference 2012: “Psoriasis - a global health challenge”, Dermatol Ther 2,10, S12. doi: 10.1007/s13555-012-0010-x

Peslyak MY, Korotky NG. (2019). Metagenomes of blood and psoriatic skin. Research project., Moscow, Antipsoriatic Association "The Natural Alternative", ISBN 9785905504068, doi: 10.5281/zenodo.2667679.

Piccioli D, Tavarini S, Borgogni E, Steri V, Nuti S, Sammicheli C, et al. (2007). Functional specialization of human circulating CD16 and CD1c myeloid dendritic-cell subsets. Blood. 109:5371-9. doi:10.1182/blood-2006-08-038422

Pieterse E, Rother N, Yanginlar C, Hilbrands LB, van der Vlag J. (2016). Neutrophils Discriminate between Lipopolysaccharides of Different Bacterial Sources and Selectively Release Neutrophil Extracellular Traps.Front Immunol. 7:484. doi:10.3389/fimmu.2016.00484

Pietrzak A, Jastrzebska I, Chodorowska G, Maciejewski R, Dybiec E, Juszkiewicz-Borowiec M, et al. (2009). Psoriasis vulgaris and digestive system disorders: Is there a linkage? Folia Histochem Cytobiol. 47:517-24. doi:10.2478/v10042-009-0107-y

Pietrzak D, Pietrzak A, Krasowska D, Borzęcki A, Franciszkiewicz-Pietrzak K, Polkowska-Pruszyńska B, et al. (2017). Digestive system in psoriasis: an update Arch Dermatol Res. 309:679-693. doi:10.1007/s00403-017-1775-7

Pinegin B, Vorobjeva N, Pinegin V. (2015). Neutrophil extracellular traps and their role in the development of chronic inflammation and autoimmunity. Autoimmun Rev.14:633-40. doi:10.1016/j.autrev.2015.03.002

Polkowska-Pruszyńska B, Gerkowicz A, Krasowska D. (2020). The gut microbiome alterations in allergic and inflammatory skin diseases – an update. J Eur Acad Dermatol Venereol. 34:455-464. doi:10.1111/jdv.15951

Quigley EM. (2019). The Spectrum of Small Intestinal Bacterial Overgrowth (SIBO). Curr Gastroenterol Rep. 21:3. doi:10.1007/s11894-019-0671-z

Rachakonda TD, Dhillon JS, Florek AG, Armstrong AW. (2015). Effect of tonsillectomy on psoriasis: A systematic review. J Am Acad Dermatol. 72:261-75. doi: 10.1016/j.jaad.2014.10.013

Rai G. (2019). NETosis: Immunity, Pathogenesis and Therapeutics. Academic Press, 200 p. ISBN 978-0-12-816147-0

Rankin SM. (2010). The bone marrow: a site of neutrophil clearance. J Leukoc Biol. 88:241-51. doi:10.1189/jlb.0210112

Reich K, Papp KA, Matheson RT, Tu JH, Bissonnette R, Bourcier M, et al. (2015). Evidence that a neutrophil-keratinocyte crosstalk is an early target of IL-17A inhibition in psoriasis. Exp Dermatol. 2015 Jul;24(7):529-35. doi:10.1111/exd.12710

Reizis B. (2019). Plasmacytoid Dendritic Cells: Development, Regulation, and Function. Immunity. 50:37-50. doi:10.1016/j.immuni.2018.12.027

Rodriguez-Rosales YA, Kox M, van Rijssen E, van Cranenbroek B, van Welie M, Pickkers P, et al. (2019). Long-Term Effects of Experimental Human Endotoxemia on Immune Cell Function: Similarities and Differences With Sepsis. Randomized Controlled Trial Shock. 51:678-689 doi:10.1097/SHK.0000000000001222

Rohrl J, Yang D, Oppenheim JJ, Hehlgans T. (2010). Human beta-defensin 2 and 3 and their mouse orthologs induce chemotaxis through interaction with CCR2. J Immunol. 184:6688-94. doi:10.4049/jimmunol.0903984

Romaní J, Caixàs A, Escoté X, Carrascosa JM, Ribera M, Rigla M, et al. (2013). Lipopolysaccharide□binding protein is increased in patients with psoriasis with metabolic syndrome, and correlates with C□reactive protein. Clin Exp Dermatol. 38:81-4. doi:10.1111/ced.12007

Rudkovskaya ZV. Clinical and laboratory monitoring of efficiency of application of method of interval normobaric hypoxia in complex treatment of psoriasis in children. Dissertation, Moscow, 2003, 137 p. (rus). elib

Sabat R, Philipp S, Höflich C, Kreutzer S, Wallace E, Asadullah K, et al. (2007). Immunopathogenesis of psoriasis. Exp Dermatol. 16:779-98. doi:10.1111/j.1600-0625.2007.00629.x

Sabat R, Wolk K. (2011). Research in practice: IL-22 and IL-20: significance for epithelial homeostasis and psoriasis pathogenesis. J Dtsch Dermatol Ges. 9:518-23. doi:10.1111/j.1610-0387.2011.07611.x

Sabaté Brescó M, Harris LG, Thompson K, Stanic B, Morgenstern M, et al. (2017). Pathogenic Mechanisms and Host Interactions in Staphylococcus epidermidis Device-Related Infection. Front Microbiol. 8:1401. doi:10.3389/fmicb.2017.01401

Sangaletti S, Tripodo C, Chiodoni C, Guarnotta C, Cappetti B, Casalini P, et al. (2012). Neutrophil extracellular traps mediate transfer of cytoplasmic neutrophil antigens to myeloid dendritic cells toward ANCA induction and associated autoimmunity. Blood. 120:3007-18. doi:10.1182/blood-2012-03-416156

Schuster S, Hurrell B, Tacchini-Cottier F. (2013). Crosstalk between neutrophils and dendritic cells: a context-dependent process. J Leukoc Biol. 94:671-5. doi:10.1189/jlb.1012540

Schon MP. (2019). Adaptive and Innate Immunity in Psoriasis and Other Inflammatory Disorders. Front Immunol. 10:1764 doi:10.3389/fimmu.2019.01764

Schon MP, Broekaert SM, Erpenbeck L. (2017). Sexy again: The renaissance of neutrophils in psoriasis. Exp Dermatol. 26:305-311. doi:10.1111/exd.13067

Schon MP, Erpenbeck L. (2018). The interleukin-23/interleukin-17 Axis Links Adaptive and innate immunity in Psoriasis. Front Immunol. 9:1323. doi:10.3389/fimmu.2018.01323

Schonrich G, Raftery MJ. (2016). Neutrophil Extracellular Traps Go Viral. Front Immunol. 7:366. doi:10.3389/fimmu.2016.00366

Scott A, Weldon S, Buchanan PJ, Schock B, Ernst RK, McAuley DF, et al. (2011). Evaluation of the ability of LL-37 to neutralise LPS in vitro and ex vivo. PLoS One. 6:e26525. doi:10.1371/journal.pone.0026525

Singh S, Pradhan D, Puri P, Ramesh V, Aggarwal S, Nayek A, Jain AK (2019). Genomic alterations driving psoriasis pathogenesis. Review Gene. 683:61-71 doi:10.1016/j.gene.2018.09.042

Shagova YV. Clinical and prognostic value of functional and structural changes of intestine at psoriasis. Dissertation, Saratov, 2009, 160 p. (rus). elib.

Shao S, Cao T, Jin L, Li B, Fang H, Zhang J, et al. (2016). Increased Lipocalin-2 Contributes to the Pathogenesis of Psoriasis by Modulating Neutrophil Chemotaxis and Cytokine Secretion. doi:10.1016/j.jid.2016.03.002

Shao S, Fang H, Dang E, Xue K, Zhang J, Li B et al. (2019). Neutrophil Extracellular Traps Promote Inflammatory Responses in Psoriasis via Activating Epidermal TLR4/IL-36R Crosstalk. Front Immunol. 10:746. doi:10.3389/fimmu.2019.00746

Shen XF, Cao K, Jiang JP, Guan WX1, Du JF. (2017). Neutrophil dysregulation during sepsis: an overview and update. . J Cell Mol Med. 21:1687-1697 doi:10.1111/jcmm.13112

Shiryaeva YuA. Malabsorption syndrome at psoriatics. Dissertation, Krasnoyarsk, 2007, 150 p. (rus) elib. link.

b Skrzeczyńska-Moncznik J, Wawro K, Stefańska A, Oleszycka E, Kulig P, Zabel BA, et al. (2009). Potential role of chemerin in recruitment of plasmacytoid dendritic cells to diseased skin. Biochem Biophys Res Commun. 380:323-7. doi:10.1016/j.bbrc.2009.01.071

Skrzeczynska-Moncznik J, Wlodarczyk A, Zabieglo K, Kapinska-Mrowiecka M, Marewicz E, Dubin A, et al. (2012). Secretory Leukocyte Proteinase Inhibitor-Competent DNA Deposits Are Potent Stimulators of Plasmacytoid Dendritic Cells: Implication for Psoriasis. J Immunol. 189:1611-7. doi:10.4049/jimmunol.1103293

Soehnlein O, Lindbom L. (2010). Phagocyte partnership during the onset and resolution of inflammation. Nat Rev Immunol. 10:427-39. doi:10.1038/nri2779

Song M, Ye J, Zhang F, Su H, Yang X, He H, et al. (2019). Chenodeoxycholic Acid (CDCA) Protects against the Lipopolysaccharide-Induced Impairment of the Intestinal Epithelial Barrier Function via the FXR-MLCK Pathway. J Agric Food Chem.. 67:8868-8874. doi:10.1021/acs.jafc.9b03173

Sozzani S. (2005). Dendritic cell trafficking: more than just chemokines. Cytokine Growth Factor Rev. 16:581-92. doi:10.1016/j.cytogfr.2005.04.008

Sozzani S, Vermi W, Del Prete A, Facchetti F. (2010). Trafficking properties of plasmacytoid dendritic cells in health and disease. Trends Immunol. 31:270-7. doi:10.1016/j.it.2010.05.004

Stacy A., Belkaid Y. (2019). Microbial guardians of skin health. Science. 363:227-228 doi:10.1126/science.aat4326

Stenina MA, Kulagin VI, Rudkovskaya ZV et al. Role of disturbances of intestine barrier function in pathogenesis of psoriasis in children, Russian Journal of Skin and Sexually Transmitted Diseases, 2003;(2):20-23. (rus), elib.

Stepanenko RL. Changes of immunohistochemic expression of toll-like receptor 9 (TLR9) in skin at psoriasis. Ukrainian Journal of Dermatology, Venereology, Cosmetology. 2015, 58: 25-32. elib

Stuart PE, Hüffmeier U, Nair RP, Palla R, Tejasvi T, Schalkwijk J, et al. (2012). Association of β-Defensin Copy Number and Psoriasis in Three Cohorts of European Origin. J Invest Dermatol. 132:2407-2413. doi:10.1038/jid.2012.191

Sumioka R, Nakata M, Okahashi N, Li Y, Wada S, Yamaguchi M, et al. (2017). Streptococcus sanguinis induces neutrophil cell death by production of hydrogen peroxide. PLoS One. 12:e0172223. doi:10.1371/journal.pone.0172223

Sun L, Liu W, Zhang LJ. (2019). The Role of Toll-Like Receptors in Skin Host Defense, Psoriasis, and Atopic Dermatitis. J Immunol Res. 2019:1824624 doi:10.1155/2019/1824624

Tacke F, Ginhoux F, Jakubzick C, van Rooijen N, Merad M, Randolph GJ. (2006). Immature monocytes acquire antigens from other cells in the bone marrow and present them to T cells after maturing in the periphery. J Exp Med. 203:583-97. doi:10.1084/jem.20052119

Tan KS. (2008). New Insights on Classification, Identification, and Clinical Relevance of Blastocystis spp. Clin Microbiol Rev. 21:639-65. doi:10.1128/CMR.00022-08

Taudorf S, Krabbe KS, Berg RMG, Pedersen BK, Møller K. (2007). Human Models of Low-Grade Inflammation: Bolus versus Continuous Infusion of Endotoxin. Clin Vaccine Immunol. 14:250-5. doi:10.1128/CVI.00380-06

Teague HL, Varghese NJ, Tsoi LC, Dey AK, Garshick MS, Silverman JI, et al. (2019). Neutrophil Subsets, Platelets, and Vascular Disease in Psoriasis. JACC Basic Transl Sci. 4:1-14. doi:10.1016/j.jacbts.2018.10.008

Ten Bergen LL, Petrovic A, Aarebrot AK, Appel S. (2020). Current knowledge on autoantigens and autoantibodies in psoriasis. Scand J Immunol. e12945. doi:10.1111/sji.12945

Terui T, Ozawa M, Tagami H. (2000). Role of neutrophils in induction of acute inflammation in T-cell-mediated immune dermatosis, psoriasis: a neutrophil-associated inflammation-boosting loop. Exp Dermatol. 9:1-10. doi:10.1034/j.1600-0625.2000.009001001.x

Tervaniemi MH, Katayama S, Skoog T, Siitonen HA, Vuola J, Nuutila K, et al. (2016). NOD-like receptor signaling and inflammasome-related pathways are highlighted in psoriatic epidermis. Sci Rep.6:22745 doi:10.1038/srep22745

a Thorleifsdottir RH, Eysteinsdóttir JH, Olafsson JH, Sigurdsson MI, Johnston A, Valdimarsson H, Sigurgeirsson B. (2016). Throat Infections are Associated with Exacerbation in a Substantial Proportion of Patients with Chronic Plaque Psoriasis. Acta Derm Venereol. 96:788-91. doi:10.2340/00015555-2408

Thorleifsdottir RH, Sigurdardottir SL, Sigurgeirsson B, Olafsson JH, Sigurdsson MI, Petersen H, et al. (2017). Patient-reported Outcomes and Clinical Response in Patients with Moderate-to-severe Plaque Psoriasis Treated with Tonsillectomy: A Randomized Controlled Trial. Acta Derm Venereol. 97:340-345 doi:10.2340/00015555-2562

Tonel G, Conrad C. (2009). Interplay between keratinocytes and immune cells - Recent insights into psoriasis pathogenesis. Int J Biochem Cell Biol. 41:963-8. doi:10.1016/j.biocel.2008.10.022

Traub S, von Aulock S, Hartung T, Hermann C. (2006). MDP and other muropeptides - direct and synergistic effects on the immune system. J Endotoxin Res. 2006;12(2):69-85. J Endotoxin Res. 12:69-85. doi:10.1179/096805106X89044

Trauner M, Claudel T, Fickert P, Moustafa T, Wagner M. (2010). Bile acids as regulators of hepatic lipid and glucose metabolism. Dig Dis. 28:220-4. doi:10.1159/000282091

Uhl B, Vadlau Y, Zuchtriegel G, Nekolla K, Sharaf K, Gaertner F, et al. (2016). Aged neutrophils contribute to the first line of defense in the acute inflammatory response. . Blood. 128:2327-2337 doi:10.1182/blood-2016-05-718999

Uspenskaya YB. Chronic skin diseases viewed through gastro-intestinal tract pathologies. Effective pharmacotherapy. 2016. 30:34-46. (rus), elib.

Valdimarsson H, Thorleifsdottir RH, Sigurdardottir SL, Gudjonsson JE, Johnston A. (2009). Psoriasis - as an autoimmune disease caused by molecular mimicry. Trends Immunol. 30:494-501. doi:10.1016/j.it.2009.07.008

van den Berg JM1, Weyer S, Weening JJ, Roos D, Kuijpers TW. (2001). Divergent effects of tumor necrosis factor alpha on apoptosis of human neutrophils. J Leukoc Biol. 69:467-73. doi:10.1189/jlb.69.3.467

van de Kerkhof PC, Gerritsen MJ, de Jong EM, (1996). Transition from symptomless to lesional psoriatic skin. Clin Exp Dermatol. 21:325-9. doi:j.1365-2230.1996.tb00115.x

van de Kerkhof P.C.M. (2007). The evolution of the psoriatic lesion. Br J Dermatol. 157:4-15 doi:10.1111/j.1365-2133.2007.07907.x

van Lier D, Geven C, Leijte GP, Pickkers P. (2019). Experimental human endotoxemia as a model of systemic inflammation. Biochimie. 159:99-106. doi:10.1016/j.biochi.2018.06.014

Visser MJE, Kell DB, Pretorius E. (2019). Bacterial Dysbiosis and Translocation in Psoriasis Vulgaris. Front Cell Infect Microbiol. 9:7 doi:10.3389/fcimb.2019.00007

Vissers WH, Arndtz CH, Muys L, Van Erp PE, de Jong EM, van de Kerkhof PC. (2004). Memory effector (CD45RO+) and cytotoxic (CD8+) T cells appear early in the margin zone of spreading psoriatic lesions in contrast to cells expressing natural killer receptors, which appear late. British Journal of Dermatology. 150:852–859. doi:10.1111/j.1365-2133.2004.05863.x.

Vorobjeva NV, Pinegin BV. (2014) Neutrophil extracellular traps: mechanisms of formation and their role in health and disease, Biochemistry (Moscow), 12:286-1296. doi:10.1134/S0006297914120025.

Wang A, Bai Y. (2020). Dendritic cells: The driver of psoriasis. J Dermatol. 47:104-113. doi:10.1111/1346-8138.15184

Wang F, Lee E, Lowes MA, Haider AS, Fuentes-Duculan J, Abello MV, et al. (2006). Prominent Production of IL-20 by CD68+/CD11c+ Myeloid-Derived Cells in Psoriasis: Gene Regulation and Cellular Effects. J Invest Dermatol. 126:1590-9. doi:10.1038/sj.jid.5700310

Wang J, Arase H. (2014). Regulation of immune responses by neutrophils. Ann N Y Acad Sci.1319:66-81. doi:10.1111/nyas.12445

Weatherhead SC, Farr PM, Jamieson D, Hallinan JS, Lloyd JJ, Wipat A, Reynolds NJ (2011). Keratinocyte Apoptosis in Epidermal Remodeling and Clearance of Psoriasis Induced by UV Radiation J Invest Dermatol. 131:1916-26. doi:10.1038/jid.2011.134

Weisenseel P, Laumbacher B, Besgen P, Ludolph-Hauser D, Herzinger T, Roecken M, et al. (2002). Streptococcal infection distinguishes different types of psoriasis. J Med Genet 39:767-768. doi:10.1136/jmg.39.10.767

Weisenseel P, Prinz JC. (2005). Incidental detection of S. pyogenes-DNA in psoriatic skin by PCR. Arch Dermatol Res. 296:573-6. doi:10.1007/s00403-005-0559-7

Weiss DI, Ma F, Merleev AA, Maverakis E, Gilliet M, Balin SJ, et al. (2019). IL-1β Induces the Rapid Secretion of the Antimicrobial Protein IL-26 from Th17 Cells. J Immunol. 203:911-921. doi:10.4049/jimmunol.1900318

Wenk K, Arrington K, Ehrlich A. (2011). Psoriasis and non-alcoholic fatty liver disease. J Eur Acad Dermatol Venereol. 25:383-91. doi:10.1111/j.1468-3083.2010.03841.x

Xu Y, Itzek A, Kreth J (2014). Comparison of genes required for H2O2 resistance in Streptococcus gordonii and Streptococcus sanguinis. Microbiology. 160:2627-2638. doi:10.1099/mic.0.082156-0

Zaba LC, Fuentes-Duculan J, Eungdamrong NJ, Abello MV, Novitskaya I, Pierson KC, et al. (2009). Psoriasis Is Characterized by Accumulation of Immunostimulatory and Th1/Th17 Cell-Polarizing Myeloid Dendritic Cells. J Invest Dermatol. 129:79-88. doi:10.1038/jid.2008.194

Zhang Z, Wang FS. (2005). Plasmacytoid dendritic cells act as the most competent cell type in linking antiviral innate and adaptive immune responses. Cell Mol Immunol. 2:411-7. PMID 16426490

Zhang H, Hou W, Henrot L, Schnebert S, Dumas M, Heusèle C, Yang J. (2015). Modelling epidermis homoeostasis and psoriasis pathogenesis. J R Soc Interface. 12. pii: 20141071. doi:10.1098/rsif.2014.1071

Zilberstein B, Quintanilha AG, Santos MA, Pajecki D, Moura EG, Alves PR, et al. (2007). Digestive tract microbiota in healthy volunteers. Clinics (Sao Paulo). 62:47-54. doi:10.1590/s1807-59322007000100008