# CHRONIC PRURITUS IN ATOPIC DERMATITIS

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**ABSTRACT** Atopic dermatitis (AD) is an inflammatory skin disease which characterized by chronic recidive skin rash and accompanied by complaints of pruritus. Chronic pruritus is reported to occur in 87-100% of AD patients and often affecting patient's quality of life. Management of chronic pruritus with antihistamines in AD is often ineffective, thus different pruritogens are considered to undergone the histamine-independent itch pathway.

**KEYWORDS** Chronic pruritus, atopic dermatitis, histamine-dependent, histamine-independent pathway

## Background

Pruritus or itching defined as an unpleasant sensation that leads to a scratching reflex.[1],[2] Pruritus is categorized as acute pruritus and chronic pruritus.[2] When the itch last anywhere from instant to 6 weeks, it is termed as acute pruritus.[3] Acute pruritus of the skin is often triggered locally by pruritogens, and the execution of scratching behaviour is said to have a protective role by removing the irritants.[2] While acute pruritus lasts less than six weeks, an itch that remains present after more than six weeks is termed chronic pruritus.[1–3] The prevalence of chronic pruritus is reported to range from 8.4-13.9% of human population.[4] Atopic dermatitis (AD), a skin disease with chronic pruritus complaints,[1],[3],[4] with the prevalence of chronic pruritus was reported in the range of 87-100%.[4] Chronic pruritus could be maladaptive and causes significant decreased in patient's quality of life, as it leads to sleep disturbances, attention deficit, unattractive feelings, stigmatization, stress, and depression.[1],[5],[6]

AD is an inflammatory skin disease, characterized by a chronic recidive skin rash. The complex pathogenesis of AD involves predisposing genetic factors and external triggering factors (environmental and psychological).[7] Itch is the initial symptoms of AD that causes scratching reactions. Scratching process will stimulate the inflammatory reaction which in turn aggravates itch and leads to itch-scratch cycles.[5] Several studies had examined the physiological process of pruritus in AD and revealed that it involves genetic abnormalities, immunological dysfunction, or defect of the skin barrier function.[4],[5]


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## Genetic and pruritus in AD

Genes associated with the epidermal barrier and enzymes affiliated to homeostasis maintenance are widely linked to the pathogenesis of AD. Mutation of Filaggrin gene (FLG) is found in 10%-50% of patients.[8] FLG or filament protein aggregation is a structural protein which supports epidermal structure and function through the formation of the outer epidermal barrier by aggregation of intermediate filaments.[9],[10] FLG is essential in maintaining epidermal homeostasis. Therefore impairment of FLG function is considered an AD predisposing factor.[4],[8] Mutations of FLG genes and SPINK5 genes (kazal-type five serine protease inhibitors) are also associated with impaired epidermal differentiation and skin barrier formation.[7]

Nattkemper et al (2017) reported that an increased in transcription of the substance P (SP) neuropeptide gene and neurokinin receptor (NK-1R), increased expression of several genes such as phospholipase A2 IVD, SP, Nav1.7, transient receptor potential vanilloid 1 (TRPV1), TRPV2, transient receptor potential ankyrin 1 (TRPA1), protease-activated receptor 2 (PAR2), PAR4 and increased cytokines such as interleukin (IL) -17A, IL-23A, and IL-31 were found in patients with AD.[11]

## Skin barrier dysfunction and pruritus in AD

Skin functions as a barrier mantle that protects the body from external hazards such as microbes and toxic materials. The epidermis consists of 4 main layers namely the stratum corneum (horny layer), stratum granulosum (granular layer), stratum spinosum, and stratum basale. Stratum corneum is the outermost layer

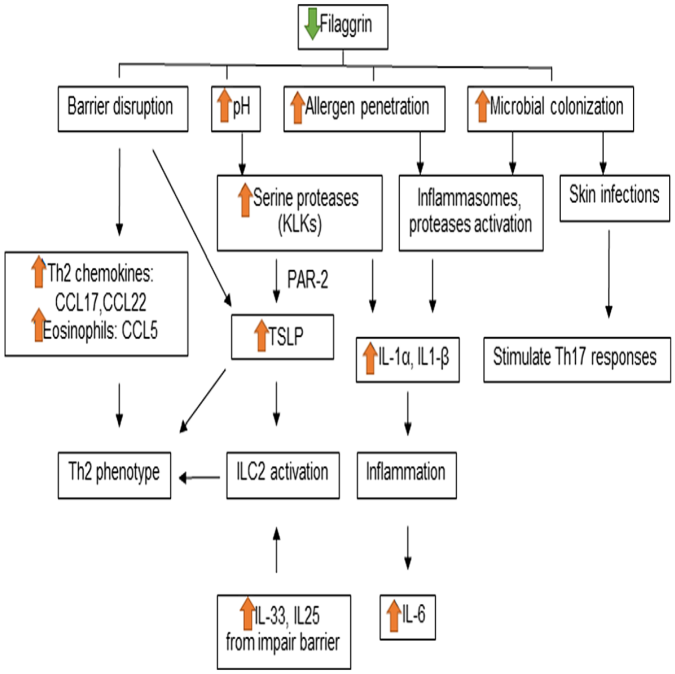


**Fig.1.** The role of filaggrin in the development of AD.[10]

of the epidermis which is assembled from unnucleated corneocytes and intercellular (brick and mortar) lipids.[4],[10] These cells are bound together by the tight junction (TJ) which restrict the circulation of pathogens and large molecules through the skin.[12] Tight junction is composed of transmembrane proteins which are essential in maintaining the adhesion of keratinocytes and constructing a second physical barrier below the stratum corneum.[13] Tight junction consists of claudins and occludins which are responsible for regulating paracellular transport of water and dissolved materials.[10],[13] Zonula occludens are the principal cytosolic accountable for the TJ arrangement.[10]

Skin barrier disruption in AD patients is mainly characterized by a disturbance of the skin's microenvironment, derangement of filaggrin and claudin, and disruption of lipid synthesis.[8],[13] Any disorders of the skin barrier may cause an increase in transepidermal water loss (TEWL) which facilitates the penetration of allergens, initiation of allergic sensitization, and exacerbation of inflammation in AD.[4],[8] Increased TEWL leads to an increase in pH which stimulates the activation of serine proteases such as the stratum corneum chymotryptic enzyme (SCCE). Protease is known to be a pruritogen in AD.[4] Disruption of the skin barrier might as well causes an increase in IL-1 from keratinocytes, thus activates endothelial vascular to induce the expression of adhesion molecules, causing inflammation of the skin.[8] Dysregulation of the skin homeostasis promotes direct and indirect stimulation of nerve endings sensory and induces pruritus.[4] The role of filaggrin in the development of AD can be seen in figure 1.

## The mechanism of pruritus in AD

Pruritus generally mediated by a number of cytokines released by keratinocytes in regards to elevated pH and increased protease activity including thymic stromal lymphopoietin (TSLP), IL-4, IL-13 and IL-3.[14] Keratinocytes are cells that are actively involved in complex interactions with structural proteins (e.g. keratin, filaggrin), enzymes (e.g. proteases), lipids, and antimicrobial peptides (e.g. defensins).[4] The mechanism of pruritus in AD are intricate and not fully understood.[14] During the pruritus progression, keratinocytes will release pruritogenic molecules (e.g. opioids, protease, SP, nerve growth factor, neurotrophin 4, endocannabinoids) and express various receptors involved in itchy sensations, such as PAR2, TRPV, tyrosine kinase receptor A (TrkA), TrkB, cannabinoid 1 receptor, IL-31 receptor, and $\mu$ and k opioid receptors. Keratinocytes also have voltage-gated adenosine triphosphate (ATP) channels and adenosine receptors.[4] Furthermore, keratinocytes secrete neurotransmitters of acetylcholine (ACH) which directly activate sensory nerves or indirectly affect them by lowering the activation threshold of other stimuli.[4] It can be concluded that keratinocytes act as itch receptors in which they play a role as initiators of the itching sensation and as well responsible for itch signal communication in the skin sensory nerves.[4] Pruritic sensation occurred from the activity of special itch nerve fibres found in the dermal-epidermal junction, that extend to the stratum granulosum and other epidermal cells including keratinocytes on the free nerve endings of the skin.

Pruritus sensation is then transmitted to the brain via waves and electrical impulses passing through the peripheral nerves, where the brain obtains information and stimulates bodily reactions.[15] Also, cutaneous hyperinnervation is involved in itch sensation at the periphery.[4],[16] In AD, the density of epidermal nerve fibres is higher compared to that in healthy skin. Epidermal hyperinnervation is mainly generated by imbalance state between nerve elongation factors, including nerve growth factor (NGF), and nerve repulsion factors such as semaphorin 3A (Sema3A) which are produced by keratinocytes.[16]

Pruritic transmission possibly conducted through two pathways, namely the histamine pathway (histamine-dependent) and non-histamine (histamine-independent) pathway.[4],[17] Both mechanisms have their respective receptors and skin nerve fibres that connected to the central nervous system (CNS).[6]

Signal activation on the peripheral nerve endings in dorsal root ganglion (DRG) neurons are then transmitted to the brain via anterolateral spinothalamic tract (STT) quadrant located in the spinal cord. Itch signals went through histamine and non-histamine pathways via the STT.[4] The mechanism of pruritus involves many receptors and ligands.[4],[15] Most pruritic receptors are members of the G protein-coupled receptors (GPCR) superfamily.[4] The itch receptors reside in sensory nerve endings located in the epidermal-dermal connection mainly involve histamine, serotonin/5-HT, SP, and prostaglandins.[18] Schematic illustration of the pruritus mechanism can be seen in figure 2.[19]

Figure 2. Schema illustration of pruritus pathway.[19] (a) Polymodal C-fibers is activated in the epidermis by cowhage, the non-histaminergic pruritogen. Box A: cowhage releases mucunin which activates PAR2 in the peripheral terminal. PAR2 activation activates phospholipase C (PLC) and will sensitize TRPV1 and TRPA1 channels. PAR2 leads to membrane depolarization by inhibiting the voltage K+ channel. (b) Histamine is released by mast cell activating CMI and releasing calcitonin gene-related peptide (CGRP). H1 Receptor activates PLC and phospholipase A (PLA), which leads to sensitization of TRPV1. The chloroquine receptor Mgrp3 is present in histamine responsive fibres. The bradykinin receptors (B1, B2) are also expressed on histamine responsive DRG. (c) Both non-histaminergic C-polymodal fibres and CMI fibres terminate centrally in the dorsal horn of the spinal cord. Polymodal C-fibres and CMI fibres release excitatory neurotransmitters and peptide neurotransmit-

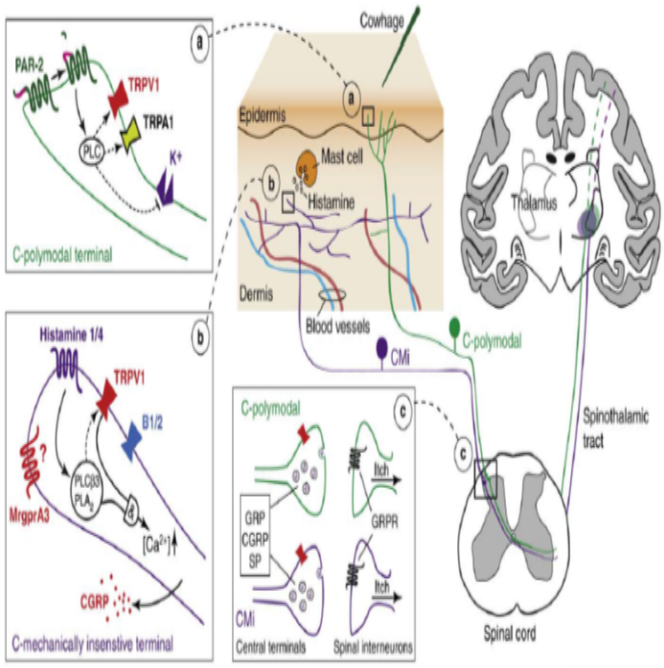


**Fig.2.** The mechanism of Pruritus in AD.

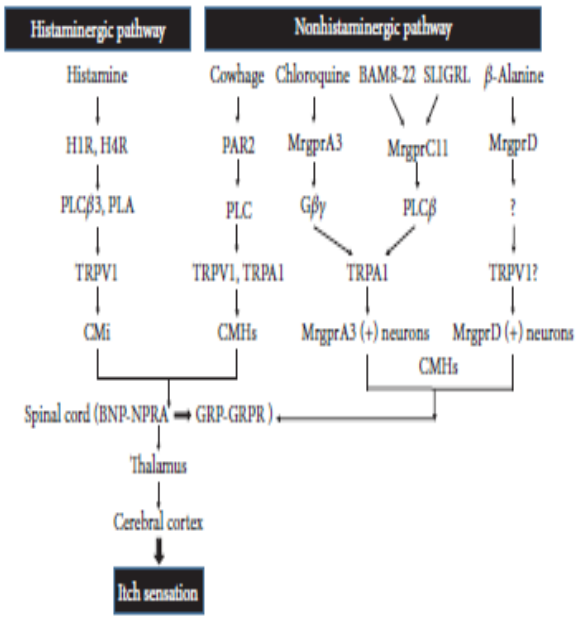


**Fig.3.** Schematic illustration of pruritic signalling pathway.[18]

ters such as SP, CGRP, and the gastrin-releasing peptide (GRP). The central terminal of primary afferent neurons forms synapses with spinal interneurons that express the GRP receptor, GPR.

### Histamine-dependent signalling pathway

Currently, there are four histamine receptors (H1R, H2R, H3R, H4R) known.[18],[20] Among these receptors, H1R and H4R are expressed in itch-sensing DRG neurons and accentuate histamine induced-itch.[20] H1R is expressed in DRG, while H4R is expressed mainly on mast cell, dendritic cell and eosinophils cell.[21] Histamine signalling pathways are provoked by the group of mechanically insensitive C-type fibres (CMi). Following stimulation by itch mediators, CMi conveys signals to the dorsal horn of spinal cord, continued to the spinal cord to the lamina nuclei of the thalamus, and the cerebral cortex (somatosensory area), eventually produce itch sensation.[18] Neuronal activation of histamine-dependent pathway requires the presence of TRPV1 and TRPV4.[20]

Histamine has been the most studied itch mediator, and the use of antihistamine drugs is considered as the first choice in treating pruritus.[1] Several recent studies have shown that antihistamine drugs do not significantly improve pruritus condition. Therefore hypotheses arise that different pruritogens are thought to play a role through the histamine-independent itch pathway.[2],[22] The pathogenesis of chronic pruritus is presumed to be induced by a non-histamine (histamine-independent) pathway.[4]

### Histamine-independent signalling pathway

Data from conducted studies shown that histamine levels in skin lesions of AD patients are not different compared to healthy controls, thus supporting the possible role of non-histamine pathways.[4] Non-histamine signalling pathways are mediated by the class of mechanically sensitive C-type fibres (CMHs) whose nerve ending mainly distributed in the epidermis. Itch signals are transferred to the CNS via CMHs.[18] CMHs can be stimulated by tropical leguminous plant-cowhage, which induces strong itch sensation. Cowhage also possesses active component, the 36 KD cysteine protease, called mucunain that able to stimulate PAR2 and PAR4. [18]

Afferent neurons encompass another neuronal receptor-like TRPA1, PAR2, endothelial 1, TSLP and serotonin receptors which take part in the non-histamine pathway.[6] Present study suggest that transient receptor potential (TRP) cation channel is the downstream target of the itch signalling pathway, and PAR2.[18] Other studies activate this component have found that histamine-independent itch pathway is mediated by related GCPR such as Mas-related G protein-coupled receptor (Mrgprs), PAR2, and transient receptor potential channels (figure 3).[16],[18],[23]

### Mas-related G protein-coupled receptor (Mrgpr)

Mrgpr is a family of GCPR which is expressed in nociceptive nerve fibres. Mrgpr can attach pruritogens in the peripheral nervous system,[24],[25] and mediate non-histamine itching.[24–26] MrgprA3, MrgprC11, and MrgprD in mice and MrgprX1, MrgprX2, and MrgprD in humans, expressed in small-diameter sensory neurons in DRG and trigeminal ganglia, and is thought to be involved in the transmission of itch.[27] MrgprA3 and MRGPRX1 are known to be responsive towards chloroquine and initiate scratching reactions in rats induced by chloroquine. MrgprC11 is activated by SLIGRL and SLIGKV, ligand peptides in mice, and PAR2 in humans.[26] Pruritogen-sensing GPCR, MrgprA3 and MrgC11 ligands-associated itch widely known to be TRPA1 mediated.[28]

### Protease-Activated Receptor (PAR)

PAR is a family of GCPR which can be activated by the proteolytic cleavage of their own extracellular N terminus.[4] PAR is expressed by various immune cells namely neutrophils, eosinophils, monocytes, macrophages, and mast cells.[29] PAR

is beneficial in maintaining skin barrier homeostasis, processing inflammation, itching, and pain on the skin. PAR consists of 4 members termed PAR1-4.[28] Increased PAR 2 expression in keratinocytes is noticed in the skin with and without lesion where the highest expression level is found in AD skin lesions.[4],[13]

Activation of PAR2 and PAR4 by endogenous and exogenous proteases might induce non-histaminergic itch.[4],[18] PAR2 and PAR4 are expressed in numerous cell types, including keratinocytes and pruriceptive neurons in DRG mutation.[4] Mutation of the SPINK5 gene leads to increased regulation of KLK5 activity involved in the formation of AD lesions through PAR2.[29]

Various endogenous and exogenous proteases take parts in the mechanism of pruritus in PAR2.[4] Tryptase is an endogenous agonist PAR2, of which the expression increased significantly in AD.[4] Exogenous proteins include those originate from allergens such as dust mites, cockroaches, and Staphylococcus aureus.[13] When PAR2 agonist is injected into the skin, the prolonged itch is observed in AD patients.[4] Activation of PAR2 in keratinocytes induces the release of LTB4, which promotes itching through neurons expressing BLT1. Research showed PAR2 plays an important role in keratinocyte TSLP production and the correlation between PAR2 activity and TSLP expression in the skin of AD patients and a mouse model of atopic disease is established.[2] Activation of PAR2 in keratinocytes will induce the release of TSLP and will eventually stimulate TRPA sensory neurons.[29]

### Transient Receptor Potential (TRP) Chanel

TRP channels are nonselective calcium-permeable cation channels that compose the TRP ion channel superfamily.[30] TRP composed of a membrane protein that transmits positive ions across cell membrane.[4] TRP is widely distributed in almost all human bodies including the epidermis (epidermal keratinocytes),[6],[31] CNS and peripheral, endothelial and smooth muscles in blood vessels, inflammatory cells in the skin and intestine.[31] TRP receptors are capable of direct neuronal signals mediation through depolarization along afferent neurons towards CNS, which resulted in the perception of itch, pain, tingling, and burning. The depolarization involves calcium ion influx to the neuronal cells.[32] TRP subfamilies such as TRPV1, TRPV3, TRPV4, TRPA1, Transient Receptor subfamily M (TRPM), and serotonin receptors play an essential role as pruritogenic pathways in AD.[28]

### Transient Receptor Potential Vanilloid 1 (TRPV1) channel

TRPV1 is located in keratinocytes, free nociceptive sensory nerve endings in the epidermis and dermis, inflammatory cells such as mast cells, Langerhans cells, fibroblast cells, endothelial cells, sebocytes in follicular appendages, spinal nerve DRG, and in CNS.31 TRPV1 receptors are exposed to menacing stimuli from the environment such as heat, chemicals, pain, and itch.[6] Hyperactivity of TRPV1 contributes to the condition of sensitive skin, such as dry skin, or the changes in neurovascular responses.[31] Activation of TRPV1 is involved in itching mediated through histamine pathways.[4] Histamine 1 (H1) may interact with TRPV1and transmits neuronal itching signals to CNS.[6]

Depolarization signals happen through the entry of calcium cations. Afferent neurons have TRPV1 receptors on their free nerve endings that could be activated by SP, local Nitric oxide (NO), and DRG neurons.[6] Activation of TRPV1 may as well causes secretion of SP in DRG neurons.

SP is known as a potent neurotransmitter signal that can stimulate the initiation of the glutamate pathway and together with the entry of calcium through the N methyl-D-aspartate (NMDA) receptor, cause an itchy sensation.6,31 SP also causes inflammatory response on local tissue via some mediators and cytokines (i.e. IL-1, IL-2, IL-4, IL-13, IL-31) which lead to the development pruritus.[6],[31] In addition to SP, pruritogens such as Calcitonin Gene-Related Peptide (CGRP) and tachykinin are also produced.[31] Persistent activation of TRPV1 causes neurogenic inflammatory cascade with the release of inflammatory mediators namely interleukin-1 (IL-1), IL-8, prostaglandin E2 (PEG2), transforming growth factors $\beta$2 (TGFb2) and matrix metalloproteinases 1 (MMP1).[31]

### Transient Receptor Potential Vanilloid 3 (TRPV3) channel

TRPV3, found on the surface of keratinocytes, can be activated by heat with the release of vasoactive nitric oxide (NO) from keratinocytes, which are independent of the enzymatic pathway NO synthetase.[28],[31] Gain-of-function mutation, TRPV3Gly573Ser, causes hair loss, complaints itching, and AD-like lesions.[28],[32],[33] TRPV3 also activates keratinocytes to secrete PGE2 mediators. NO, and PGE2, cause neuronal activation in addition to vasodilation.[28] Excessive activity of TRPV3 will cause the unleash of epidermal protease Epidermal Growth Factor Release (EGFR) ligand namely TGF-$\alpha$. (30) TRPV3 additionally causes activation of transglutaminase in keratinocytes which create defects in the release of skin barriers.[31],[34]

### Transient Receptor Potential Vanilloid 4 (TRPV4) channel

TRPV4 is widely expressed on keratinocytes and is thought to play a role in epidermal barrier homeostasis, based on the observation that TRPV4 activation will increase intracellular calcium in keratinocytes and will trigger ERK phosphorylation.[30],[35] Researchers revealed that TRPV4 affects the perception of itching. The role of TRPV4 on histamine and non-histamine pathways seemed to be facilitated by TRPV1.[36] Recent studies reported that TRPV4 is involved in serotonin-induced itch.[30],[37] Experts attempt to find the correlation between serotonin and TRPV4. They found out that 90% of sensory neurons that respond to serotonin also express TRPV4. Studies concluded that at least two serotonin mechanisms mediate itching: TRPA1 dependent pathways and pathways that depend on TRPV4.[35]

### Transient Receptor Potential Ankyrin 1 (TRPA1) channel

TRPA1 and TRPV1 take parts in epidermal repair, homeostasis, and pro-inflammatory activity.[28] TRPA1 is present in keratinocytes, sensory nociceptive nerves, melanocytes, fibroblasts, and some inflammatory cells, especially in mast cells.[4],[31] It can be activated by heat and mechanical stimulation.[30] TRPA1 plays a role in several sensory transmissions such as cold, pain and pruritus, and also in neurogenic inflammation.[4],[31] TRPA1 has direct activity and conducts nociceptive signal transmission activity via neuronal depolarization due to the calcium entry. Coupled receptors: MrgprA3 and MrgprC11 ligands cause mediated non-histamine pathway with the help of TRPA1.[17],[28],[31],[36]

TRPA1 expression in the dermal sensory nerve, mast cells, and epidermis was found to be elevated in skin lesion biopsy of AD patients compared to healthy controls.[4]

The role of TRPA1 pathophysiology in AD is still unknown. Contradicting facts obtained, where activation of TRPA1 plays a role in itch transmission, whereas the administration of TRPA1 agonists in experimental animals is found to accelerate skin barrier repairment. The administration of TRPA1 antagonists in animals showed inhibition of skin barrier restoration in AD, therefore researchers should consider the impact balance of drug agonists and antagonists in the development of chronic pruritus therapy in AD.[4] Endogenous pruritogen also produce scratching behaviour through TRPA1, for instance, the TSLP produced by keratinocytes will activate TRPA in the downstream TSLP receptor. TRPA1 is regulated in sensory neurons and administration of TRPA1 antagonists can reduce itching in transgenic AD models with excessive expression of IL-13.[36]

In mice subjects, activation of TRPA1 and 5-Hydroxytryptamine 7 (HTR7) receptors is needed for AD to occur.[27] Activation of HTR7 receptors triggers serotonin activation which will cause the opening of the TRPA1 channel and induces itching.[17],[27],[30] HTR7 and TRPA1 distributed to the central nervous system, including the brain, and functionally pairs in causing an itch reaction.[28]

### Transient Receptor Potential subfamily M member 8 (TRPM8) channel

TRPM8 is a calcium-regulating channel that is sensitive to temperature, found in the sensory nerves of the skin, mast cells, and epidermal keratinocytes. It is expressed in both A-delta fibres and C fibres .[38] TRPM8 is activated by menthol, eucalyptol, and icillin, where activation of TRPM8 allow intracellular calcium ion entry and the occurrence of cold sensation.[4] TRPM8 is also involved in maintaining epidermal barrier and homeostasis.[4],[32] Supporting evidence showed that when topical menthol was administered, the repair of skin barrier damage due to mechanical injury in mice is accelerated.[4] In AD patients, cooling abolished spontaneous and histamine-induced itch.[39]

## Conclusion

The mechanism of pruritus in AD is complex and not fully understood yet. It involves genetic abnormalities, immunological dysfunction, or defect of skin barrier function. In pruritus process, keratinocytes will release pruritogenic molecules, express various receptors involved in itch sensations, and act as initiators of the itching sensation and responsible for itching signal communication in the sensory nerves of the skin. Pruritic sensation originated from the activity of special itch nerve fibres in the dermal-epidermal junction which transmitted to the brain via waves and electrical impulses, then passed through the peripheral nerves where the brain receives information and induces bodily reactions. Pruritic transmission conducted through two pathways; the histamine pathway (histamine-dependent) and non-histamine (histamine-independent) pathway. In AD management, antihistamine drugs do not significantly improve pruritus condition thus suggesting chronic pruritus possibly induced by a non-histamine (histamine-independent) pathway.

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