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REVIEW ARTICLE

Immune regulation in pathophysiology and targeted therapy for itch in atopic dermatitis

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ABSTRACT

Itch is an unpleasant perception that provokes one to desire to scratch. It results from the activation of free nerve endings by noxious stimuli in the skin. Atopic dermatitis (AD) is a prototypic inflammatory skin disease that always occurs with an intense itch. AD involves many components of skin-associated lymphoid tissue (SALT). As a disease with polarized T helper 2 cell activation, AD involves eosinophil infiltration and immunoglobulin E, interleukin (IL)-2, IL-4, IL-13, and IL-31 production. As a disease involving an impaired skin barrier, AD is characterized by the enhanced transepidermal entry of allergens and the production of thymic stromal lymphopoietin (TSLP) from epidermal keratinocytes, which worsen atopic march and disease progression. Both immune and epidermal events interact with cutaneous nerve components, including transient receptor potential (TRP) channels and opioid receptors, causing both the perception and propagation of itch from the skin to the brain. In addition to treating itch through TRP channels and opioid receptors, it might be possible to target the various cellular components of SALT, including keratinocytes, eosinophils, and soluble factors, such as IL-31, IL-4, IL-13, IL-31, and TSLP.

Introduction

Atopic dermatitis (AD) is a common chronic relapsing disease with intense itch. AD usually accompanies a personal or familial history of allergic diseases, including allergic rhinitis, asthma, and allergic conjunctivitis.[1] Itch is the cardinal symptom of AD. It severely interferes with the life quality of patients and their caregivers and it may impair school and work performance and trigger anxiety and depression.[2] The prevalence of AD is estimated to be 6–9% in Taiwan.[3] While the exact pathogenesis of AD remains to be investigated, both impairment of the skin barriers and aberrant immune activation play significant roles in its pathogenesis.[4,5]

Itch perception: From skin initiation to brain activation

Itch is a unique perception that provokes one to desire to scratch to get rid of noxious stimuli.[6] Cough, which may be induced by noxious chemicals or particles, is a similar action used to expel such stimuli. The epidermis is innervated by small unmyelinated C fiber. The perception of itch is transmitted from the peripheral free nerve endings (C fiber) in the epidermis back to the neuron body in the dorsal root ganglion located at the spinal cord. Subsequently, a synapse in the spinal cord transmits the signal in the contralateral spinothalamic tract to the thalamus, and eventually the signal radiates to the cortical neurons.[7]

In skin, the propagation of itch could result from both inflammatory and noninflammatory diseases. AD is a prototypic inflammatory skin disease that is always accompanied by intense itching.[8] People affected by other inflammatory skin diseases, such as lupus erythematosus and pityriasis lichenoides, may or may not experience itch. Among the noninflammatory skin diseases, some diseases (e.g., uremic pruritus) may cause itch, but others (e.g., stable vitiligo) may not. In diseases with inflammatory conditions, immune factors may play a significant role in the initiation of itch. On

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the other hand, in those diseases with noninflammatory conditions, neurogenic factors may play a more significant role in itch pathophysiology.

Several functional imaging studies have been performed to observe the functional activation of itch signals in the brain. However, different diseases associated with itching can cause differences in the activation of the brain cortex. Furthermore, histamine-induced or non-histamine-induced itch causes differences in the chronological and topological activation of the brain cortex.[9] Based on the principle of near-infrared spectroscopy, one of our previous studies demonstrated that brain cortex activation, reflected by changes in oxygenated and deoxygenated hemoglobin levels, in histamine-induced itch is distinctly different from push–pull gauge-induced pain.[10]

Impaired skin barrier and itch perception

AD is characterized by the impairment of the skin barrier. The epidermis is an intact tissue that protects the human body from harsh outside environments and is fully organized with ordered differentiated keratinocytes and has a densely packed corneal layer equipped with "brick and mortar." However, the impaired skin barrier in AD allows the entry of potential allergens, which subsequently aggravate the inflammatory responses and thereby further deteriorate the impaired skin barrier, creating a vicious cycle.[11] Filaggrin, an important protein that binds to keratins associated with keratinocyte differentiation, is important to the integrity of the skin barrier. In AD, approximately half of the patients are affected by the mutations in filaggrin.[12] The loss or mutation of filaggrin, which decreases the skin's ability to hold water, impairs skin barrier function. On the other hand, enhancing the barrier function of the skin increases the therapeutic effects on AD.[13] We previously found an association between barrier dysfunction, an increase in transepidermal water loss (TEWL), and itch intensity.[14] The greater the TEWL, the worse the itch. In fact, increased TEWL has been positively correlated with an increase in skin pH, promoting the activity of serine proteases to their disruption of the skin barrier and inducing pruritus.[15]

Skin-associated lymphoid tissue

Before we discuss the role of aberrant immune responses in the pathophysiology of AD, the topic of skin-associated lymphoid tissue (SALT) needs to be reviewed. In the gastrointestinal tract, lymphoid structures are present in some submucosal areas, which are also referred to as mucosa-associated lymphoid tissue (MALT).[16] MALT is specialized in the appropriate antigen presentation independently of the secondary lymphoid organs (lymph nodes). This is evidenced by the fact that MALT lymphoma can derive directly from several gastrointestinal mucosal tissues, independently of its associated lymph nodes. Noting similarities in antigen presentation and T cell trafficking from skin to lymph nodes, Streilein et al[17] introduced the term "skin-associated lymphoid tissue" (SALT) and proposed that SALT acts as an integrated immunosurveillance system for the skin. Like MALT lymphoma, SALT by itself can develop several cutaneous lymphomas with different lymphoid cell origins independent of the lymph nodes. SALT is comprised of: (1) epidermal Langerhans cells; (2) T cells; (3) keratinocytes; and (4) a set of draining lymph nodes, along with endothelial cells and several dermal cells.[18] Ono and Kabashima[19] proposed the term "inducible SALT" as they found that the interleukin (IL)-1α produced by keratinocytes activated perivascular macrophages, which attracted dermal dendritic cells via CXCL2 signaling under an inflammatory condition in a model of contact dermatitis. We then discuss the role of several lineages of immune cells of SALT in the pathophysiology of itch in AD, a proinflammatory disease with dynamic innate and adaptive immune responses.

Role of cellular and soluble components of SALT in AD

Eosinophils

The association between eosinophil infiltration and itch perception is well known with regard to scabies infestation.[20] Patients with scabies experience intense itching, and their skin is densely infiltrated by eosinophils. Patients with bullous pemphigoid also experience a significant itch and have moderate eosinophil-rich dermal inflammation. Eosinophil-deficient mice (PHIL mice) have impaired hapten-induced hypersensitivity responses, reduced scratching behavior, and decreased PGP9.5 stained nerve endings.[21] However, there remains some debate as to whether eosinophils and itch might have just a serendipitous relationship via the interactions of immunoglobulin E (IgE) and mast cells.[20]

Fibroblasts

Keloid scarring occurs with a proliferation of fibroblasts and an unregulated deposition of extracellular matrix, and there is often intense itch as the disease progresses.[22] Keloid skin scars have more nerve fibers. It has also been noted that dermal fibroblasts secrete artemin, a neurotrophic factor, in response to substance P and that these artemin-expressing fibroblasts are increased in AD skin.[23]

Keratinocytes

The extent of skin innervations depend on the balance between nerve elongation factors [e.g., nerve growth factor (NGF)] and nerve repulsion factors (e.g., semaphorin 3A), both of which can be produced by epidermal keratinocytes. The blood concentration of NGF correlates well to itch intensity in patients with AD, while epidermal semaphorin 3A levels are low in AD patients who also have increased epidermal nerve density.[24] Furthermore, in a previous study of keratinocytes, we found that IL-31 induces stromal interaction molecule 1 (STIM1) activation, signal transducer and activator of transcription 3 (STAT3) phosphorylation, and beta-endorphin release,[25] and in another study, we found that the blood levels of beta-endorphins correlate well to subjective itch intensity.[14]

Thymic stromal lymphopoietin (TSLP), another cytokine produced by keratinocytes, plays an important role in the pathophysiology of AD. Expression of TSLP is increased in keratinocytes in AD. TSLP contributes to the progression of atopic march in a variety of disorders ranging from the sensitization of AD in skin to the development of asthma and other allergic diseases.[26] In mice, overexpression of TSLP induces AD-like skin.[27] Keratinocyte signaling through TSLP to immune cells may play an important role in AD. Keratinocyte-derived TSLP directly activates cutaneous sensory neurons to promote itch perception.[28] In fact, the signaling from the Ca^{2+} release-activated Ca^{2+} channel (ORAI1), which interacts with STIM1 in the cell membrane of keratinocytes, can induce the production of TSLP, which then activates transient receptor potential cation channel, subfamily A, member 1 (TRPA1) and thereby induces itch.[28] Undoubtedly, keratinocytes play a pivotal role in the initiation of itch. In fact, one of our previous international studies found an association between the genetic predisposition of ORAI1 and the development of AD. That study found an association between the single gene polymorphism of ORAI1, a calcium channel protein, and the development and severity of AD in both Japanese and Taiwanese populations.[29]