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REVIEW

Skin neurogenic inflammation

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Abstract

The epidermis closely interacts with nerve endings, and both epidermis and nerves produce substances for mutual sustenance. Neuropeptides, like substance P (SP) and calcitonin gene-related protein (CGRP), are produced by sensory nerves in the dermis; they induce mast cells to release vasoactive amines that facilitate infiltration of neutrophils and T cells. Some receptors are more important than others in the generation of itch. The Mas-related G protein-coupled receptors (Mrgpr) family as well as transient receptor potential ankyrin 1 (TRPA1) and protease activated receptor 2(Par2) have important roles in itch and inflammation. The activation of MrgprX1 degranulates mast cells to communicate with sensory nerve and cutaneous cells for developing neurogenic inflammation. Mrgprs and transient receptor potential vanilloid 4 (TRPV4) are crucial for the generation of skin diseases like rosacea, while SP, CGRP, somatostatin, β-endorphin, vasoactive intestinal peptide (VIP), and pituitary adenylate cyclase-activating polypeptide (PACAP) can modulate the immune system during psoriasis development. The increased level of SP, in atopic dermatitis, induces the release of interferon (IFN)-γ, interleukin (IL)-4, tumor necrosis factor (TNF)-α, and IL-10 from the peripheral blood mononuclear leukocytes. We are finally starting to understand the intricate connections between the skin neurons and resident skin cells and how their interaction can be key to controlling inflammation and from there the pathogenesis of diseases like atopic dermatitis, psoriasis, and rosacea.

Introduction

The old term "neurodermitis," which indicates atopic eczema or allergic dermatitis, defines a close relationship between nerves and skin. It reflects the clinical observation that the development and the progression of allergic dermatitis is sensitive to emotional stress and environmental stimulation. It has been a longstanding clinical observation that chronic inflammatory skin disorders such as atopic dermatitis (AD), psoriasis, and rosacea are exacerbated by stress [1]. "Neurogenic inflammation" describes a mechanism by which sensory nerves contribute to inflammation [2]. In 1876, Stricker observed the phenomenon that cutaneous blood flow was increased in innervated areas when the corresponding dorsal roots were stimulated [3]. Together with similar findings [4], this phenomenon was defined as neurogenic vasodilation [4]. Later, it led to the concept of neurogenic inflammation, which describes the vasodilation and protein extravasation caused by inflammatory neuropeptides [5].

Both the somatosensory nervous system and the immune system are essential for the host defense against potential harmful infection and tissue damage [6]. While the immune system, which is the traditional host defense system, protects the host by combacting infective agents and restores tissue integrity, the somatosensory nervous system helps to avoid the noxious stimuli by removing the danger. There are abundant nociceptors in the skin which cover and protect the host from the outer environment. They respond to any noxious stimuli instantaneously and transduce them to electrical activity to produce sensation and reflex. Nociceptor neurons can transmit the action potentials antidromically, from the branch points to the periphery, as well as orthodromic input from the periphery to the central nervous system (CNS), which is called axon reflex [7]. Thus, the neuronal mediators are released from the depolarized axon terminals to the stimulated area, enabling a rapid response, well before the immune system is activated [6].

Skin mechanisms of neurogenic inflammation

Nervous system in skin

One of the major roles of the skin is to sense and respond to signals from the outer environment as well as protect our

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bodies. Abundant nerve fibers, including autonomic and sensory nerves, are densely distributed over all skin layers. They can communicate with different cell populations in different layers of the skin by releasing various types of neuropeptides. Almost all cutaneous cells express functional receptors for neuropeptides, through which they receive signals from the nervous system. In return, skin cells produce neuropeptides and neurotrophins, which in turn stimulate nerve fibers. This exchange creates a positive bidirectional feedback loop able to augment inflammatory response [8–12]. The finding that various kinds of chronic inflammatory skin disorders, such as AD and psoriasis, have common features of increased neurotrophin expression and peptidergic nerve fibers supports this pathophysiologic phenomenon [8].

In the epidermis, neuropeptides released from the nerve fibers stimulate keratinocytes to produce proinflammatory cytokines such as interleukin (IL)-1α, IL-6, and IL-8 [13–16]. On langerhans cells (LCs) in the epidermis, neuropeptide substance P (SP) enhances their migration and antigen presentation, leading to promotion of allergic sensitization [17–19]. In the dermis, sensory nerve fibers are intermingled with noradrenergic and acetylcholinergic nerve fibers containing additional neuropeptides such as neuropeptide Y (NPY) or vasoactive intestinal peptide (VIP). Sensory nerve fibers are commonly found in close contact with mast cells, blood vessels, or hair follicles in the dermis. Dermal mast cells have a particularly close relationship with the nervous system in terms of neurogenic inflammation. Neuropeptide SP released from the sensory nerve endings induces mast cell degranulation and subsequent proinflammatory effects of mediators such as histamine [8, 9, 20]. In turn, histamine, released from mast cells, evokes the release of neuropeptides acting on the histamine receptors on the sensory nerve endings, which establish a bidirectional loop between mast cells and sensory nerves. Moreover, SP induces vascular endothelial growth factor (VEGF) release from mast cells, which promotes endothelial cell proliferation and vascularization, facilitating the inflammatory process. Fibroblasts in the dermis also express receptors for SP as well as SP production, both of which are enhanced after exposure to SP or interferon (IFN)-γ [21, 22]. Thus, neuropeptides and neurotrophins contribute to the exaggeration of the inflammatory process in acute skin inflammation which overexpresses SP, nerve growth factor (NGF), and IFN-γ and later contribute to fibrosis in chronic skin inflammation [5].

Sensory nerve and neuropeptides

Neurogenic inflammation is mediated by the release of neuropeptides such as SP and calcitonin gene-related protein (CGRP). When sensory nerves are stimulated by certain stimuli, they release biologically active neuropeptides to transfer signals. SP and CGRP are the classic neuropeptides which act directly on the vascular endothelial cells and smooth muscle cells, thereby mediating vascular effects [23, 24]. SP increases vascular permeability with subsequent plasma extravasation and edema [23, 24]. The release of SP increases intercellular adhesion molecules (ICAMs) and vascular cell adhesion molecules (VCAMs) on vascular epithelial cells [25] and induces VEGF release from mast cells [26, 27], which facilitate hypervascularization and infiltration of inflammatory cells. CGRP is a potent microvascular vasodilator which contributes to the majority of the neurogenic vasodilation and is involved in recruitment of inflammatory cells [28, 29]. It was shown that CGRP enhanced LC antigen presentation on Th2 responses, while inhibiting presentation for the Th1 response, thereby shifting LCs toward Th2 responses [30]. Both SP and CGRP act through their subsequent G-protein-coupled receptor (GPCR), neurokinin (NK)-1 receptor for SP, and the CGRP receptor complex for CGRP [31, 32]. Recently, an NK-1 antagonist, aprepitant, was demonstrated to inhibit itch in AD mouse models and showed efficacy in chronic pruritus in humans [33]. The selective CGRP receptor antagonist as well as anti-CGRP antibodies have been developed and are currently under clinical trial showing promising results for migraine in which CGRP is the critical player in the pathogenesis [34]. Like CGRP, pituitary adenylate cyclase-activating polypeptide (PACAP) and VIP also inhibit LC antigen presentation for the generation of Th1 cells while enhancing presentation for Th2 responses. Also, PACAP and VIP enhance presentation for differentiation of Th17 cells, thereby shifting Th cells toward Th17 as well as Th2 responses [35] (Fig. 1).

PARs and Mrgprs

The release of neuropeptides from the sensory nerve is triggered by a rise in the cytosolic Ca^{2+} concentration [36]. Cutaneous sensory nerves express GPCRs in addition to voltage-gated Ca channels, the activation of which increase cytosolic Ca^{2+} concentration. There are five specific GPCRs that are mainly involved in cutaneous neurogenic inflammation, which includes protease-activated receptors 2 and 4 (PAR-2 and PAR-4) and Mas-related G-coupled protein receptors C11, A3, and X (MrgprC11, MrgprA3, and MrgprX) [37–41]. Calcium channels such as nociceptive transient receptor potential vanilloid 1 (TRPV1) and transient receptor potential ankyrin 1 (TRPA1) co-localize with them [42]. PAR-2 is involved in pruritus and various skin diseases such as atopic dermatitis [43, 44] while PAR-4 is involved in edema formation, leukocyte recruitment, and analgesia [45–49]. Mrgprs are shown to be involved in histamine-independent itch pathways such as chloroquine-induced [50] or bovine adrenal medulla (BAM) 8–22-induced pruritus [51]. In the Mrgpr family, there are nine subfamilies including MrgprA to MrgprH and MrgprX [52]. Among them, MrgprA3, C11, and X1 are known to be involved in peripheral itch

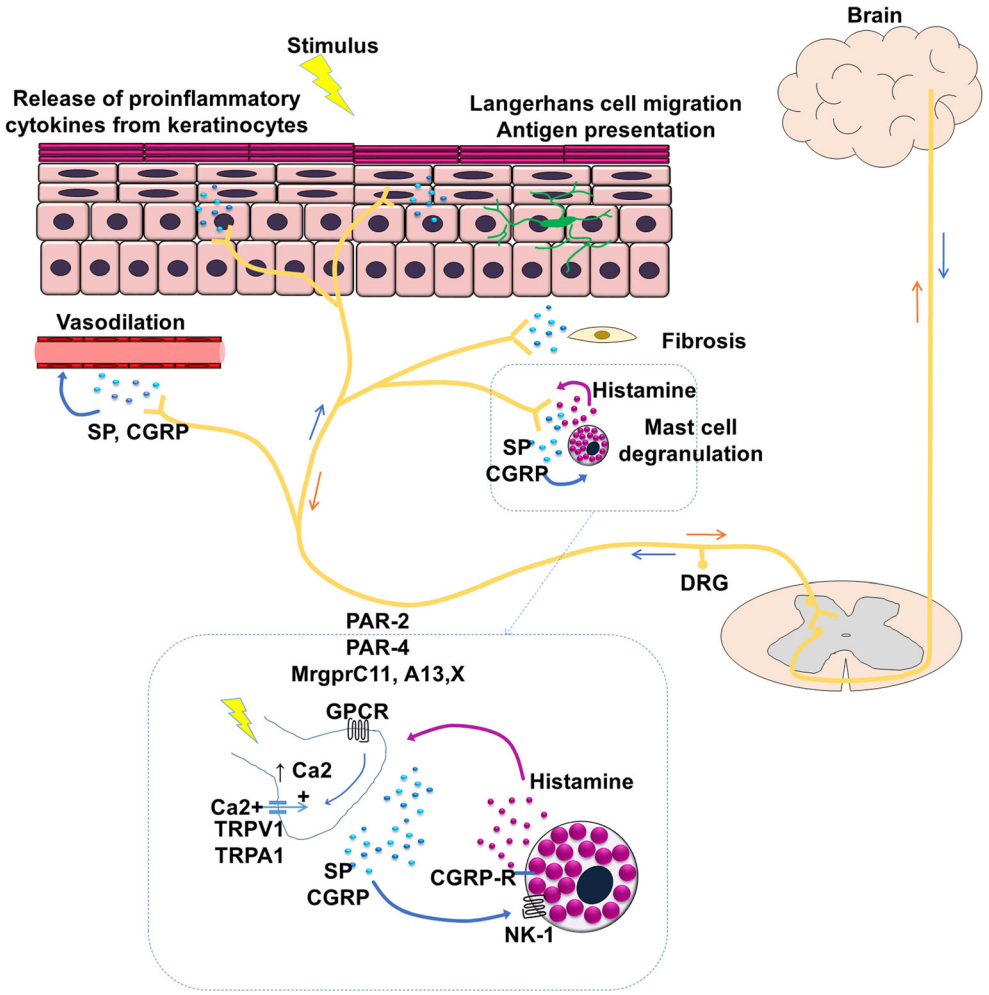

Fig. 1 Densely distributed nerve fibers in skin communicate with mast cells, endothelial cells, keratinocytes, Langerhans cells, and fibroblasts. By releasing neuropeptides, such as substance P (SP) or calcitonin gene-related receptor protein (CGRP), neurons activate skin cells that, in return, release histamine or proinflammatory cytokines—which activate sensory nerve terminals generating a bidirectional positive feedback loop that results in increased inflammation. Abbreviations: transient receptor potential cation channel subfamily V member 1 (TRPV1); transient receptor potential ankyrin 1 (TRPA1); G protein coupled receptors (GPCR); protease activated-receptor 2 (PAR-2); protease activated receptor 4 (PAR4) A13 receptor family (A13, X)

transduction and scratch behavior. MrgprX1 is expressed on mast cells while MrgprA3 and C11 are located on the sensory nerves. This is the only case discovered until now that Mrgpr is expressed in non-neuronal cells [53]. Mrgpr activation on mast cells strongly evokes scratch behavior to itch which subsequently results in skin barrier disruption and loss of immune homeostasis in skin. MrgprA3 and C11, co-localized with various neuropeptides, can sensitize TRPV1 and TRPA1 channels in sensory neurons and induce cellular secretion of neuropeptides [50, 51]. The activation of MrgprX1 degranulates mast cells to communicate with sensory nerve and cutaneous cells for developing neurogenic inflammation [54].

TRP channels

Cationic channels expressed on the sensory nerve endings include some TRP channels, which are involved in neuropeptide release. TRPV1 is a nociceptive cationic channel responsive to high temperature (> 43 °C), and capsaicin is its natural agonist [55]. When TRPV1 is activated by these direct activators, Ca^{2+} influx is initiated and neuropeptides such as SP and CGRP are released to induce neurogenic inflammation. Like PAR and Mrgpr, TRPV1-mediated Ca^{2+} influx in skin can regulate proinflammatory gene expression to affect immune cells, in addition to neuropeptide release. In addition to the sensory nerve, TRPV1 is also found in cutaneous cell functioning as a sensor for pain and chemical stimuli, including keratinocytes, mast cells, dendritic cells, sebocytes, dermal blood vessels, hair follicles, and sweat glands [56]. In endothelial cells and smooth muscle cells, TRPV1-mediated Ca^{2+} influx induces vasodilation by releasing nitric oxide (NO). Meanwhile, TRPA1 is a ligand-gated non-selective Ca^{2+} channel which responds to cold thermal sensation (< 17 °C), contrary to TRPV1. TRPA1 is localized to approximately 60–75% of sensory C fibers, which are also TRPV1-

positive [57]. Topical application of cinnamaldehyde, a TRPA1 agonist, in human skin induces significantly increased itch sensation, which implies a central role for TRPA1 in the itch mechanism [58]. TRPA1 has been shown to play a critical role in itch, including endothelin (ET)-1-mediated itch and chloroquine-induced itch [51, 58, 59] while TRPV1 has shown a contradictory role in itch [60–62]. TRPA1 has been widely investigated on its role in chronic skin inflammation. In addition to thermal stimuli, several inflammatory mediators such as growth factors, bradykinins, proteases and thymic stromal lymphopoietin (TSLP) have been found to act on TRPA1 indirectly [63–65]. TSLP, a central cytokine in Th2-mediated inflammation such as AD, has recently been found to activate TRPA1 by binding a specific receptor, the TSLP receptor (TSLPR), on the sensory nerve in the skin of atopic dermatitis patients [66]. In addition, TRPA1 plays an important role in Th2 cell-dependent itch mediated by the IL-31 receptor expressed on sensory nerves. In a mouse model of AD of transgenic mice overexpressing IL-13, itching was significantly reduced in TRPA1 antagonist-treated mice [67]. Therefore, TRP channels, especially TRPA1, are considered to act like a "gatekeeper" which mediates cytokine signaling of cutaneous inflammation into sensory nerve activation [68–70].

Skin diseases with neurogenic inflammation

Neurogenic inflammation in rosacea

Rosacea is a chronic inflammatory skin disorder which is represented by facial flushing, telangiectasia, and inflammatory papules and pustules on the central location of the face. It has heterogeneous clinical manifestations depending on subtypes: erythematotelangiectatic rosacea (ETR) which has non-transient episodes of flushing and persistent central facial erythema, papulopustular rosacea (PPR) which has transient papules and pustules in addition to the characteristics seen in ETR, phymatous rosacea which has a thickened skin with irregular surface nodularity, and lastly, ocular rosacea which accompanies characteristic ophthalmic symptoms [71]. Although the pathogenesis of rosacea is not fully elucidated, dysregulation of the innate immune system, imbalance of commensal skin microbiota, and abnormal neurovascular signaling are considered to be implicated in the development of rosacea. Trigger factors of rosacea such as exposure to sunlight, heat, or cold; alcohol; spicy foods; or exercise can activate peripheral sensory nerve endings, which implies the particular role of neurogenic inflammation in the pathogenesis of rosacea [71].

Affected rosacea skin has a significantly lower threshold for heat and chemicals compared to non-affected skin, which defines it as sensitive skin [72]. The density of the sensory neuron is increased in the ETR subtype [73]. In addition, the density of TRP ion channels is increased on the sensory neurons and blood vessels as well as immune cells in all subtypes of rosacea [74, 75]. Dermal immunolabeling of TRPV2 and TRPV3 and gene expression of TRPV1 are significantly increased in ETR. PPR showed an enhanced immunoreactivity for TRPV2 and TRPV4, and phymatous rosacea for TRPV3 and TRPV4 [74]. Each subtype of TRPV has different functions, respectively: TRPV1 has a role in vasoregulation and nociception and activated by capsaicin, heat, and inflammation; TRPV2 in innate immunity, nociception, inflammation, vasoregulation, and heat sensing; and both TRPV3 and TRPV4 in heat sensing [76–78]. Beyond TRPV1–4, TRPA1 has been shown to be related to pathogenesis of rosacea. TRPA1 is activated by spices such as cinnamaldehyde and mustard oil as well as thermal stimuli. In mouse experiments, topical cinnamaldehyde induced vasodilation in a TRPA1-dependent mechanism, which could be involved in the flushing phenomenon in rosacea patients [79]. TRPA1 can also sense oxidants, which could support the role of reactive oxygen species (ROS) in the development of rosacea [80]. In rat neurons, TRPA1 is co-localized with PAR-2 which can be activated by proteases to induce inflammation in the human skin [63]. Therefore, it is supposed that the increased amount of serine protease in rosacea might induce TRPA1-mediated inflammation via upregulation of PAR [63].

Meanwhile, neuropeptides such as PACAP, SP, VIP, and CGRP are increased in rosacea [81, 82]. VIP and PACAP, as well as CGRP, play as potent vasodilators, acting on the smooth muscle cells in arterioles, while SP is critical for edema via the NK-1 receptor on postcapillary venules in rosacea [83]. PACAP can also stimulate NO release from endothelial cells which results in indirect vasodilation [84]. Neuropeptides also activate mast cells to release histamine which induces vasodilation and tryptase which is a chemotactic agent for fibroblasts and matrix metalloproteinases (MMPs), contributing to fibrosis in rosacea [85, 86]. In addition, neuropeptides stimulate IL-1β production and activate leukocyte migration via upregulation of VCAMs in rosacea [25, 87]. There is literature that shows promising efficacy of intradermal botulinum toxin injection for treating refractory erythema and flushing in patients with rosacea, which needs further investigation [88].

Neurogenic inflammation in psoriasis

Psoriasis is one of the common chronic inflammatory skin disorders with the prevalence ranging from 0.5 to 11.4% in adults worldwide [89]. It is characterized by hyperproliferation of abnormally differentiated keratinocytes and cutaneous immune cell infiltration including T cells, dendritic cells, and neutrophils. Clinically, psoriasis manifests as well-demarcated red indurated plaques with silvery thick scales over any body area, especially on the prominence such as elbows or knees. The pathogenesis of psoriasis has been rapidly evolving in recent years, in which the IL-23/Th17 cell axis plays a major role in close interaction with keratinocytes

[90]. However, there has been multiple literature reporting on clinical symptom changes in psoriatic patients after having acquired central or peripheral nerve damage. The patients showed spontaneous clearance or improvement of the skin lesion which was limited to the area affected with nerve damage while the non-affected area did not [91–99]. Similarly, in a murine model of psoriasis, cutaneous denervation by traumatic nerve injury resulted in reduction of clinical symptoms of psoriasis [100]. These observations imply that the nervous system may be critical for the pathogenesis of psoriasis.

Immunohistochemical studies in psoriatic patients display an altered expression of various neuropeptides and of their receptors, as well as a marked proliferation of the cutaneous nerve in the skin [101]. These neuropeptides include SP, CGRP, somatostatin, β-endorphin, VIP, and PACAP, which can modulate the immune system during psoriasis development [101]. SP initiates the inflammatory process, leading to proliferation of specific T-lymphocytes and mast cell degranulation, in the early stages of psoriasis [102, 103]. CGRP has a role as a potent vasodilator in the pathogenesis of cutaneous inflammation in psoriasis, and synergizes with SP [104]. VIP modulates mast cell degranulation and the production of pro-inflammatory cytokines, such as IL-6, IL-8, and RANTES (regulated upon activation, normal T cell expressed and secreted, also known as CCL5), in addition to vasodilation, all of which are involved in the pathogenesis of psoriasis [105]. Aberrant expression of these neuropeptides is especially important for pruritus in psoriasis, which is present in 60–90% of patients with psoriasis [106]. There is a significant correlation between the number of SP-positive nerve fibers and NK-2 receptor-immunoreactive cells in the psoriatic skin lesion and intensity of pruritus [107]. Psoriasis patients with pruritus also showed higher expression of receptors for SP and CGRP compared to non-pruritic patients, while the immunoreactivity of SP, CGRP, VIP, and PACAP did not show significant difference [108]. In addition, the expression of NGF and its receptors is upregulated in pruritic lesions of psoriasis skin and correlated with the intensity of pruritus [108, 109]. NGF plays a role in modulating nerve innervation and neuropeptide release. It is mitogenic to endothelial cells, activates lymphocytes, degranulates mast cells, and induces keratinocyte hyperproliferation, all of which constitute the development of psoriasis [110, 111]. On the contrary, semaphorin-3A, which inhibits neuronal outgrowth of sensory C fibers, is downregulated in the dermis of pruritic psoriasis skin lesion and negatively correlated with pruritus [112, 113]. Thereby, upregulated NGF with downregulated semaphorin A might contribute to the hyperinnervation of sensory C fibers in psoriatic lesion which clinically induces pruritus.

The clinical trials of botulinum toxin A administration to treat psoriasis by inhibiting neuropeptide release has been reported in a few studies. Zanchi et al. reported significant efficacy of botulinum toxin A injection in the patients of inverse psoriasis, a variant of psoriasis which affects the intertriginous area [114]. The patients showed favorable clinical improvement although it is possible that the observed improvement is due to reduced sweating and maceration in the flexural area due to the anti-hydrotic effect of botulinum toxin and not from the inhibition of neurogenic inflammation. A study using murine model of plaque psoriasis showed marked reduction of acanthosis and lymphocyte infiltration after botulinum toxin A injection [115]. However, recent clinical trials of botulinum toxin A injection on the patients with plaque psoriasis did not show significant efficacy compared with control [116].

Neurogenic inflammation in atopic dermatitis

AD is a chronic relapsing inflammatory skin disease which is characterized by skin barrier disruption and immunological alteration. Clinically, it manifests as eczematous skin eruptions with severe pruritus with continued flares and remission in chronic course. AD most frequently occurs in infancy or childhood with 10–20% prevalence worldwide, which decreases to 2–3% in adulthood [117]. Although the etiology of AD is not fully elucidated, it is considered a multifactorial disorder with genetic and environmental background. However, one of the key histological findings of AD is the excessive density of cutaneous sensory nerve fibers in skin lesion, which implies the role of innervation and neuropeptides in the pathogenesis of AD [118, 119]. The skin of AD lesion is hyper-innervated with increased SP- and CGRP-positive nerve fibers in the epidermis and papillary dermis with increased mast cell-nerve fiber contacts, compared to the non-lesional skin [120–122]. NGF and its receptor are highly upregulated in the keratinocytes of AD patients compared with healthy keratinocytes, which contribute to neurite overgrowth and the increased proportion of CGRP-positive neurite length [119, 123]. NGF levels are also increased in plasma of AD patients and correlate with clinical severity and eosinophil counts [124]. In the NC/Nga AD mouse model, the topical high-affinity NGF receptor inhibitors improved clinical symptoms and decreased the epidermal density of the nerve fibers [125]. In addition to NGF, neurotrophin-4 production is increased in the epidermis of AD lesion [126] and the brain-derived neurotrophic factor (BDNF) level is also elevated in plasma and eosinophils from AD patients, which is chemotactic for eosinophils [125]. On the other hand, the production of semaphorin 3A, the epidermal axon repulsion factor, is decreased in atopic keratinocytes, which consequently contributes to the hyper-innervation in AD skin together with increased neurotrophins [127]. The alteration of epidermal Sema3A and NGF levels with the modulation of epidermal innervation was demonstrated after phototherapy in AD patients [118]. Nerve fiber sprouting has also been observed in the skin lesions of patients with nummular eczema and allergic contact eczema [120, 128]. The plasma levels of neuropeptide SP are increased in AD patients, and remain elevated even after AD remission [129]. The increased level of SP, in AD, induces the release of

IFN-γ, IL-4, TNF-α, and IL-10 from the peripheral blood mononuclear leukocytes [130, 131].

The plasma levels of CGRP are not elevated in AD patients although they are significantly higher in AD patients with intense pruritus compared to the AD patients without pruritus [129]. CGRP upregulates IL-13 and human leukocyte antigen (HLA)-DR expression in circulating cutaneous lymphocyte-associated antigen (CLA)-positive T cells in AD patients, which does not in healthy controls [132]. CGRP also increases the IL-13/IFN-γ ratio after culture, which supports its immunomodulatory ability in AD [132].

In a mouse model of AD, stress deteriorated AD symptoms with increased neurogenic inflammation presented by mast cell degranulation, interstitial neuropeptidergic dense core granules, mast cell apoptosis, and endothelial gapping [133]. However, in mice lacking the NK-1 SP receptor, AD worsening was not observed, underlining the importance of NK-1 receptors on the sensorial terminations. Interestingly, the total $CD4^+$ cell number was not changed by stress but the cytokine profile shifted toward Th2 in the skin, which is allergy-relevant. Taken together, stress exacerbates AD via SP-dependent neurogenic inflammation and subsequent shifting of local cytokine milieu toward Th2 [133]. In accordance with these findings, SP-induced scratch behavior in mice is mediated by NK-1 receptor activation [134, 135]. The administration of NK-1 receptor antagonist BIIF 1139 CL decreased scratching behavior in mouse models [136]. Aprepitant (Emend™), a selective high-affinity NK-1 receptor antagonist which was originally developed for the prevention of chemotherapy-induced emesis, significantly improved pruritus in patients with chronic pruritus including AD [33, 137, 138]. A mouse model of AD showed that systemic aprepitant administration decreased both the serum IgE levels and the density of SP-positive nerve fibers in lesional skin [139, 140]. Thus, pharmacologic interference of SP-mediated neurogenic inflammation can be a promising alternative therapeutic target in the treatment of recalcitrant AD.

Neurogenic inflammation in prurigo nodularis

Prurigo nodularis (PN) is a chronic skin condition characterized by intensely pruritic lichenified or excoriated papules or nodules. It is considered as a localized form of chronic dermatitis representing a cutaneous reaction pattern to repetitive scratching or rubbing due to pruritus. Many patients of PN have a personal or family background of atopic dermatitis and elevated serum immunoglobulin E (IgE) level. Systemic diseases which potentially cause pruritus such as uremia and other pruritic skin conditions including insect bites and scabies can also trigger PN [141]. The histology of PN frequently shows neural hyperplasia in dermal nerves as well as hyperkeratosis, irregular acanthosis, fibrosis of papillary dermis with vertically arranged collagen fibers, and non-specific inflammatory cell infiltration [142]. It is increasingly accepted that such neural proliferation and neurogenic inflammation play an important role in initiating and maintaining chronic pruritus possibly leading to PN, although its exact pathogenesis is not fully elucidated.

Previous studies about PN showed that NGF and CGRP are main mediators implicated in these processes [143, 144]. An electron microscopy study demonstrated that CGRP-immunoreactive nerve fibers were increased in number in the dermis of PN lesions and were co-localized with mast cells and eosinophils which were also increased in PN compared to normal skin. On the contrary, in the area without nerve fibers, there was neither eosinophil nor mast cells [144]. This indicates the involvement of a close interaction between the neuropeptide CGRP and cutaneous immune cells such as mast cells or eosinophils in the pathogenesis of PN. CGRP is an essential mediator of vasodilation in the skin except for the adrenergic and cholinergic neurotransmitters, which may contribute to vasodilation observed in PN. CGRP can activate mast cells directly through CGRP receptors on the mast cell surface, which may lead to the bidirectional positive feedback loop between nerve fibers and mast cells [20]. CGRP, together with SP, increases eosinophil chemotaxis, activation, and survival [43]. Meanwhile, eosinophils can produce NGF themselves. NGF, which is primarily a neurotrophic factor, also has a proinflammatory effect directly or indirectly, by enhancing neuropeptide release. NGF, in turn, can activate eosinophils to release proinflammatory mediators. NGF is also associated with TRK1 activation resulting in increased TRPV1 expression on nerve fibers and subsequent release of SP and CGRP, thereby establishing a vicious cytokine "pro-itch" cycle [43]. This is supported by a immunohistochemistry study that shows that NGF- and tyrosine kinase A (trkA)-immunoreactive cells are increased in the dermis of PN lesion [143]. However, like the CGRP-immunoreactive nerve fibers, these cells are observed in the dermis, not in the epidermis. Although the main source of cutaneous NGF is keratinocytes, it is assumed that NGF-producing dermal cells, such as mast cells, eosinophils, and lymphocytes, can be the source of increased NGF in PN [143].

Future challenges in skin neurogenic inflammation

Much time has passed since the term "neurodermatitis" was first coined in 1876. Many phenomena have since been described in great detail, and the term "stress," when applied to skin inflammation, has been translated into molecular pathways and is not anymore just a psychoanalytic definition. Now we know that the epidermis closely interacts with nerve endings and that both epidermis and nerves produce substances for mutual sustenance. Neuropeptides, like SP and CGRP, are produced by sensory nerves in the dermis; they induce mast cells to release vasoactive amines that facilitate infiltration of

neutrophils and T cells. We know that some receptors are more important than others in the generation of itch. Mrgprs as well as TRPA1 and Par-2 [37–41] have important roles in itch and inflammation. The activation of MrgprX1 degranulates mast cells to communicate with sensory nerve and cutaneous cells for developing neurogenic inflammation [54]. Mostly importantly, we now know that Mrgprs and TRPV4 are crucial in rosacea [145], while SP, CGRP, somatostatin, β-endorphin, VIP, and PACAP can modulate the immune system during psoriasis development [101] and the increased level of SP, in AD, induces the release of IFN-γ, IL-4, TNF-α, and IL-10 from the peripheral blood mononuclear leukocytes [130, 131].

We are finally starting to understand the intricate connections between the different skin cell types while new challenges are rising. The borders of our skin are no longer marked by the limits of the epidermis but extended to communities of bacteria that live in symbiosis with us. Our microbiome can influence nerve endings, epidermis reactivity [146], and even the maturation of cells that are essential to pruritus such as mast cells [147, 148].

The essential role that the peripheral nerve system plays in shaping skin inflammation suggests that many skin diseases reflect an imbalance between the function of the epidermis, dermis, and the sensory nerves. An abnormal skin microbiome, along with the presence of pathogens, will likely add an additional layer of complexity. Continued research studies are required to better understand these most recent complex clinical interactions.

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