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Review Article

Mechanisms and Therapeutic Targets of Staphylococcus Aureus - Induced Itch in Atopic Dermatitis

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Abstract

Atopic dermatitis is a chronic skin disorder marked by inflammation, erythema, and pruritus, often beginning in childhood and characterized by exacerbations and remissions. Its etiology involves genetic, immunological, and environmental factors. Staphylococcus aureus, a common pathogen, exacerbates atopic dermatitis by producing toxins and enzymes such as the serine protease V8, which activates the protease-activated receptor 1 (PAR1) on sensory neurons, inducing itch. This mechanism highlights potential therapeutic targets for alleviating pruritus. Research into the physiological pathways of itch, including the role of PAR1 and other protease-activated receptors, reveals promising strategies for treatment. PAR1 antagonists could be repurposed to treat chronic itch, providing new therapeutic avenues. PAR1 and other protease-activated receptors, is crucial in developing new treatment strategies. Anti-pruritic therapies targeting these pathways, such as PAR1 antagonists, show promise in mitigating itch symptoms. Moreover, existing drugs that inhibit PAR1 could be repurposed for treating chronic itch, providing a new avenue for relief in patients with atopic dermatitis. Additionally, the evolutionary role of itch induced by microorganisms suggests pathogens may exploit neural reflexes to enhance their spread. Advancements in understanding the mechanisms behind S. aureus-induced itch and the physiological pathways involved offer promising new directions for therapeutic intervention. Advancements in understanding the mechanisms of Staphylococcal aureus-induced itch and associated physiological pathways offer promising directions for therapeutic intervention, potentially improving management and treatment outcomes for patients with atopic dermatitis and other pruritic conditions.

Keywords

Atopic Dermatitis, Pruritus, Staphylococcus Aureus, Protease-Activated Receptor 1 (PAR1), Anti-Pruritic Therapy

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1. Introduction

Atopic dermatitis is a chronic dermatological disorder characterized by cutaneous inflammation, erythema, and pruritus. Key clinical manifestations include severe pruritus, which can lead to excoriations and subsequent complications such as edema, lichenification, and fissuring of the skin. Affected areas may exhibit serous exudate, crusting, and scaling as well. Patients often experience periods of exacerbation and intervals of remission. The etiology of atopic dermatitis remains unclear, but genetic predisposition, immune system dysregulation, and environmental triggers are known to contribute to its pathogenesis. An increased risk is associated with a family history of atopic conditions such as allergic rhinitis or asthma. Epidemiological studies show a higher prevalence in non-Hispanic black children and a slightly higher incidence in females. Management strategies focus on controlling symptoms and minimizing flare-ups, and while many individuals achieve improvement by adulthood, some may experience persistent disease throughout life.

2. Staphylococcus Aureus and Its Role in Skin Infections

Staphylococcus aureus is a major bacterial pathogen that causes a wide variety of clinical manifestations, colonizing the skin, nasal passages, and other mucosal surfaces in healthy individuals [1]. In its commensal state, S. aureus contributes to maintaining the balance of the microbiote and provides innate immune defense against other pathogens. However, under specific circumstances such as compromised skin barrier integrity, the bacterium can transition into an opportunistic pathogen, precipitating a spectrum of infections [2]. These may manifest as superficial skin infections or escalate into severe systemic conditions such as sepsis. S. aureus is notable for its ability to develop resistance to antibiotics, such as in methicillin-resistant Staphylococcus aureus (MRSA), posing significant challenges for treatment [3]. Understanding the dual role of S. aureus as both a commensal organism and a potential pathogen is essential for developing effective strategies for infection control and maintaining human health.

3. Physiology of Itching

The skin serves as a protective barrier between the body and the external environment, equipped with a complex network of sensory and efferent nerve fibers that allow it to detect and respond to various stimuli, including sensations of itch. Pruritus is defined as an unpleasant sensation provoking the desire to scratch [4]. Historically, itch was thought to be a low-intensity pain, but research has since established that pruritoception (the perception of itch) is a distinct sensory process from nociception (the perception of pain) [5]. Itch can be triggered by a range of localized, systemic, peripheral, or central stimuli and is transmitted to different cerebral areas by unmyelinated C-polymodal nociceptive neurons, particularly those that are sensitive to histamine. These nerve endings, found in the epidermis, dermis, and around skin appendages, detect endogenous and exogenous itch-causing agents through specific receptors. At the clinical level, chronic itches are defined as those lasting six weeks or longer [6].

3.1. S. Aureus Toxins and Itch

S. aureus has a diverse arsenal of components and products that contribute to the pathogenesis of infection. These components and products have overlapping roles and can act either in concert or alone [2]. The serine protease V8, one of 10 enzymes known to be released upon skin contact from S. aureus, plays a key role in itch by activating the protease-activated receptor 1 (PAR1) on sensory neurons [7]. PAR1 is a member of the G-protein–coupled receptor family, and its activation is initiated by cleavage of the N terminus of the receptor to generate a new tethered ligand terminus. Normally, PAR1 is dormant, but when cleavage due to V8 protease binding occurs, it leads to activation of the receptor, initiating a signal transduction pathway that the brain interprets as itch. This interaction between V8 and PAR1 highlights a novel mechanism through which S. aureus contributes to pruritus, particularly in conditions like atopic dermatitis where the bacterium is commonly present on the skin. Understanding this pathway opens potential therapeutic avenues for targeting the V8-PAR1 interaction to alleviate itch and improve the quality of life for patients with allergic and atopic diseases [8].

3.2. Pathways and Mechanisms of S. Aureus-Induced Itch

Several pathological pathways are associated with the stimulation of itch by S. aureus:

1. Inflammatory Response: S. aureus can trigger an inflammatory response in the skin, leading to the release of pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). These cytokines can sensitize nerve fibers in the skin, resulting in itch sensation.
2. Bacterial Toxins: S. aureus produces toxins such as staphylococcal enterotoxins and toxic shock syndrome toxin-1 (TSST-1), which can directly stimulate sensory nerves in the skin, leading to itch.
3. Skin Barrier Dysfunction: S. aureus can compromise the integrity of the skin barrier through various mechanisms, including disrupting tight junctions between skin cells and releasing enzymes that degrade skin proteins. This disruption allows allergens and other itch-inducing substances to penetrate the skin more easily, leading to

increased itchiness.

4. Activation of Immune Cells: S. aureus can activate immune cells such as mast cells and eosinophils, which are involved in the allergic response. Mast cells release histamine and other itch-inducing mediators upon activation, contributing to itch sensation.
5. Chronic Infection: In cases of chronic or recurrent S. aureus infection, persistent inflammation and immune activation can lead to chronic itchiness, even after the infection has been cleared.

Overall, S. aureus-induced itch is a multifactorial process involving inflammation, immune activation, and direct stimulation of sensory nerves. Effective management often requires addressing both the underlying infection and the associated itch symptoms.

3.3. V8 Protease and PAR1 Receptor Interaction

The V8 protease, also known as staphylococcal serine protease-like protein (SspA), is locally produced by S. aureus. This enzyme plays a role in bacterial pathogenesis and has been implicated in various aspects of host-pathogen interactions, including modulation of the host immune response. One of the known targets of the V8 protease is the protease-activated receptor 1 (PAR-1) [9]. When activated by specific proteases, including thrombin and certain bacterial proteases like the V8 protease, PAR-1 undergoes proteolytic cleavage. This activation triggers various downstream signaling pathways, including intracellular calcium mobilization, activation of protein kinase cascades, and changes in gene expression. The activation of PAR-1 by the V8 protease has been implicated in several biological processes, including inflammation, coagulation, and vascular permeability. By cleaving PAR-1, the V8 protease may modulate host responses to S. aureus infection, potentially promoting bacterial survival and dissemination. Additionally, PAR-1 activation by the V8 protease may contribute to the pathogenesis of certain S. aureus-associated diseases, such as skin infections and sepsis. Understanding the interplay between bacterial proteases like the V8 protease and host receptors like PAR-1 is important for elucidating the mechanisms of bacterial pathogenesis and may provide insights into the development of novel therapeutic strategies for combating S. aureus infections [10].

3.4. Pathways, Markers, and PARs Receptor for Itch

Specific pathways have been identified in rodents that are involved in encoding non-histaminergic itching. These include functional markers for primary pruriceptive afferent neurons like MrgprA1, MrgprC11, MrgprD, and human MrgprX1 [11]. Peripheral mediators primarily linked to itching rather than pain behavior include interleukin-13 (IL-13), IL-31, autotaxin, lysophosphatidic acid (LPA), and central transmitters and pathways for itch processing like B-type natriuretic peptide (BNP) and gastrin-releasing peptide (GRP) [12, 13]. Treatment approaches that correct or interrupt the flow of information between the skin and dorsal root ganglia have been shown to be effective for chronic itches associated with inflammatory skin diseases.

Corticosteroids have long been used to reduce inflammation with the benefit of relieving itch, demonstrating a link betweenthe immune and nervous systems. Blocking the activity of interleukin-31 rapidly alleviates itch in patients with atopic dermatitis while inflammation is maintained, perhaps allowing for unlinking the immune and nervous systems. In mice, four PAR subtypes have been identified (PAR1–4) [14]. For their stimulation, three molecules are being used so far. Tryptase, the most abundant secretory granule-derived serine proteinase contained in mast cells, acts on PAR2 (and PAR1 only at high concentrations); trypsin acts on PAR1, PAR2, and PAR4, but not PAR3; and thrombin acts on PAR1, PAR3, and PAR4, but not PAR2 [15]. Evidence suggests the involvement of PAR1 in itch, but the involvement of the other PARs remains unknown.

4. PAR1 Receptor

The protease-activated receptor 1 (PAR1) emerges as a pivotal therapeutic target with profound implications across diverse medical domains. Acting as a critical mediator in platelet aggregation, PAR1 inhibitors, exemplified by vorapaxar, exhibit remarkable efficacy in mitigating thrombotic events, thus offering indispensable therapeutic effects in cardiovascular pathologies, particularly among high-risk cohorts characterized by a history of myocardial infarction and ischemic stroke. Furthermore, the modulation of PAR1 holds promise in the management of inflammatory disorders such as asthma and chronic obstructive pulmonary disease (COPD), while its involvement in neuroinflammation underscores potential neuroprotective roles in conditions like Alzheimer's disease. Remarkably, emerging evidence suggests its potential in ameliorating chronic pruritus associated with dermatological conditions such as atopic dermatitis [16].

5. PAR1-2 Receptor Antagonists

In the context of skin dysbiosis, characterized by an imbalance in the skin microbiota, pruritus or itchiness emerges as a significant symptom. Potential therapeutic interventions involving PAR1 antagonists hold promise for addressing this symptomatology [17]. Mechanistically, these antagonists may exert their anti-itch effects through several plausible pathways. Firstly, by modulating neurogenic inflammation, PAR1 activation prompts the release of inflammatory mediators and neuropeptides integral to itch transmission, a process attenuated by PAR1 blockade. Secondly, PAR1 antagonists may regulate sensory neuron excitability, thereby diminishing the

perception of itchiness transmitted by these neurons. Lastly, PAR1 activation by pruritogens can instigate signaling cascades culminating in itch sensation, a process potentially disrupted by antagonistic action on PAR1, thus ameliorating itch perception in skin dysbiosis. An example of the potential effect, tryptase, a PAR2 agonist proteinase, induces scratching in mice, which is inhibited by anti-PAR2 antibody and the PAR2 antagonist FSLLRY-NH2 [14].

6. New Anti-Pruritic Therapeutic Strategies

FDA-approved anticlotting drugs that inhibit the PAR1 receptor may pose a treatment option [9]. Proven in clinical trials, they appear to be effective in stopping itch in mice and human neurons. This outcome opens the door for the use of the active ingredient as a base for the development of anti-itch topical creams.

7. Evolutionary Function/Benefit of Itch for Microorganisms

These new findings prompt a fundamental inquiry: Why would a microorganism provoke itchiness? From an evolutionary standpoint, what advantages does itchiness offer to the bacterium? One potential explanation is that pathogens might exploit itch and other neural reflexes for their benefit. For instance, previous investigations have indicated that the Mycobacterium tuberculosis directly stimulates vagal neurons to induce coughing, potentially enhancing its transmission between hosts. Speculatively, the itch-scratch cycle could serve the interests of microbes, facilitating their dissemination to distant body sites and uninfected hosts.

8. Conclusions

The evolutionary function of itch induced by microorganisms like S. aureus raises intriguing questions. It is hypothesized that pathogens may exploit neural reflexes such as itching to facilitate their spread to new hosts or body sites. This understanding underscores the complex interplay between microbial activity and host responses.

Understanding the physiological pathways of itch, including the role of PAR1 and other protease-activated receptors, is crucial in developing new treatment strategies. Anti-pruritic therapies targeting these pathways, such as PAR1 antagonists, show promise in mitigating itch symptoms. Moreover, existing drugs that inhibit PAR1 could be repurposed for treating chronic itch, providing a new avenue for relief in patients with atopic dermatitis.

In summary, advancements in understanding the mechanisms behind S. aureus-induced itch and the physiological pathways involved offer promising new directions for therapeutic intervention. Continued research into these areas holds the potential to significantly improve management and treatment outcomes for patients suffering from atopic dermatitis and other pruritic conditions.

Abbreviations

PAR1	Protease-Activated Receptor 1
IL	Interleukin

Conflicts of Interest

The authors declare no conflicts of interest.

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