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Review Article

Tight Junction's role in atopic dermatitis

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Abstract The pathophysiology of atopic dermatitis (AD) is complex and multifactorial, primarily involving barrier dysfunction. Tight junctions (TJs) are intercellular junctions that are important for establishing the epithelial barrier and maintaining its polarity. Tight junctions have an essential role in the development and function of the stratum corneum, indicating that diseases with TJ dysfunction will cause a disruption on the stratum corneum homeostasis. Atopic dermatitis is a skin disorder that affects 20% of the human population. The complex interactions between damaged skin barrier, skin inflammation, and itching contribute to the development, progression, and duration of AD. Elevated epicutaneous sensitization and skin sensitivity to exogenous stimuli are both caused by skin barrier dysfunction. Desmosomes and TJs hold a complex matrix of structural proteins and lipids that make up the skin barrier together. These aspects form the foundation of barrier disruption in AD. The discovery of the TJ protein Claudin-1 plays a key role in human epidermal tissue and keratinocyte proliferation. Barrier disruption in patients with AD is not only confined to the stratum corneum but also to the TJs, and regulation of these barriers may provide opportunities for new therapies in people with AD or other atopic diseases.

Key words
Atopic dermatitis; Tight Junction; Claudin-1; Human and health.

Introduction

Atopic dermatitis is characterized by disruption of the skin's protective barrier, chronic inflammation, and severe itching. Atopic dermatitis affected almost one-fifth of the developing country's population and is thought to afflict up to 20% of children.[1,2] The number of AD cases in the Dermatology and Venereology Outpatient Clinic Dr. Soetomo General Academic Hospital was dominated by boys and the most prevalent age group was 5-14 years according to a study.[3] Atopic dermatitis has a complex and multi-factorial pathophysiology, primarily involving barrier disruption, IgE-mediated hypersensitivity, cell-mediated alteration of the immune response, and external factors.[4]

Tight junctions are intercellular junctions that are important for establishing the epithelial barrier and maintaining its polarity.[5] Claudins are cell adhesion molecules located at TJs between cells in the epithelial.[6] However, recent findings have revealed independent aspects of claudin on TJ structure and function, as well as junctional adhesion molecules, membrane lipids, phase separation of the zonula occludens family of scaffold proteins, and mechanical strength have been proposed to be the key role in TJ structure and function.[5]

It has been reported that pathogen infiltration into the epidermis elevate the TJ function through toll-like receptor signaling. This suggests that effectively controlled TJs have a

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very important role to prevent further pathogen invasion and maintain skin barrier homeostasis and the function of TJs alters in response to the environmental factors. Thus, TJs have an essential role in the development and function of the stratum corneum, indicating that diseases with TJ dysfunction will cause a disruption on the stratum corneum homeostasis. People with psoriasis and AD have abnormal distribution of claudin-1, which may cause the stratum corneum barrier more susceptible.[7]

Review

Atopic dermatitis is a skin disorder that affects 20% of the human population.[8] Atopic dermatitis is usually characterized by a dry skin rash accompanied by intense itching. The occurrence, progression, and duration of AD are influenced by the complex interactions between skin barrier failure, skin inflammation, and itching.[9]

Atopic dermatitis affects up to 20% of children in the United States, North and Western Europe, Australia, Japan, urban Africa, and other developed nations, making it a serious global health concern.[2,10] Atopic dermatitis was originally considered an early childhood disease (children <7 years old), but recent data suggests that AD affects 7–10% of adults. Approximately 230 million individuals worldwide suffer from AD with annual period prevalence of 3.5% worldwide according to Global Health Data Exchange by the World Health Organization, and AD is the biggest contributor to the non-fatal disease burden among skin diseases.[11]

Genetics alone cannot explain the rising prevalence of AD worldwide because its etiology is multifactorial which may involve interactions between genetics, immune and environmental factors. It is fundamental to understand these deeply interconnected factors in order to develop focused strategies to reduce the occurrence of this disease.[12]

Three key aspects, including damage of the barrier, allergy, and pruritus, are responsible for the pathogenesis of AD. Through their complex interactions, these factors make a positive feedback loop. Intrinsic barrier disruption can become more severe when external factors such as soaps and detergents worsen the breakdown of the epidermal barrier, and then the irritant or allergen interacts with the immune system and causes inflammation of the skin.[13]

Skin barrier disruption causes skin to be more susceptible to external stimuli that leads to epicutaneous sensitization. This inflammation reduces the expression of filaggrin (FLG) in keratinocytes and aggravates epidermal barrier impairment.[4] Structural alterations in the FLG gene as well as decreased expression of FLG have been found in both pathologically altered and intact skin of AD patients. The dose-dependent alterations in the function of the epidermal permeability barrier appear to be predicted in advance by this alterations.[14] The T helper type 2 (Th2) cytokines including interleukin (IL)-4 and IL-13 regulate filaggrin cleavage, which is linked to increased levels of total IgE, increased sensitization, and a progression of more severe AD.[15] Furthermore, the etiology of itching in AD is caused by interaction between keratinocytes, the immune system, and non-histaminergic sensory neurons. Decreases in total ceramide levels and changes in ceramide structure happen under these conditions. It has also been shown that AD patients exhibit down regulation of markers associated to epidermal differentiation, including FLG, loricrin (LOR), and involucrin (IVL). Due to this abnormality, the normal barrier function cannot work effectively, resulting in elevated transepidermal water loss (TEWL) and reduced SC hydration in AD patients.[9]

Skin barrier disruption and aberrant immune reactions from Th2/Th22 are the underlying disorders in AD. Filaggrin genetic mutations cause dehydration and damage the barrier, allowing allergens to penetrate the skin barrier. The epidermis with a disrupted barrier releases abundant thymic stromal lymphopoietin (TSLP), which stimulate a Th2/Th22 immune response. When the disease progresses from acute to chronic AD or from childhood to adulthood, there is further enhancement of the Th2/Th22 deviation. Additionally, Th1 cells take role in the chronic stage of AD rather than Th17 cells. B cells are stimulated by IL-4 and IL-13 to generate IgE antibodies against allergens as well as some self-antigens. IgE autoreactivity also has a part in the development of the disease. Additionally, powerful suppressors of FLG expression are IL-4, IL-13, and IL-22. The TSLP and IL-31 produced by Th2 cause pruritus, and continuous scratching aggravates the damage of the epidermal barrier. The calcium influx needed for TSLP release from keratinocytes is controlled by the ORAI calcium release-activated calcium modulator 1 (ORAI1) channel. The TSLP/Th2/Th22 and ORAI1 pathways can both be targeted in order to reduce atopic inflammation **(Figure 1)**.[8]

Desmosomes and TJs bind a complex matrix of structural proteins and lipids that make up the skin barrier. Barrier disruption in AD is primarily caused by an imbalance in these components, including a decrease of keratinocyte differentiation and immunological dysregulation. A crucial barrier function is provided by the skin's barrier, which is made up of a cornified envelope (CE). Late differentiated keratinocytes, structural proteins (FLG, LOR, and IVL), and lipids form CE.[16]

Epidermis, which plays a role as skin barrier, has intercellular adhesion structures known as TJs. Tight junctions are highly intricate intercellular barriers that regulate cellular permeability selectively. As a component of the epidermal barrier, TJs in the granular layer control the paracellular transportation of water and substances. The TJ strands consist of a transmembrane moiety, of which claudin and occludin represent the most abundant components. Tight junctions serve as a second physical barrier in the epidermis and are found in the cellular membrane of keratinocytes in the granular layer of the skin.[9]

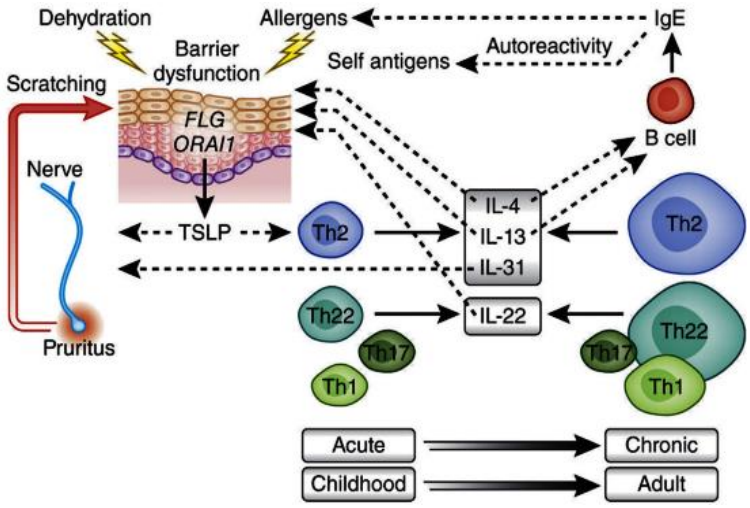

Figure 1 The pathogenesis of atopic dermatitis. Abbreviations: FLG, filaggrin; ORAI1, ORAI calcium release-activated calcium modulator 1; TSLP, thymic stromal lymphopoietin; Th, T helper; IgE, immunoglobulin E. Reprinted from Furue M, *et al*., 2017.[8] Copyright 2016 by Japanese Society of Allergology.

Tight junctions have the fence function which separate the apical and basolateral cell surfaces to establish cell polarity. Tight junctions are also involved in signal transduction, which controls epithelial cell growth and differentiation.[15]

Tight junctions are transmembrane proteins that regulate the decreased epidermal permeability in AD.[16] Claudin-1, a transmembrane protein presents in the basal and suprabasal layers of the epidermis, is a significant component of TJs.[17] When claudin-1 was knocked out as the most significant adhesion protein in TJs of mice, a severe epidermal barrier deficiency was found, demonstrating the significance of TJs and claudin-1.[9,18]

Tight junctions serve as gatekeepers to limit the entry of exogenous antigens that can lead to inflammation and tissue damage by regulating paracellular flux and epithelial permeability. Tight junctions operate in a bidirectional manner, indicating that if the TJ becomes leaky for some reason, the direction of the leakage depends on the molecular gradient on each side. These junctions are composed of transmembrane proteins including junctional adhesion molecules, claudins, occludin, and zonula occludens. These proteins mediate the membrane structure and their associated attachment to the cytoskeleton. Impaired TJs leads to the altered skin barrier function seen in AD. Claudin-1 expression was found to be inversely associated with Th2 cytokines in AD. The presence of Th2 cytokines suppresses claudin-1 expression and compromises keratinocyte differentiation processes. Tight junctions, FLG, desmosomal keratin, and cadherins, are down regulated by Th2 cytokines. Following skin barrier disruption, keratinocytes produce type 2 mediators such as TSLP, IL-25, and IL-33 **(Figure 2)**.[15]

In stratum granulosum, TJ protein colocalization occurs in TJ barrier-forming structures, but surprisingly, all TJs are not limited to these barrier-forming structures including the stratum granulosum. Occludin is found in different structures in the stratum granulosum. Studies have shown that in every layer of viable cells (claudin-1, claudin-7, junctional adhesion molecule-A) or in the stratum spinosum (claudin-4 or zonula occludens-1 and zonula occludens-2) as well as further TJs were also found.[19]

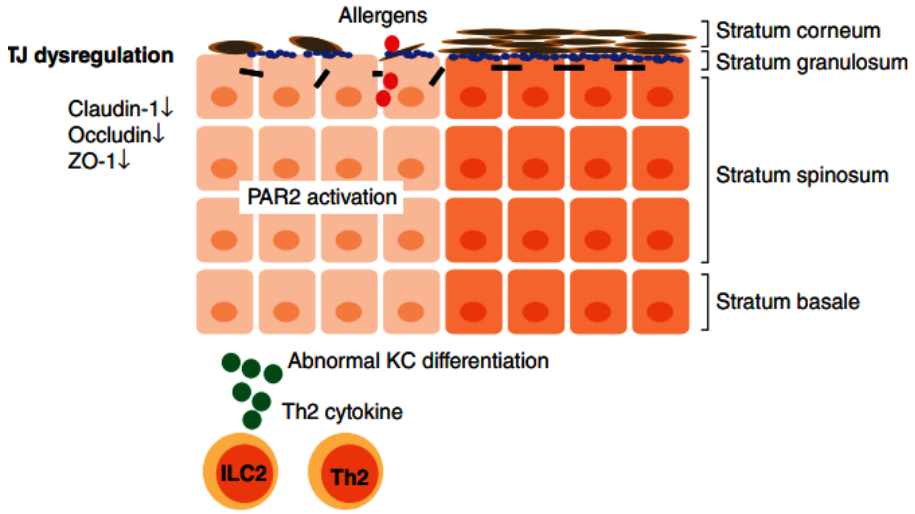

Figure 2. Tight junction disruptions in atopic dermatitis. Abbreviations: TJ, tight junction; ZO-1, zonula occludens-1; PAR2, protease-activated receptor 2; KC, keratinocyte, ILC2, type 2 innate lymphoid cells; Th, T helper. Reprinted from Sugita K and Kabashima K, 2020.[15] Copyright 2020 by Society for Leukocyte Biology.

Studies have shown that occludin knockdown can reduce sensitivity to induction of cell death and adherence cells. Because of this, TJ proteins serve more than just barrier functions.[20] Furthermore, the significance of the skin microbiome in interacting with the immune response has received a lot of attention. Toll-like receptor 2 (TLR2) activation by microbial flora also causes mast cell induction and TJ improvement, resulting in a stronger skin barrier.[21]

Water, ions, and substances can pass through the paracellular route via TJ, which acts as a "gate". The distribution of a pical and basolateral membrane components is controlled by TJ as well. Some studies have proposed that TJs might control the lipid elements present in stratum corneum. As a result, it has been hypothesized that these two skin barrier structures interact dynamically to create a strong barrier of the skin. A variety of transmembrane proteins, including occludin, tricellulin, claudin, and junctional adhesion molecule-A, are found in TJs.[20]

Tight junction dysfunction in keratinocytes can explain the many causes of a broken skin barrier. For instance, elevated TEWL, which is a major cause of skin barrier disruption and is especially escalated in lesional and non-lesional skin in AD patients, has not yet been linked with mutations of FLG. Thus, the breakdown of the skin barrier due to genetic or acquired disorders may explain the increase in TEWL and the occurrence of dry skin found in AD. Immunological effects may arise from impaired TJ structure and function. According to research, activated Langerhans cells, which are antigen-presenting cells found in the epidermis, approach the exogenous antigens by extending dendrites through epidermal TJs.[20]

When the epidermal TJ is compromised, Langerhans cells have a higher chance to sample surface allergens and antigens. This, along with the findings that Langerhans cells are dendritic cells specialized to cause the development of undifferentiated CD4+ T cells into Th2 cells, significantly supports the idea that invasion at TJs may be an important element in the onset of AD **(Figure 3)**. There are studies that have observed that CLDN-1 is selectively supressed in the epidermis of people with AD and CLDN-1 may be a novel susceptibility gene in AD. Compared to healthy control, epidermal samples from AD patients revealed significant abnormalities in resistance and ion transport. It was also found that selective reduction of CLDN-1 expression significantly enhanced paracellular permeability, reduced resistance, and indicated an increase in proliferation of the wound healing response.[20]

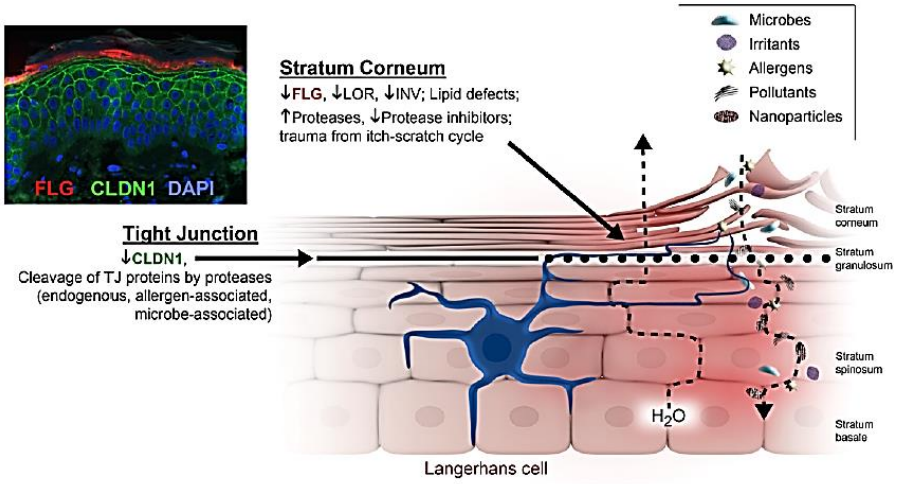

Figure 3. Tight junction as a skin epithel barrier structure. Abbreviations: FLG, filaggrin; LOR, loricrin; INV, involucrin; CLDN1, claudin-1; DAPI, 4′,6-diamidino-2-phenylindole dihydrochloride; TJ, tight junction. Reprinted from de Benedetto A, *et al*., 2011.[20] Copyright 2011 by American Academy of Allergy, Asthma & Immunology.

Discussion

The increasing prevalence of AD globally is not only related to genetics, but is an interaction between genetics, immune and environmental factors. The disruption of the natural skin barrier is one of the key pathological concepts for AD. Desmosomes and TJs bind a complex matrix of structural proteins and lipids that make up the skin barrier. Barrier disruption in AD is primarily caused by an imbalance in these components, including a decrease of keratinocyte differentiation and immunological dysregulation. Disruption of the epidermal barrier causes increased epidermal permeability, pathological inflammation, and percutaneous allergen sensitization.

The discovery of the TJ protein Claudin-1 plays an important role in its function in human epidermal tissue and keratinocyte proliferation. Tight junction dysfunction in keratinocytes causes damage to the skin barrier.

In this review it can be hypothesized that reduction of epidermal Claudin-1 expression of AD patients may increase penetration of many antigens from the external environment, leading to allergen sensitization and increase the skin's susceptibility to irritants or pollutants. The opposing correlation between Claudin-1 and total blood IgE levels implies that this dysfunction may boost induce the Th2 response. This review shows that barrier dysfunction in patients with AD is not only confined to the stratum corneum but also to the TJs, where TJs serve as the second stage of the barrier structure, and regulation of these barriers may provide opportunities for new therapies in people with AD or other atopic diseases

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