IMMUNE ASPECTS OF THE PATHOGENESIS OF VITILIGO

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***Resume*.** Autoimmune (immune) theory, proposed in 1959 by A.Lorincz (Lorincz A.I., 1959), who found autosensitization to their own melanocytes and tyrosinase in patients with vitiligo. At present time the idea of vitiligo as an autoimmune disease is based based on a few basic facts. Vitiligo may show skin-infiltrating cytotoxic T-lymphocytes close proximity to melanocytes (Wijngaard R., 2000), as well as antibodies against melanocytic antigens (Bystrun J.C., 1989), which is direct confirmation of the existence of an autoimmune response. ABOUT the involvement of the immune system in the pathogenesis of vitiligo speaks and changes balance of cytokines that regulate the functions of cells of the immune system.

Keywords: Autoimmune (immune), TNF-a, IL-1, IL-6, IL-8 and indirectly – IFNg.

Finally, in some patients, vitiligo is accompanied by diseases having an autoimmune origin. Research on many patients showed a significant number of cases of combination of vitiligo with thyroid dysfunction and the presence of organ-specific antibodies to thyroid proteins (Schallreuter K.U. et al., 1994). Except In addition, as mentioned above, the expression products of most genes, for which an association with vitiligo has been found, are related to functioning of the immune system.

Another indirect confirmation of the autoimmune nature of vitiligo is an immunosuppressive and immunomodulatory effect of many types of reasonably effective treatments for vitiligo, such as UV radiation, systemic and topical steroids, cytostatics, immunomodulators (Korsunskaya I.M., 2004; Kuzmina T.S. et al., 2005;
Hann S.K. et al., 1997).

Cellular immunity in vitiligo As noted above, at the border of the vitiligo-affected area of the skin infiltrates of T-lymphocytes are detected (in the absence of B-cells) with progressive stage of the disease, even in the absence of a phenotypically severe inflammation, which is rare in vitiligo. Emerging genetic association of vitiligo with the major complex haplotype type I histocompatibility also suggests involvement of a T-cell response in the pathogenesis of vitiligo. At the same time, the ratio of CD4+ and CD8+ T-lymphocytes shifted towards the latter compared to normal skin, which also suggests the presence of a cytotoxic response during the spread of foci depigmentation. On the formation of a pro-inflammatory environment around foci of vitiligo speaks and an increased local level pro-inflammatory cytokines: TNF-a, IL-1, IL-6, IL-8 and indirectly - IFNg, and also elevated serum levels of IL-6 and IL-2 (Yu H.S. et al., 1997). About the direct role of TNF-a in the pathogenesis of vitiligo says the presence of a correlation between the level of TNF-a and the severity of vitiligo (Kim N.H. et al., 2011). The direct role of IFNg in the

pathogenesis of autoimmune component of vitiligo has recently been demonstrated as experimentally (Gregg R.K. et al., 2010) and clinically (Proshutinskaya D.V., 2006). It should be noted, however, that the secretion of some of these cytokines can be carried out by keratinocytes (IL-1, TNFa) and melanocytes (IL-1), the deregulation of which can thereby lead to induction of a local immune response. Proof of the real the existence of a cytotoxic immune response against melanocytes serves as a demonstration of the cytotoxic activity of T cells isolated from areas of the border of active lesions, which, as well as according to the results
analysis of biopsy specimens were characterized by a shift in the balance towards CD8+ cells and secretion of predominantly type 1 cytokines, stimulating a cellular immune response. The main antigen in T- cellular cytotoxicity, a melanocytic marker was identified MART-1, as well as T-cells reactive with tyrosinase and
gplOO (Proshutinskaya D.V. et al., 2008).

The development of a local immune response against melanocytes requires migration of lymphocytes in the skin, which is determined by the expression on CLA molecules (antigen of skin lymphocytes) in lymphocytes. Really, T-lymphocytes infiltrating the skin are characterized by increased CLA expression. In addition, melanocytes can release a large the amount of Hsp70 chaperone protein in response to stress, the thereby contributing to the induction of the immune response (Kroll T.M. et al., 2005). Role Hsp70 in the induction of an immune response against melanocytes was demonstrated experimentally: Hsp70 vaccination in conjunction with melanocyte antigens led to more pronounced manifestations vitiligo in mice, suggesting a role for Hsp70 in antigen internalization dendritic cells (Denman C.J. et al., 2008). This mechanism can explain the initiation of vitiligo through an autoimmune pathway at sites of injury and etc. (Köbner phenomenon).

Normally, immunoreactivity with autoantigens is controlled regulatory T cells (Treg). Recent studies have shown that, despite the lack of differences in the population of patients with vitiligo and healthy Treg donors in the blood, the number of regulatory T cells significantly reduced in all skin of vitiligo patients compared to control group. This fact suggests that the deficit regulatory T cells in the skin due to defects in their migration is cause of an autoimmune reaction. A possible mechanism for this defect is a reduced expression of the chemokine CCL22 in the skin of patients with vitiligo involved in the migration of regulatory T cells (Klarquist J. et al., 2010). It should be noted that the secretion of CCL22 in the skin is carried out dendritic (Vestergaard C. Et al., 1999) and endothelial (Rottman J.B. et al., 2001) cells, as well as keratinocytes. At the same time, the secretion of CCL22
keratinocytes is induced by type 1 cytokines (IFNg and TNFa) (Rottman J.B. et al., 2001; Albanesi C et al., 2001). Thus, it is possible suggest that in patients with vitiligo, keratinocytes, which, as known, are characterized by certain anomalies, may be are defective in CCL22 secretion and/or its induction by type 1 cytokines, which
leads to a deficiency of regulatory T cells and contributes to the development autoimmune reaction.

Thus, the available data unequivocally indicate that T- cellular cytotoxicity plays an essential role in active vitiligo. The main cause of the development of an autoimmune response is considered to be a violation balance between populations of THI (T-helper cells 1), producing type 1 cytokines, and Tp2 cells (T-helper cells 2) and Treg. Besides, can play a certain role in this process even relatively recently
open T-helper cells 17 (THI 7), characterized by the production interleukin-17. In the study of biopsy specimens and blood sera of the skin patients with vitiligo were found to have elevated levels of IL-17 compared with the control group, as well as a positive correlation between the level of IL-17 and the duration of the disease and the area affected skin (Bassiouny D.A., Shaker O., 2011). In line with these data, Th17 cells were detected at the border of the affected areas and elevated IL-17A transcript (Wang C.Q. et al., 2011).

The data obtained indicate that not only T1, but also T17 cells may play an important role in the pathogenesis of vitiligo, similar to their role in pathogenesis of other autoimmune diseases.

In addition to T cells, CD68 has also been found in vitiligo lesions. immunopositive macrophages. The content of macrophages is especially high in skin at the border of vitiligo lesions. Macrophage markers expressed by Langerhans cells and melanocytes. Maybe, macrophages are used to eliminate melanocytes in which
cytotoxic T-lymphocytes stimulated apoptosis (Wijngaard R., 2000).

With vitiligo, changes in Langerhans cells were also found. Noticeable a decrease in the pool of Langerhans cells was found in the epidermis of patients non-segmental form of vitiligo with disease progression (Wijngaard R., 2000). The authors propose two possible mechanisms of depletion of Langerhans cells during progression diseases. First, Langerhans cells are destroyed by cytotoxic factors released during the destruction of melanocytes in the active phase vitiligo. Second, Langerhans cells leave the epidermis and migrate to regional lymph nodes for presentation of antigens secreted during the destruction of melanocytes. Since different types repigmentation therapy leads to a decrease in the number of cells Langerhans in the epidermis suggest that a decrease in the number of cells Langerhans helps repigmentation (Kao S.N., Yu H.S., 1990). However, in other studies have shown an increase in the number of Langerhans cells in lesions of vitiligo, especially at the stage of repigmentation (Montes L.F. et al., 2003).

Humoral immunity in vitiligo

One of the evidence of changes in the immune status and possible participation of the immune system in the pathogenesis of vitiligo is the presence antibodies against melanocytes in the blood serum of patients with vitiligo andtheir absence in the blood of healthy donors (Naughton G.K. et al., 1983). At In this case, the presence of antibodies is usually more frequently observed in patients with vitiligo in an advanced stage, as well as with a more pronounced skin lesions. Reactivity with melanocytic antigens in various studies ranged from 30 to 100% in patients with vitiligo compared to 0-62% in healthy donors. Antigen analysis showed that among them there are proteins specific for melanocytes: components of melanin synthesis, tyrosinase and tyrosinase associated

proteins (TRP1 and TRP2), melanosome matrix protein gplOO, melanin- concentrating hormone MCHR1, etc. (Li Q. et al., 2011).

The cause of the appearance of autoreactive antibodies may be deregulation of the B- and T-cell network, as well as the induction of an immune response when death of melanocytes. Direct involvement of anti-melanocytic antibodies in pathogenesis of vitiligo is confirmed by their ability to cause complement-mediated death of melanocytes and antibody-dependent cellular cytotoxicity. Further research showed that these antibodies belong to IgG (Bystrun J.C., 1989).

Another possible mechanism of pathogenesis may be a change adhesive properties of melanocytes with their subsequent death due to loss contacts with the extracellular matrix, which is suggested by the obtained results on the ability of the sera of 9 out of 13 patients with vitiligo to cause detachment of melanocytes in reconstructed epithelium in vitro.

In general, the role of humoral immunity in the pathogenesis of vitiligo remains unclear, and the current concept suggests that most anti-melanocyte antibodies are not the root cause of vitiligo, but their appearance is secondary, although it may contribute to the further development diseases. However, according to many authors, the content and level antibodies to melanocytes correlates with the activity of the disease, the degree depigmentation and the presence of other autoimmune diseases (Naughton G.K., 1986; Harning R., 1991; Cui J., 1993). The level of autoantibodies decreases in vitiligo patients responding positively to PUVA therapy or after systemic administration of steroids (Moellmann G., 1982; Park Y.K., 1996).

Innate immunity in vitiligo

The role of the innate branch of the immune system in the pathogenesis of vitiligo has been only recently suggested. The innate immune system, apart from

direct defense against pathogens, plays an essential role in regulation and acquired immunity. On the possible involvement of congenital immune system says the detected association of vitiligo with allelic variants of the NALP1 gene, which is a component inflamasome - a cytosolic complex of proteins involved in the transmission signals from the receptors of the innate immune system (Jin Y. et al., 2007).

Activation of the inflamasome leads to the secretion of pro-inflamatory cytokines IL-15 and IL-18, activating a local immune response, as well as can cause direct apoptotic cell death. Except in addition, systemic changes in the cell population have been described in vitiligo immune system, suggesting the possible involvement of NK cells in pathogenesis of vitiligo (Basak P.Y. et al., 2008). Although there are clear prerequisites and grounds for the study of the role of the components of congenital immune system in the pathogenesis of vitiligo, its actual role in this process remains unclear.

Thus, the important role of immune changes in vitiligo recognized by almost all researchers, but the data they receive are often controversial, and exposure-based therapies on various links of immunological reactions, is far from perfect.

It is necessary to conduct further study of the immunopathogenesis of vitiligo and the search for new effective drugs

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