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Neuroimmune Interactions in Atopic and Allergic Contact Dermatitis

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Abstract

The skin is a barrier organ populated by many types of skin-resident immune cells and sensory neurons. It has become increasingly appreciated that neuro-immune interactions are an important component of inflammatory diseases such as atopic dermatitis (AD) and allergic contact dermatitis (ACD). Neuropeptides secreted from nerve terminals play an important role in mediating cutaneous immune cell function and soluble mediators derived from immune cells interact with neurons to induce itch. In this review, we will explore emerging research describing neuronal effector functions on skin immune cells in mouse models of atopic and contact dermatitis. We will also discuss the contributions of both specific neuronal subsets and secreted immune factors to itch induction and the associated inflammatory processes. Finally, we will explore how treatment strategies have emerged around these findings and discuss the relationship between scratching and dermatitis.

Keywords

Atopic dermatitis; itch; contact dermatitis; neuroimmunology

Introduction

The skin is a barrier organ populated by many distinct skin-resident immune cells and sensory neurons. It has become increasingly appreciated that complex neuroimmune interactions exist between these cell types. Disruptions in this complex environment may lead to inflammatory diseases such as atopic dermatitis (AD) and allergic contact dermatitis (ACD). Both conditions have a high lifetime prevalence and share similar symptoms: pruritic lesions and rashes, disrupted barrier function, and a presumed itch-scratch cycle. AD and ACD have mechanistically distinct pathophysiology, both clinically and biologically.

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Neuropeptides secreted from nerve terminals play an important role in mediating cutaneous immune cell function, and soluble immune factors interact with neurons to induce itch under inflammatory conditions. In this review, we will explore emerging research on neuronal effector functions on resident immune cells that have been described in mouse models of atopic and contact dermatitis. In these models, we will also discuss the contributions of both specific neuronal subsets and secreted immune factors to itch induction and the associated inflammatory processes. Finally, we will explore how treatment strategies have emerged around these findings and discuss the relationship between scratching and dermatitis.

Overview of cutaneous neuron subsets:

Cutaneous sensory afferent neurons are diverse in their phenotype and function. The broadest sensory neuron classification is the dichotomy of peptidergic and non-peptidergic, a classic division which has been validated with single cell RNASeq of dorsal root ganglia (DRG) (1). Classically, peptidergic neurons are defined by expression of the neuropeptides such as Substance P (SP) and Calcitonin Gene-related Peptide (CGRP) (2, 3). Peptidergic neurons often express the ion channel Transient receptor potential vanilloid 1 (TRPV1) as well as a variety of other neuropeptides with immunogenic and immunomodulatory effects such as neurokinins (4). Non-peptidergic neurons are classically defined based on the lack of neuropeptide expression. They have been the subject of a recent explosion of research to define their role in cutaneous inflammation and itch. These neurons are phenotypically and functionally distinct from peptidergic neurons, and while canonically termed “non-peptidergic,” some subsets do express TRPV1 as well as neuropeptides and neurotransmitters such as CGRP, glutamate and neuromedin B (5, 6). These neurons are classified into three main groups based on single cell RNASeq clustering of murine DRG: NP1, NP2, and NP3 (5, 7–10). While most robustly characterized as contributors to itch, these neurons also transduce painful sensation and have complex neuroimmune interactions (11, 12). NP1 neurons primarily express Mas-related G-protein-coupled receptor D (MrgprD), which is a G-protein-coupled receptor (GPCR) for beta alanine and, like most neurons, release glutamate (13). This is a polymodal neuronal population that has been found to mediate both itch and mechanical allodynia (14–16). NP2 neurons primarily express the GPCR MrgprA3, which is responsive to the classic pruritogen chloroquine, and can mediate both pruritic and painful sensation (17–19). NP3 neurons are defined by the expression of the IL-31 receptor complex—a dimer of IL-31 receptor A (IL-31RA) and oncostatin M receptor (OSMR), as well as the expression of *Nppb*, which is the gene for the pruritogen Brain Natriuretic Peptide (BNP) (20). It should be noted that these classifications of sensory afferents were derived from studies in mice. While recent transcriptomic analysis of human DRG neurons observed grouping of neuron subtypes that were similar to those observed in murine DRG, there were also many genetic differences. Thus, studies in murine models are likely informative in determining overall principles but there will almost certainly be specific differences between human and mouse [116].

Atopic Dermatitis

Atopic Dermatitis (AD) is an inflammatory and pruritic condition which has a 15 to 20% lifetime prevalence (21). The etiology of AD is complex, with genetic and microbial factors

underlying the disease state. Mutations in filaggrin, an epidermal barrier protein, comprise the strongest genetic risk factor to AD pathogenesis (22, 23). Highlighting the inflammatory nature of this disease, mutations in the cytokine cluster of IL-4 and IL-13 have also been associated with increased risk of developing AD (24). IL-4 and 13-specific treatments—particularly IL-4 receptor (IL-4R) antagonists and Janus Kinase (JAK) inhibitors that target downstream of IL-4R signaling, have been shown to be highly effective in treating both pruritis and inflammation in AD (25, 26). As many as 90% of pediatric AD patients develop lesions that are colonized by *Staphylococcus aureus* (*S. aureus*) (27). Characterizations of these lesions have revealed a complex inflammatory milieu, with a predominantly Type 2 immunological signature and a shift to a Type 17 immune signature in chronic lesions (23, 28). In both lesions and blood, AD patients have increased levels of Th2-skewing alarmins, Thymic Stromal Lymphopoietin (TSLP) and IL-33, indicating the involvement of both innate and adaptive immune effectors (29–31). Consistent with the cytokine profiles, both ILC2s and Th2 cells are increased in AD lesions (32). Elevated levels of circulating IgE have also been documented in 80% of AD patients, pointing towards a role for IgE-responsive effector cells, such as mast cells and basophils in established disease (33). Scratching is the predominant symptom of AD and a significant source of morbidity, leading to decreased quality of life through loss of sleep and discomfort. In addition, itch may be mechanistically linked to the maintenance of AD, as patients on IL-4R inhibitors experience reduced itch prior to the resolution of inflammation, highlighting the neuroimmune nature of AD (25).

Murine Models of AD

Many murine models of AD recapitulate aspects of human AD with varying degrees of accuracy. Genetic models include mice which spontaneously develop AD (Nc/Nga), and mice with mutations in the FLG gene (34). We will focus on three inducible AD models in which neuroimmune connections to itch in AD have been defined: MC903, ovalbumin, and house dust mite. Not only do these models recapitulate many inflammatory characteristics of AD, but they also involve neuro-inflammatory loops. These loops, comprised of interactions between cutaneous neurons and the inflammatory milieu, reciprocally sustain the inflammation and itchy condition through the respective release of neuropeptides and soluble immune factors (Figure 1).

In the MC903 model, mice are sequentially treated with the vitamin D3 analogue calcipotriol/MC903. After 7–14 days of daily treatment, mice develop lesions with consistent with AD inflammation, characterized by increased serum IgE, expression of TSLP and IL-4 and an inflammatory infiltrate. Pathology of the MC903 model is driven by the innate arm of the immune system, as demonstrated by unimpaired inflammation in Rag1^{-/-} mice (35). MC903 induces TSLP release from keratinocytes, which induces an AD-like inflammation through a basophil-ILC2 axis. In this model, TSLP binds to receptors on basophils, which proliferate and produce IL-4, leading to ILC2 expansion and inflammation (36, 37). In addition, aspects associated with Type 1 inflammation such as interferon-gamma expression and neutrophil infiltration have also been observed in this model (35).

In the ovalbumin (OVA) model of AD, mice are epicutaneously sensitized with the model antigen OVA under occlusion. After 3 weeks of treatment, mice exhibit features of AD

paralleling patients, including epidermal thickening and elevated levels of OVA-specific IgE. Similar to the MC903 model, the ovalbumin model of AD-like inflammation generates a Type 2 inflammatory milieu (38). Unlike MC903 however, ovalbumin induces an adaptive immune response. This is characterized by increased Th1 and Th2 CD4+ T cell infiltrates and expression of associated cytokines. There is also an increased DC infiltration following systemic OVA sensitization and subsequent expansion of Th1 and Th2 CD4+ T cell infiltrates (39). OVA also induces CD4+ T cells and Th2 cytokines when epicutaneously challenged following systemic sensitization (40).

Finally, in the House Dust Mite (HDM) AD model, HDM extract (either from *dermatophagoides farinae* or *dermatophagoides pteronyssinus*) is epicutaneously sensitized with staphylococcal enterotoxin B (SEB). HDM predominantly generates a Th2 response characterized by elevated levels of HDM-specific IgE, and includes Th1 components such as IFN-gamma expression. While this inflammatory pattern is similar to OVA, the HDM AD model has the advantage of being more clinically translational since AD patients have been found to have significant populations of HDM-specific T cells as measured by skin patch testing (41). Inflammation in this model is enhanced by the addition of staphylococcus enterotoxin B (SEB) which provides an adjuvant effect. The enhancing effect of SEB mimics *S. aureus* colonization in patients with AD (27). In the HDM and SEB AD model, dysregulated signaling in keratinocytes leads to compromised barrier function of the epidermis, which contributes to both initiation and maintenance of inflammation (42). T cells and mast cells are required for inflammation in this model (43). The cysteine protease activity of HDM is also required for inflammation, perhaps through the cleaving and activation of alarmins and/or protease receptors to precipitate inflammatory responses (44, 45).

Notably, these models induce pruritus and induce quantifiable scratching behavior in mice. (46–48). Thus, these models are often used in the evaluation of neuroimmune interactions in skin which will be discussed below.

Peptidergic Neurons in murine AD models

Studies involving genetic and chemical ablation of TRPV1-expressing neurons have demonstrated their necessity for triggering inflammation in response to imiquimod and *Candida albicans* (*C. albicans*) infection (49, 50). This, however, appears to vary by pathogen as the host response to *Streptococcus pyogenes* is improved in the absence of these neurons (51). Moreover, optogenetic activation of TRPV1-expressing neurons in the absence of other inflammatory stimuli triggers Type 17 inflammation thus demonstrating that these neurons are sufficient to initiate inflammation (52). Additionally, TRPV1-expressing neurons have been found to be required for the induction of AD-like inflammation in the HDM and SEB AD model. Mast cells have long been recognized as a key cell type responding to HDM and clinical responses are reduced in mast cell-deficient mice (43). More recently, HDM was found to directly activate peptidergic neurons leading to the release of SP (53). Resiniferatoxin (RTX) treated mice lacking TRPV1-expressing neurons and mice lacking the SP receptor on mast cells, MrgprB2, had decreased inflammation in response to HDM and SEB treatment. Similarly, IgG-mediated neutralization of SP also led to reduced

mast cell degranulation in response to HDM+SEB. Thus, unexpectedly, SP-expressing neurons which are a large subset of neurons expressing TRPV1 play a central role in the development of HDM-mediated dermatitis by both detecting the HDM and triggering mast cell activation through the neuropeptide SP. Taken together, this demonstrates the role of SP-expressing neurons in initiating inflammation by activating mast cells.

Thus, there appears to be an emerging paradigm in which SP-expressing neurons play a central role in detecting pathogens (54) as well as irritants such as HDM (Figure 1). The subsequent release of SP then triggers mast cell activation which is an obligate component in the response in many cases. This model is involved in the response to irritant Croton oil and likely hapten sensitizers such as DNFB which are discussed below (13, 55). It should be noted that Th2 priming in response to papain requires SP-expressing neurons and SP but does not require mast cell activation (56). Rather, SP directly activates CD301b⁺ dermal DC via MrgprA1 to promote Th2 responses. Other neuropeptides may also play a role in AD pathogenesis. For instance, *S. aureus* and *streptococcus pyogenes* directly trigger CGRP release from peptidergic neurons to suppress neutrophilic activity and impair clearance (51, 57). Given the high association of *S. aureus* with AD lesions, the activity of peptidergic neurons may facilitate staphylococcal persistence in AD patients.

Non-peptidergic neurons in AD models

While TRPV1-expressing neurons are required for the initiation of inflammation in models of AD, non-peptidergic neurons appear to be largely required for itch sensation and the resulting scratching behavior (Figure 1). Using the MC903 AD model, neuronally expressed IL-4 receptor and subsequent JAK/STAT signaling was demonstrated to be required for scratching behavior. Upon MC903 treatment, scratching was decreased in mice with neuron-specific ablation of *Jak1* or *IL4r*. Furthermore, pharmacological inhibition of JAK signaling using ruxolitinib resulted in decreased scratching in MC903-treated mice (40). Leukotriene C₄ (LTC₄) was also established as a potent itch mediator in this model (58, 59). DRG imaging demonstrated that NP3 neurons express cysteinyl leukotriene receptor 2 (CysLTR2). Furthermore, reconstitution of CysLTR2^{-/-} recipients with bone marrow from wild-type donors showed decreased itch in MC903 AD, demonstrating that non-hematopoietic cells (e.g. neurons) responding to LTC₄ are required for itch (58). When the MC903 AD model was paired with intradermal OVA injections in an AD flare model, depleting basophils, the primary source of LTC₄, and pharmacologically blocking CysLTR2 signaling resulted in decreased scratching (59). These studies highlight the capacity for cutaneous neurons to respond to endogenous pruritogens resulting from Type-2 immunity to promote itch and scratching behavior (60, 61).

In addition to responding to LTC₄, NP3 neurons express high levels of the IL-31 receptor. The IL-31 receptor complex is composed of two subunits, OSMR and IL-31RA. Similar to IL-4 receptor activation, IL-31 signals via JAK/STAT signaling resulting in transcriptional changes and activation in neurons (62). The biology of IL-31 is complex. It is primarily expressed by Th2 cells and mast cells, which have been shown to produce IL-31 in response to immunogenic stimuli such as staphylococcus enterotoxin and alarmins, respectively (63–65). IL-31 is a strong pruritogen and directly activates NP3 neurons to induce itch

through the release of the pruritogen BNP from sensory afferents to activate spinal dorsal horn neurons (20, 66). Though much emphasis has been placed on the expression of the IL31R and Cys1tR2 on NP3, it is important to note that many other receptors for pruritogens including IL-4, IL-13, histamine, and other leukotrienes that arise during Type 2 inflammation are expressed by many other subsets of cutaneous neurons. Thus, it is likely that additional endogenous pruritogens and neuron subsets other than NP3 participate in transducing pruritic sensation (7). Finally, it is worth noting that the contributions of NP3 and other non-peptidergic neuron subsets in promoting Type-2 inflammation remains a poorly explored area.

Targeting Neuroimmune pathways in AD

Clinical applications of neuroimmune research in AD centers around the two categories of neuroimmune interactions: peptidergic neuron-mediated neurogenic inflammation and non-peptidergic neurons driving itch. Treatment using botulinum toxin, which disrupts neuropeptide release through proteolytic cleavage of the SNARE proteins, results in decreased pruritus and neurogenic inflammation (67). Clinical Scoring of Atopic Dermatitis (SCORAD) was significantly decreased in AD patients treated with botulinum toxin, likely through disrupting the secretion of immunogenic neuropeptides to alleviate inflammation (68). This provides evidence for the importance of neuroimmune circuits driving inflammation and could potentially provide a clinical benefit. Application of a recently developed topical TRPV1 selective antagonist PAC-14028 has shown promise in improving both SCORAD and pruritus (69). Since itch is the predominant symptom in AD, there has been strong interest focusing on IL-31 receptor inhibition (70). IL-31 inhibition by the antibody nemolizumab robustly decreased itch and improves rash severity in some studies (71, 72). As discussed above, both IL-4 and JAK inhibitors are highly effective treatments for both dermatitis and itch for AD patients in clinic (25, 26, 73), likely through both immune and neuronal inhibition.

Contact hypersensitivity

Allergic contact dermatitis (ACD) is a common and often debilitating disease with a lifetime prevalence of 20% (74). ACD or contact hypersensitivity (CHS) in mouse models is a T cell-mediated delayed type-IV hypersensitivity, which is defined by two immunological phases: sensitization and challenge (75). In the sensitization step, a low molecular weight hapten with otherwise low immunogenicity binds to self-proteins to form neo-antigens. These neo-antigens are taken up by antigen-presenting cells, which then drive expansion of antigen-specific T cells. This second phase of elicitation takes place when the hapten is re-encountered and an effector response results in symptoms, typically in the form of a pruritic dermatitic rash (76). Importantly, sensitization is typically an asymptomatic step, and all patients with ACD have previously been sensitized. AD and ACD share some mechanistic similarities but there does not appear to be an association between AD patients and risk of allergen sensitization (77).

Unlike AD, which is primarily a Type 2 and Type 17 mixed inflammatory condition, contact dermatitis can be mediated by Type 1, Type 2, or Type 17 inflammation, and is

normally characterized by elements of more than one type of immunity: Halo-benzenes (DNFB, TNCB) are a Th1/Th17 model (78–81), oxazolone is a Th1/Th2 model (82–84), FITC is a Th2/Th17 model (85–87), while urushiol is a Th2 model (88, 89). While there are multiple models which have varying immune phenotypes, all CHS models contain the following sequence of immunological events: during the sensitization stage, a hapten creates neoantigens and activates resident innate immune cells—mast cells and DCs, which then migrate to draining lymph nodes and present the neoantigens to T cells (90). Other cells such as neutrophils and endothelial cells are also required for this process (91–95). During the challenge phase, reapplication of the hapten creates neoantigens and activates resident immune cells, which then present the antigen to an expanded population of T cells (96). Mast cells also play an active role through their release of numerous inflammatory factors following activation via SP, inflammasome activation or neoantigen-specific IgE cross-linking (84). As CHS reactions are highly pruritic, neurons also play critical roles not only in transmitting itch, but also in modulating the sensitization and challenge phases.

Peptidergic neurons in CHS

The primary function of peptidergic neurons in models of AD is the secretion of immunogenic neuropeptides which have effector functions on resident immune cells (Figure 2). As mentioned with the HDM model, SP can activate both mast cells and CD301b⁺ DC (53, 56). While AD and ACD are distinct disorders, in both conditions mast cells play a significant roles in the initiation of skin inflammation (97). Thus, it would seem likely CHS would involve activation of mast cells via SP released from peptidergic neurons. However, the situation is more complex. CHS in response to both TNCB and oxazolone requires the SP receptor, MrgprB2, for the development of pruritus as monitored by scratching behavior and cellular infiltration, however ear thickness was unchanged in *Mrgprb2*^{−/−} mice (98). Therefore, it is likely that interactions between SP and mast cell-expressed MrgprB2 initiates DC migration, resulting in T cells priming during hapten sensitization. However, this neuroimmune axis may be redundant following hapten challenge (99, 100).

Neuropeptides other than SP such as CGRP and pituitary adenylate cyclase-activating polypeptide (PACAP) appear to be important in CHS. Release of PACAP from peptidergic neurons during the sensitization phase is required for oxazolone-induced CHS. PACAP increased expression of CCR7 and CXCR4 on DC (101). Peptidergic neurons are an important source of CGRP, whose receptor is a dimer comprised of receptor activating modifying protein (RAMP1) and calcitonin receptor-like receptor (CRL). CGRP is required for a variety of immune functions, from inducing DCs to polarize Th2 cells to acting on vascular cells to induce vasodilation (102) and is well-studied in the context of CHS. *Ramp1*^{−/−} mice that cannot respond to CGRP have attenuated CHS to FITC (Th2) but exacerbated in response to TNCB (Th1/17) CHS (103). This is consistent with the observation that CGRP promotes Langerhans cell-mediated Th2 priming *in vitro* (104). CGRP signaling in endothelial cells is required for both the sensitization and challenge phases DNFB (Th1/17) CHS (105).

Although the role of CGRP on endothelial cells during the CHS response is clear, CGRP has manifold actions on many immune cell types in other contexts. CGRP is required

for neuropeptide-mediated inflammation and host defense against *C. albicans* (50, 52). CGRP also suppresses neurotrophic function in the skin, where blocking CGRP augments host defense against dermonecrotic *S. Pyogenes* infection (51). At a cellular level, CGRP suppresses release of TNF from macrophages, induces keratinocyte proliferation, and promotes CD8⁺ T cell exhaustion (106, 107). Thus, the immunological effects of CGRP are complicated with both positive and negative function in many immune cell types and the precise function of CGRP in CHS remains to be fully elucidated.

Peptidergic neurons are also required for scratching behavior in CHS. TRPV1 and TRPA1, which are generally expressed on peptidergic neurons, are necessary for Squaric Acid Dibutylester SADBE-induced scratching (108). Yet despite the generally pro-inflammatory role of peptidergic neurons, *Trpv1*^{-/-} and *Trpa1*^{-/-} mice develop increased SADBE CHS. The decoupling of scratching behavior and inflammation in peptidergic neurons is an interesting finding which challenges how we may view scratching and the role of peptidergic neurons in inflammation and highlights the context-dependent nature of neuronal effector function in inflammation.

Non-peptidergic neurons in CHS

Similar to peptidergic neurons, non-peptidergic neurons have a complex role in mediating inflammation and itch in CHS beyond the transmission of Type 2 cytokine-induced scratching observed in AD models. The three non-peptidergic neuron subsets NP1, NP2, and NP3 have all been studied in multiple models of CHS. Contrary to their namesake, non-peptidergic neurons do express neuropeptides, pruritic mediators, and other neurogenic immune effectors. We have demonstrated that MrgprD-expressing neurons suppress responses to croton oil irritant dermatitis and DNFB CHS, two models of skin inflammation which require mast cell function (Figure 2). MrgprD-expressing neuron-derived glutamate was found to suppress mast cells through a transcriptional ‘reprogramming’ that reduced expression of the SP receptor *Mrgprb2* as well as many genes associated with granule contents (13).

NP2 neurons, defined by the MrgprA3 receptor, have been studied in the context of CHS-mediated scratching behavior. In the SADBE model of CHS, MrgprA3 expression is increased and the *Mrgpr* gene cluster is required for scratching but not changes in ear thickness (109, 110). In addition, oxazolone CHS replicated the findings in SADBE, demonstrating increased numbers of MrgprA3 and MrgprC11-expressing neurons and the requirement of the Mrgpr cluster in oxazolone-induced scratching (Figure 2). Curiously, while the Mrgpr cluster was required for scratching, it was not required for changes in ear thickness (111). Further study of this neuron subset has resulted in a comprehensive characterization of RNA expression of MrgprA3⁺ DRGs in SADBE CHS (112). However, the role of MrgprA3⁺ neurons in other models of CHS and immune contexts remains to be explored. NP3 neurons have been the subject of both behavioral and immunological study in CHS. In the model of urushiol CHS, siRNA- knock-down of the IL-33 receptor ST2 in the DRGs demonstrated the reduction of both scratching and inflammation (113). As would be expected, IL-31 was required for scratching behavior following FITC and DNFB challenge. Intriguingly, IL-31 was not required for the inflammation in both models,

implying the decoupling of scratching behavior from inflammation (114). The mechanistic role of non-peptidergic neurons in both cutaneous inflammation and pruritic behavior in CHS is still nascent and many details remain to be explored.

When is scratching required for inflammation?

Conventional wisdom held by primary care physicians and dermatologists alike is the importance of scratching in development and maintenance of lesions of atopic dermatitis. The “itch-scratch cycle” is a commonly used concept to characterize this observed phenomenon: inflammation leads to the release of pruritic factors which then trigger a scratching response leading to barrier disruption. This then generates further inflammation through the release of alarmins and entry of pathogens, which then perpetuates the cycle. However, the relationship between pruritus and inflammation is complex and not always as cyclical as would be suggested by this paradigm. Hence the question remains: Is AD the rash that itches or the itch that rashes? A healthy body of research done in mouse models of AD have shown that Type 2 inflammation is sufficient to generate scratching behavior through a variety of mechanisms. Yet the question of whether scratching is required for inflammation is not as clear. Support for scratching driving inflammation comes from the IL-31 overexpression mouse model which develop spontaneous rashes, likely due to the excessive scratching. In mice given oxazolone CHS, preventing ear scratching with Elizabethan collars greatly reduced inflammation (101). In patients, there are several diseases such as prurigo nodularis and chronic idiopathic pruritus where pruritus is the initial event and subsequent scratching leads to the development of clinical lesions. In contrast, there are examples in which reducing scratching does not affect inflammation. *IL-31^{-/-}* mice exhibited a marked reduction in scratching in FITC and DNFB CHS models, but inflammation as measured by ear thickness was not affected (114). Similarly, disrupting leukotriene signaling reduced scratching in the MC903 model, inflammation in the ear thickness was not affected.

Although it does not address the question of which comes first, recently developed highly effective therapies for AD and ACD directly target neurons to suppress pruritus and immune cells to suppress inflammation. Tofacitinib and delgocitinib are topical JAK inhibitors which have demonstrated efficacy in reducing both disease severity and itch in their phase 2 and 3 clinical trials, respectively (73, 115). Similarly, targeting the IL4R directly suppresses activation of itch-sensing neurons and limits the development of Th2 inflammation (40). Thus, the efficacy of these treatments may be due to targeting not only effector immune cells, but also itch-sensing neurons. The clinical success of exploiting this particular neuroimmune pathway is evidence of the homologies shared by the murine and human nervous system. It should be noted, however, that even though there are transcriptional and functional similarities between human and mouse sensory neurons, there are also significant differences (116). Nevertheless, the current pace of neuroimmune research has the promise of revealing many additional therapeutic neuroimmune targets in both AD and ACD.

Conclusions

In this review we have discussed how specific subsets of cutaneous neurons have distinct functions in inflammatory loops of AD and ACD. In AD, peptidergic neurons initiate and sustain inflammation through the secretion of immunogenic neuropeptides which act on mast cells to drive DC migration and Th2 priming, while non-peptidergic neurons, primarily the NP3 subset, respond to inflammatory signals to drive pruritus and scratching behavior. In ACD, the role of such neurons is similar, yet there are hapten-specific differences. Despite the remarkable recent progress in this field, many unanswered questions remain. For instance, peptidergic neurons are required to initiate inflammation, but do they sustain ongoing inflammation in neuroimmune loops? In addition, while non-peptidergic neurons do appear to have some immune effector function independent of scratching, the underlying mechanisms are poorly described. Finally, relationship between scratching and inflammation is clearly critical to the pathogenesis of Type-2 inflammatory diseases, but mechanistic details of the itch-scratch cycle need further exploration. In sum, the relationship between cutaneous sensory neurons and Type-2 inflammation in the skin remains nascent with many fundamental pathways and relationships and potential therapies yet to be discovered.

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Abbreviations used:

AD	atopic dermatitis
ACD	allergic contact dermatitis
CHS	contact hypersensitivity
SP	Substance P
CGRP	Calcitonin Gene-related Peptide
TRPV1	Transient receptor potential vanilloid 1
Mrgpr	Mas-related G-protein-coupled receptor
OSMR	oncostatin M receptor
BNP	Brain Natriuretic Peptide
JAK	Janus Kinase
<i>S. aureus</i>	<i>Staphylococcus aureus</i>
TSLP	Thymic Stromal Lymphopoietin
OVA	Ovalbumin
HDM	House Dust Mite

SEB	staphylococcus enterotoxin B
<i>C. albicans</i>	<i>Candida albicans</i>
RTX	Resiniferatoxin
LTC₄	Leukotriene C ₄
CysLTR2	Cysteinyl leukotriene receptor 2
SCORAD	Clinical Scoring of Atopic Dermatitis
DNFB/TNFB	Di/Trinitrofluorobenzene
RAMP1	receptor activating modifying protein
CRL	receptor-like receptor

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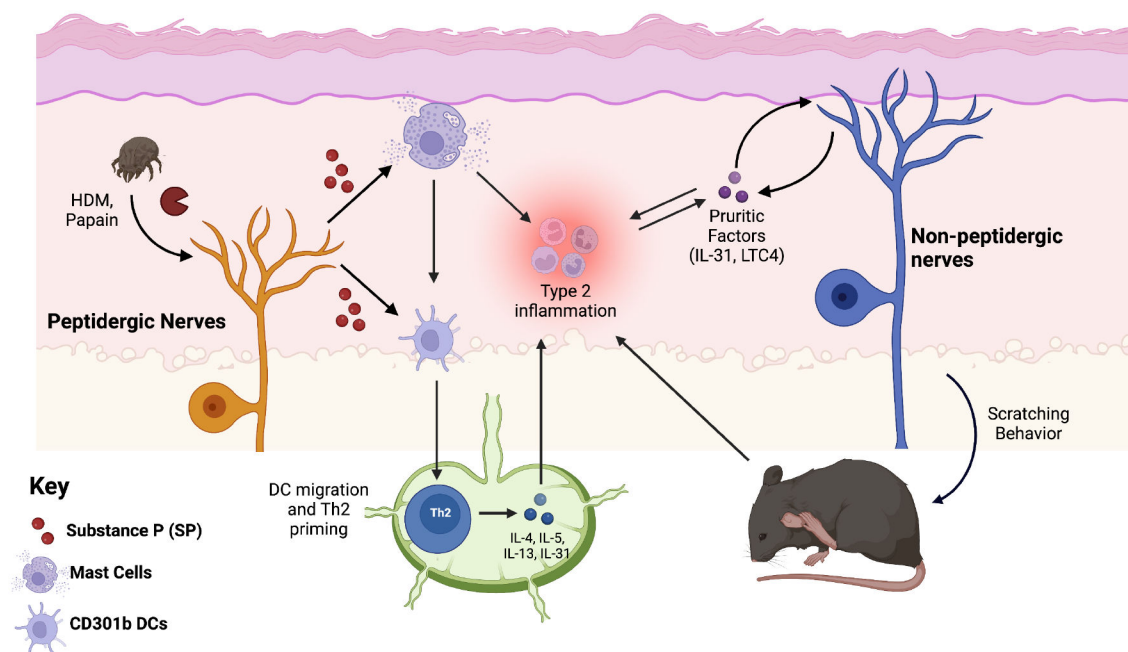


Figure 1.
Scheme of neuroimmune function in Atopic Dermatitis.

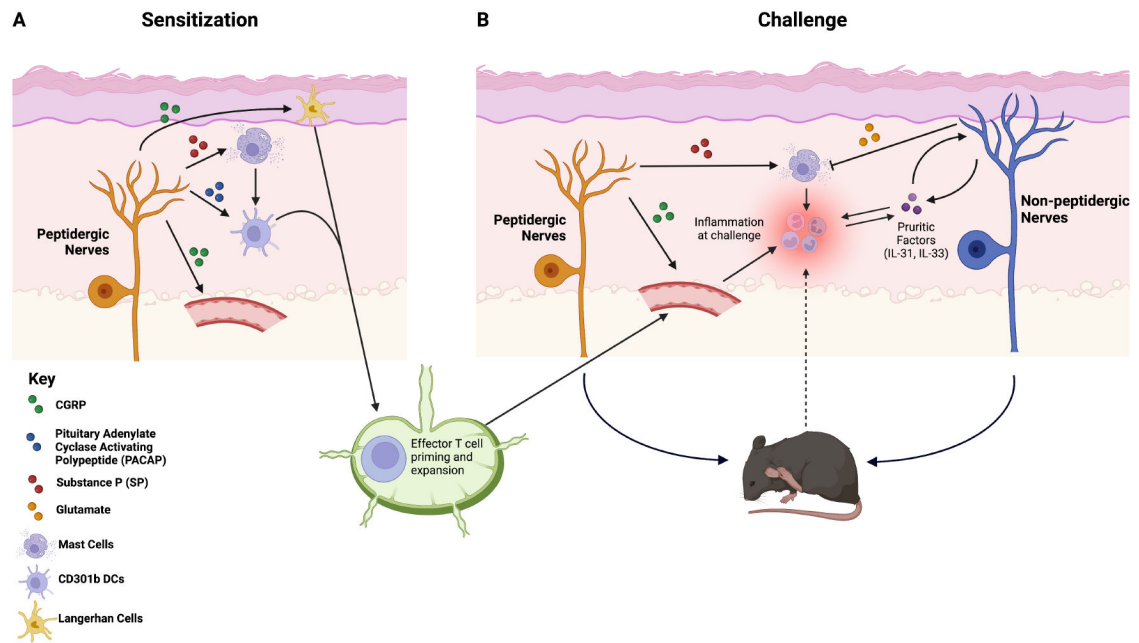


Figure 2.
Scheme of neuroimmune function in contact hypersensitivity.