Pruritus Pathogenesis in Psoriasis

Subjects: Pathology
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Psoriasis is a chronic, systemic inflammatory disease with a genetic background that involves almost 3% of the general population worldwide. About 70-80% of psoriatic patients suffer from pruritus. Despite its high prevalence in psoriasis, its pathogenesis still remains unclear.

Keywords: psoriasis ; palmoplantar pustulosis ; pruritus

1. Introduction

Psoriasis is a chronic, inflammatory, immune-mediated skin and joint disease with genetic background, affecting even 3% of the general population. The most characteristic skin lesion of psoriasis is erythematosus plaque covered with silvery scales. Approximately 70–90% of patients with psoriasis suffer from pruritus, an unpleasant sensation that provokes a desire to scratch [1]. Due to the systemic inflammation that characterizes psoriasis, several comorbidities have been recently linked with this disease and they may also contribute to triggering, maintaining, or even worsening the psoriasis-related pruritus. The subjective and multidimensional nature of this symptom renders it challenging for clinicians and researchers to measure it appropriately and to provide optimal therapy. However, it is important to be able to control pruritus in psoriasis to prevent the Koebner phenomenon (i.e., development of new psoriatic lesions due to minor trauma to apparently healthy skin) [2] and worsening of skin lesions as well as to improve patients' quality of life. Remarkably, itching is often considered by patients as the most troublesome and unpleasant symptom of psoriasis. Pruritus in subjects with psoriasis most often appears at night and in the evening, but less frequently in the morning or around noon. According to various studies, pruritus causes difficulty in falling asleep in approximately 50–66% of patients [1][3][4][5]. Approximately 70% of patients experience itching at the sites of the lesions, in the remaining 30% it also affects unchanged skin [1][3]. More than 70% of patients experience itching on a daily basis [1][3]. The most important factors that exacerbate itching in psoriasis patients are dry skin and emotional stress, but other factors also may play a significant role [4][6]. In order to develop more effective and safer antipruritic therapies, a better understanding of complex and multifactorial pathogenesis of pruritus in psoriasis is needed. In this article, we have systematized the current knowledge about pruritus origin in psoriasis.

2. Histamine and Mast Cells

Despite the lack of well-designed controlled studies that would confirm the effectiveness of antihistamines in psoriatic pruritus, some physicians use them to relieve the itch in psoriatic patients. Authors such as Prignano et al. [7], Amatya et al. [8], or Yosipowitch et al. [9] based on their questionnaire studies, noticed some antipruritic effect of antihistamines in psoriatic patients, but each time they only paid attention to the short effectiveness of these drugs. In 2017 Domagala et al. published results of a double-blinded, randomized, and placebo-controlled study evaluating the efficacy of clemastine—first-generation histamine-1 receptor (H1R) antagonist, or levocetirizine—second-generation H1R antagonist, in reducing pruritus in psoriasis as an addition to the standard psoriasis treatment. They found a significantly higher decrease in mean visual analog scale (VAS) scoring for the worst pruritus as well as a significant reduction in the mean scoring of 12-Item Pruritus Severity Scale in clemastine and levocetirizine groups when compared to placebo. Despite favorable findings, this study had also major limitations such as a short follow-up period and the small number of observed patients (n = 61) [10]. However, similar results on the effectiveness of levocetirizine were described by Mueller et al. [10]. They noted that, in addition to a rapid reduction in pruritus intensity, levocetirizine had also improved dermatology-related quality of life, stress, anxiety, and global level of functioning [11].

While most attention was focused on the H1R, other histamine receptor subtypes should not be overlooked. Mommert et al. [12] found that stimulation of the H4 receptor, which is highly expressed on plasmacytoid dendritic cells (pDC) in psoriasis [13], increases the production of interleukin 17 (IL-17), a cytokine that plays a major role in the pathogenesis of psoriasis. Recently, it has been also shown that blockade of H4R may help to ameliorate imiquimod-induced skin

inflammation, diminish epidermal hyperproliferation, and inhibit spontaneous scratching behavior in mice [14]. These observations suggest that histamine relevance in the pathophysiology of pruritus in psoriasis is still uncovered and further investigations are needed.

3. Substance P and Other Neuropeptides

Neuropeptides are small proteins secreted from nerve endings in the central and peripheral nervous system in response to various factors such as stress and modulate synaptic transmission [7][15]. They may activate dendritic cells, lymphocytes, macrophages, and neutrophils, degranulate mastocytes, cause vascular changes in the skin, stimulate synthesis and release of many pro-inflammatory cytokines [16][17]. The imbalance of neuropeptides in psoriatic skin is being suggested to play a role in the perception of itching. One of the neuropeptides, namely substance P (SP), an undecapeptide of the tachykinin family, has been implicated in the pathogenesis of pruritus for many years. Furthermore, other neuropeptides are believed to be involved in pruritus mediation. It was shown that SP, neurokinin A (NKA), and vasoactive intestinal peptide (VIP) may elicit itch upon intradermal injection into normal human skin [18][19].

4. Nerve Growth Factor and Innervation

Chronic itch is associated with increased levels of nerve growth factor (NGF)—a molecule that belongs to the neurotrophic factor family [20]. This protein influences an inflammatory reaction by regulating neuropeptides, angiogenesis, cell trafficking molecules, and T cell activation. Moreover, NGF exerts its action on the growth, proliferation, and survival of peripheral sensory and sympathetic neurons and on a number of brain neurons [21]. Currently, there two receptors for this molecule are known: high-affinity tropomyosin-receptor kinase A (Trk A) and low-affinity receptor p75 [22]. Nakamura et al. reported increased NGF content and increased expression of Trk A in lesional psoriatic skin with pruritus in comparison to non-pruritic skin. Additionally, the expression levels of these proteins correlated positively with the severity of pruritus [23]. Subsequent studies demonstrated that NGF expression was higher also in lesional pruritic skin than in non-lesional skin [20]. A probable consequence of the elevated concentration of NGF and Trk A is elongation and branching of epidermal nerve fibers, which results in hyperinnervation. In turn, this hyperinnervation is considered to cause hypersensitivity of itch in psoriasis. However, reports of studies remain contradictory—some investigators observed increased nerve density in psoriatic skin [23], whereas others did not see such correlation [24]. This disparity may be due to different measurement techniques or heterogeneous clinical history of lesions taken during biopsies. Therefore, increased nerve fiber density in the epidermis may not be an essential factor for the pathogenesis of psoriatic pruritus and further studies are needed to clarify their exact role.

5. Interleukins

The role of inflammation in psoriatic-related itch origin is undoubtedly relevant, as it is confirmed by the elevated concentration of a number of inflammatory mediators and by an antipruritic effect of anti-inflammatory drugs. Various immune cells secrete cytokines that directly or indirectly may aggravate or even induce itch by increasing the inflammatory response [25]. Nakamura et al. analyzed differences in cytokine expression in the epidermis between pruritic and non-pruritic psoriatic patients. Among the tested cytokines (IFN-ɣ, TNF-α, IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12) only IL-2, a SP-induced cytokine that triggers the maturation of T cells, was significantly increased in pruritic psoriatic skin [23]. Other cytokines, such as IL-4, IL-13, IL-31, and IL-33 play a key role in the pro-inflammatory and anti-inflammatory signaling pathways in patients suffering from inflammatory skin diseases such as psoriasis or atopic dermatitis [26]. In 2020, Badoor et al. published results of a study evaluating the correlation between serum concentration of IL-4, IL-13, IL-31, and IL-33 and intensity of pruritus in psoriasis and atopic dermatitis. In patients with psoriasis, similarly to atopic dermatitis, the levels of IL-4 and IL-31 were significantly elevated in comparison to healthy controls [26]. These findings were compatible with the results of another study in which elevated levels of IL-31 in the skin or serum of patients with psoriasis were demonstrated [27][28]. However, these elevated concentrations did not correlate with the intensity of itch [26]. Interestingly, Narbutt et al. proved a significant reduction in both, serum IL-31 levels and severity of pruritus after narrowband ultraviolet B (UVB) phototherapy [28]. Although there are some inaccuracies in the literature, this observation might be proof that IL-31 contributes to the induction of pruritus in psoriasis. Cytokines involved in the pathogenesis of psoriasis such as IL-17, IL-22, or IL-23 are also potential agents to evoke pruritus in psoriasis, but to date data on them in relation to pruritus are limited.

6. Vessel-Derived Molecules

Vascular abnormalities are frequently observed in psoriatic lesions and have also been suspected to be relevant in the pathogenesis of psoriasis-associated pruritus. This suggestion was supported by the positive correlation between the density of E-selectin-positive venules and the intensity of pruritus in patients with psoriasis [23]. The key role in the angiogenesis of psoriatic lesions is played by the vascular endothelial growth factor (VEGF) [29]. Moreover, VEGF was also suggested to play a role in the perception of pruritus in psoriasis. Higher VEGF-A expression was found in the epidermis of lesional skin from the psoriatic patients with pruritus than those without pruritus [30]. In addition, Madej et al. showed that serum concentration of vascular adhesion protein-1 (VAP-1), another adhesion molecule, was significantly higher in the group of psoriatic patients with pruritus vs. those without pruritus [31]. Prostaglandin E2 (PGE2), endothelin-1 (ET-1), and endothelial leukocyte adhesion protein 1 (ELAM-1) have also been considered to be good candidates as itch mediators in psoriasis but future studies are required to confirm this hypothesis [25].

7. Endogenous Opioids

The opioid system is considered to be a modulator of pruritus in psoriasis. It is suggested that activation of the μ-opioid receptor (MOR) by a MOR ligand β-endorphin can stimulate itch, while the interaction between κ-opioid receptor (KOR) and its ligand: Dynorphin A, suppresses pruritus [32][33][34]. Opioids may also induce itch acting in the central nervous system—activation of KOR in the brain may reduce or even alleviate itch [35].

Teneda et al. followed the expression patterns of μ- and κ -opioid systems in pruritic and non-pruritic psoriatic skin as well as in healthy skin. No differences regarding μ-opioid receptor expression and β-endorphin levels in the epidermis of psoriatic patients with or without itch and healthy controls were found. However, the levels of KOR and dynorphin A were significantly decreased in the epidermis of patients with psoriasis, especially those who reported pruritus compared with the control group [24]. In an analogous study, conducted a few years later in Poland, compatible results were obtained showing no significant difference in MOR system expression in both lesional and non-lesional psoriatic skin, the same as in the healthy control skin. Regarding the κ-opioid pathway, the KOR system was downregulated in the lesional pruritic psoriatic skin, and its expression was positively correlated with itch sensation [35]. These findings indicate that the imbalance in the cutaneous expression of opioid receptors and their ligands may result in disordered neuroepidermal homeostasis in psoriasis, which could potentiate the transmission of itch. Importantly, in imiquimod-induced psoriasis-like dermatitis in mice, scratching behavior was suppressed by peripheral and a central MOR antagonist or a central KOR agonist [36]. It indicates that the central opioid receptor system is also involved in the regulation of pruritus in psoriasis.

8. Lipocalin-2

Another molecule that is suspected to play an important role in the pathogenesis of pruritus in psoriasis is lipocalin-2 (LCN2). This protein, also known as 24p3 and neutrophil gelatinase-associated lipocalin (NGAL), is stored in the specific granules of human neutrophils and secreted by activated cells [37][38]. LCN2 has been associated with neurodegeneration, cancer metastasis, insulin resistance, obesity, and inflammatory responses [39][40]. Additionally, LCN2 was found to contribute to the pathogenesis of psoriasis by modulating neutrophil function to enhance T-helper 17-type responses [40]. Aizawa et al. on the group of 59 patients suffering from psoriasis observed that serum LCN2 concentration is significantly higher in this group compared to healthy controls and that plasma LCN2 level positively correlated with the intensity of pruritus [41]. These findings may indicate that LCN2 could be another mediator involved in the aggravation of pruritus in psoriasis.

9. Future Directions to Identify New Itch Mediators

Gene expression analyses are a possible way to find factors involved in the pathogenesis of pruritus in psoriasis. Nattkemper et al. used RNA sequencing to analyze so-called “itchscriptom” and identified several possible “itch-related” genes, including also well-known and inflammatory mediators described above, such as various cytokines (IL-17A, IL-23A, IL-31), which were commonly overexpressed in itchy atopic and psoriatic skin [42]. Nowadays, part of them is a target of biological drugs used in psoriasis therapy, e.g., IL-17A. In addition, overexpression of genes encoding SP and its receptor NK-1R in both atopic and psoriatic lesional skin was observed, a finding that further supports SP’s role in the pathogenesis of pruritus in psoriasis. In addition, elevated gene transcript levels of such genes, as phospholipase A2 IVD and phospholipase C, voltage-gated sodium channel 1.7 (Nav1.7), transient receptor potential vanilloid 1 and 3 (TRPV1, TRPV3), transient receptor potential melastatin 8 (TRPM8), and IL-36 were also observed in itchy psoriatic skin [42]. Products of mentioned genes are potentially good candidates as potential targets for new antipruritic drugs.

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