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Neuroimmune crosstalk in the skin: a delicate balance governing inflammatory processes

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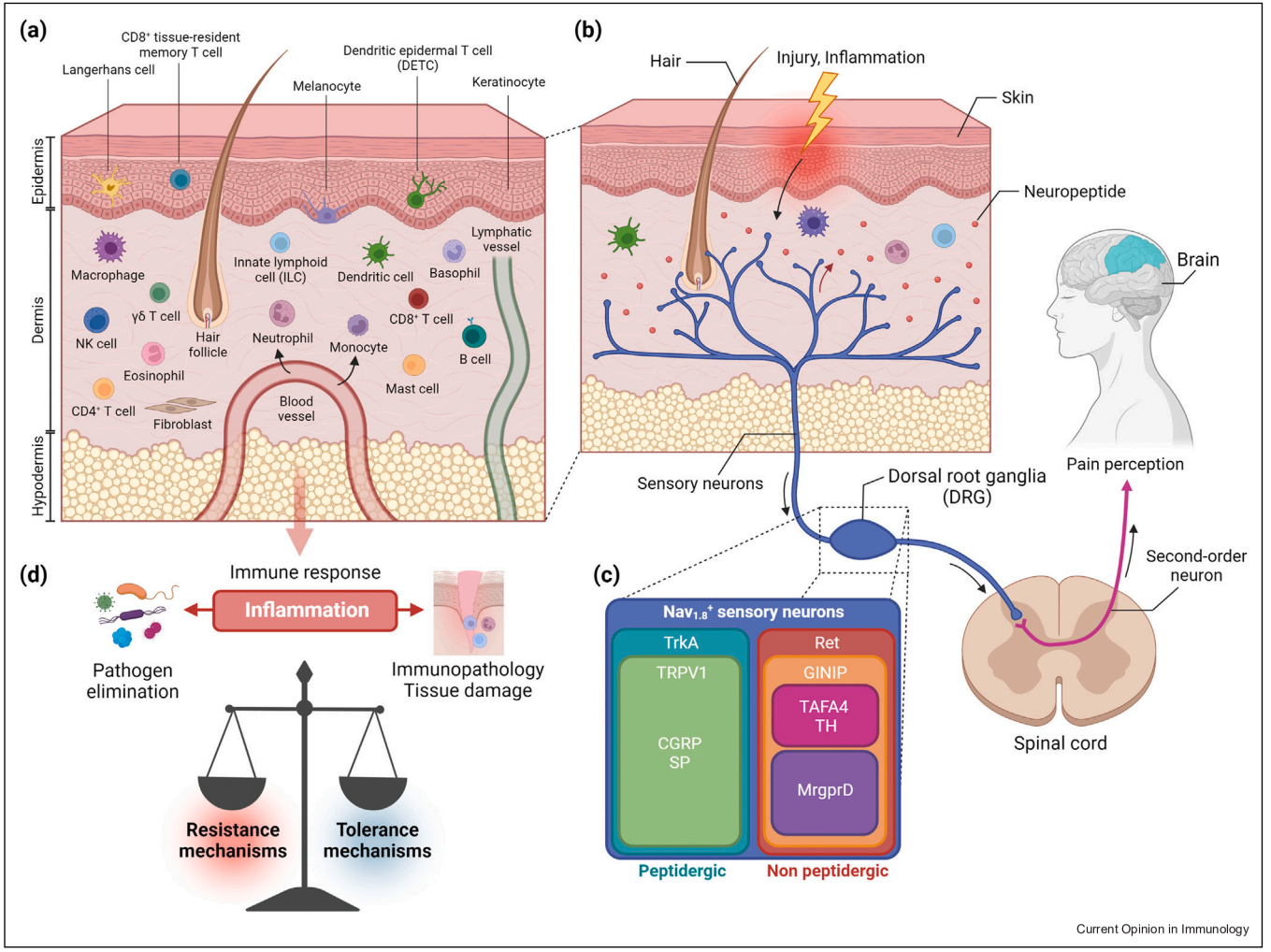
With its unique structure and large numbers of immune cells, the skin is one of the body's first lines of defense against attacks from the environment. It is also innervated by a dense meshwork of primary sensory neurons, including nociceptive fibers specializing in the detection and transduction of harmful stimuli that can elicit pain. This tissue is, therefore, a key organ for studies of neuroimmune interactions and their impact on the host response to environmental challenges. Neuroimmune crosstalk in the skin is crucial for the regulation of inflammation, tissue repair, and host defense against pathogens. A better understanding of this regulation would facilitate the identification of new molecular targets for the treatment of skin diseases.

Introduction

The skin is a barrier organ with three main layers: the epidermis, dermis, and hypodermis. The structural and biophysical properties of the skin help to maintain homeostasis and provide a first line of defense against microbial invasion [1]. Diverse immune cells within the skin perform immunosurveillance. The epidermis, the outermost layer of the skin, is in direct contact with the external environment and consists of stratified layers of keratinocytes forming an impermeable barrier. Langerhans cells (LC) and T-cell subsets are the principal immune-cell populations in the epidermis (Figure 1a). The dermis, which is rich in collagen produced by fibroblasts, lies just below the epidermis. It forms an elastic mechanical barrier containing blood and lymphatic vessels, hair follicles, and the sweat and sebaceous glands. The dermis contains many immune cells, including macrophages, mast cells, and dendritic cells (DC), together with T and B cells involved in adaptive immune responses [2,3] (Figure 1a). These cells act as sentinels, reacting rapidly to pathogen invasion or tissue injury. Their activation leads to the recruitment of additional immune cells, such as monocytes and neutrophils from the blood, inducing an inflammatory response. The hypodermis lies beneath the dermis and is a richly vascularized connective tissue that may, depending on its location, contain adipose tissue [4] (Figure 1a).

The skin is innervated by a rich network of heterogeneous primary sensory nerve endings involved in diverse physiological functions (Figure 1b). These neurons detect myriads of external stimuli through the selective expression of dedicated cell-surface molecules. These stimuli range in intensity from harmless to noxious, and may be mechanical, thermal, or chemical in nature [5]. All skin-innervating primary sensory neurons are excitatory; they have their cell bodies in the dorsal root ganglia (DRG) or trigeminal ganglia (TG), and they project centrally in the dorsal horn of the spinal cord. They include nociceptors, which specialize in the detection and transduction of high-threshold noxious stimuli, leading to the sensation of pain and eliciting defensive behaviors [6–9]. Most nociceptors are unmyelinated C- or lightly myelinated Aδ-fibers that express the sodium channel $Nav_{1.8}$. Historically, they have been classified into two subclasses on the basis of developmental cues and neuropeptide production: peptidergic and nonpeptidergic, although this classification was recently revisited using single-cell RNA-sequencing methods [10]. Peptidergic nociceptors are classically defined as expressing tropomyosin receptor kinase A (TrkA) and transient receptor-potential cation-channel subfamily-V member 1 (TRPV1) and they produce neuropeptides, such as substance P (SP) and calcitonin gene-related peptide (CGRP), whereas nonpeptidergic C-fibers express the glial cell-derived neurotrophic factor receptor Ret and the Gαi-interacting protein (GINIP) [8] (Figure 1c). This classification is now

Figure 1



Neuroimmune responses in the skin. **(a)** The skin is a complex organ composed of diverse specialized cells organized into three layers: the epidermis, dermis, and hypodermis. The epidermis is composed principally of keratinocytes, but also includes immune cells, such as LC, memory CD8 T cells, and dendritic epidermal T cells (DETCs), which are present in mice but not in humans. Many innate and adaptive immune cells are also present in the dermis at steady state, as indicated. Following tissue damage or infection, these cells are activated and produce inflammatory cytokines and chemokines, which attract neutrophils and monocytes from the blood. Activated DCs also migrate from the skin to the draining lymph nodes (LNs) through lymphatic vessels, initiating adaptive immune responses. Inspired by Ref. [2]. **(b)** The skin is also densely innervated by nociceptive sensory neurons, which are characterized by expression of the sodium channel $Nav_{1.8}$. Mediators released upon skin injury or infection are directly sensed by these neurons and noxious stimuli are transmitted to the DRG or the TG, and then to the spinal cord (black arrows). These signals are processed in the spinal cord and relayed to a second-order neuron, finally reaching the somatosensory cortex, where they induce pain perception. Activated sensory neurons can also locally produce neuropeptides (red arrow) that modulate skin homeostasis and immune-cell responses. **(c)** Schematically, $Nav_{1.8}^{+}$ sensory neurons can be split into two major populations on the basis of their

Figure 1 (suite)

molecular characteristics: peptidergic fibers, expressing TrkA and TRPV1 and producing neuropeptides, such as SP and CGRP, and nonpeptidergic C-fibers expressing Ret and GINIP. GINIP$^+$ neurons include TAFA4$^+$ TH$^+$ C-LTMR and MRGPRD$^+$ neurons. This representation provides a simplified view of these subpopulations of neurons, which are much more heterogeneous molecularly [10,11•]. **(d)** Signals from the sensory nervous-system control the inflammatory immune response governing the fine balance between resistance mechanisms ensuring microbial clearance and tolerance mechanisms preventing excessive tissue damage. This regulation promotes host resistance to disease, allowing not only pathogen elimination, but also tissue repair and the restoration of homeostasis. This figure was created with BioRender.com.

considered to be an oversimplification, as TRPV1 ex-pression is not restricted to $Nav_{1.8}$-expressing pepti-dergic nociceptors, and lower levels of CGRP, SP, and TrkA-encoding transcripts have also been detected within nonpeptidergic nociceptors [10]. Recent ana-tomic, molecular, and transcriptomic studies have re-vealed tremendous heterogeneity among nociceptors and nonnociceptive neurons [10–13].

Many factors, such as pathogen-associated molecular pat-terns, damage-associated molecular patterns, and immune-cell-derived cytokines, including tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), and IL-6, are released during skin infection or injury. These mediators are re-cognized by diverse receptors present on the peripheral nerve terminals of sensory neurons [14]. Depending on their nature, they trigger or facilitate the generation of action potentials, which are then integrated in the spinal cord and transduced to the brain for pain perception [15] (Figure 1b). The activated nociceptors release neuropeptides and neu-rotransmitters locally in the skin, inducing vasodilation and capillary permeability, and contributing to neurogenic in-flammation [16]. Nociceptors can also modulate skin im-mune responses [17,18] (Figure 1b). Early studies, mostly *in vitro*, showed that the neuropeptide CGRP can regulate LC functions [19–21]. More recently, *in vivo* studies have identified a major role for neuroimmune interactions in host defense against infections and in tissue-repair processes [22]. However, these regulatory functions are complex and highly dependent on pathological or inflammatory context. A dis-section of the precise molecular mechanisms governing this neuroimmune crosstalk will be required, to shed light on the pathophysiological processes involved. This review does not provide an exhaustive description of all the neuroimmune interactions occurring in the skin. Instead, it focuses on the role of $Nav_{1.8}^+$ lineage somatosensory neurons in regulating cutaneous immune responses. It covers three main themes: neuroimmune interactions in response to pathogens, in al-lergic and inflammatory skin diseases, and during home-ostasis and tissue-repair processes.

Neuroimmune interactions and the host response to pathogens

Pathogen invasion induces an acute inflammatory re-sponse mediated by immune-cell activation. This re-sponse is essential for pathogen elimination, but must be tightly controlled to prevent excessive tissue damage and immunopathological conditions. Recent studies have revealed nervous-system involvement in regulating the delicate balance governing inflammatory processes. This has consequences for host defense against patho-gens, but also for the induction of tolerance mechanisms for restoring tissue homeostasis (Figure 1d).

Skin infections are often associated with severe pain, generally reflecting the degree of tissue damage. The pathways regulating infection-induced pain are thought to be secondary to immune-cell-mediated inflammatory responses.

However, Toll-like receptors (TLR)3, TLR4, TLR7, and TLR9, are functionally expressed by sensory neurons [16], suggesting that these neurons may be able to detect pathogens directly. Chiu et al. showed that *Staphylococcus aureus* (*S. aureus*)-derived N-formylated peptides and α-hemolysin directly activate nociceptive sensory neurons, inducing pain sensation [23••]. In this model, the specific ablation of $Nav_{1.8}$-lineage neurons, including nociceptors, suppresses pain, but simultaneously increases local immune infiltration and lymphadenopathy, implying nociceptor involvement in downregulating inflammatory processes (Figure 2).

A downregulation of innate immune responses by nociceptors was also described in a model of *Streptococcus pyogenes (S. pyogenes)* infection. This bacterium directly activates TRPV1-expressing ($TRPV1^+$) nociceptors by producing streptolysin S, which causes pain [24]. Streptolysin S induces CGRP release by cultured nociceptor neurons *in vitro*, and $TRPV1^+$ neurons also release this neuropeptide into infected tissues. *In vitro* experiments revealed that CGRP inhibits *S. pyogenes* killing by murine neutrophils. In this infectious model, the chemical ablation of nociceptors increases neutrophil influx into skin and decreases bacterial load. Nociceptor stimulation by bacteria, thus, suppresses host defenses against *S. pyogenes* infection (Figure 2).

A role for nociceptive sensory neurons in regulating immune responses during cutaneous viral infection has also been described. A study in a mouse model of herpes simplex virus type-1 (HSV-1) infection revealed that $Nav_{1.8}^+$ sensory neurons regulate both innate and adaptive antiviral responses [25•]. They control the amplitude of the inflammatory response by decreasing neutrophil infiltration and inflammatory cytokine production by monocytes, limiting tissue damage. This modulation of neutrophil influx does not compromise virus elimination, but is necessary to promote CD8 T-cell priming by DCs in the skin-draining lymph nodes (dLNs) (Figure 2).

In these models, $Nav_{1.8}^+$ neurons limit inflammatory processes, by attenuating neutrophil responses and inflammatory cytokine production, in particular. These regulatory processes can help prevent skin lesions caused by excessive inflammation, but may have deleterious consequences for the efficacy of antimicrobial immune responses in some situations. Conversely, nociceptors may have pro-inflammatory functions in other pathological conditions. For example, the genetic ablation of $Nav_{1.8}^+$ sensory neurons or chemical ablation of the $TRPV1^+$ subpopulation protects mice from severe tissue swelling and edema following skin infection with *Bacillus anthracis*, by reducing neutrophil infiltration [26] (Figure 2).

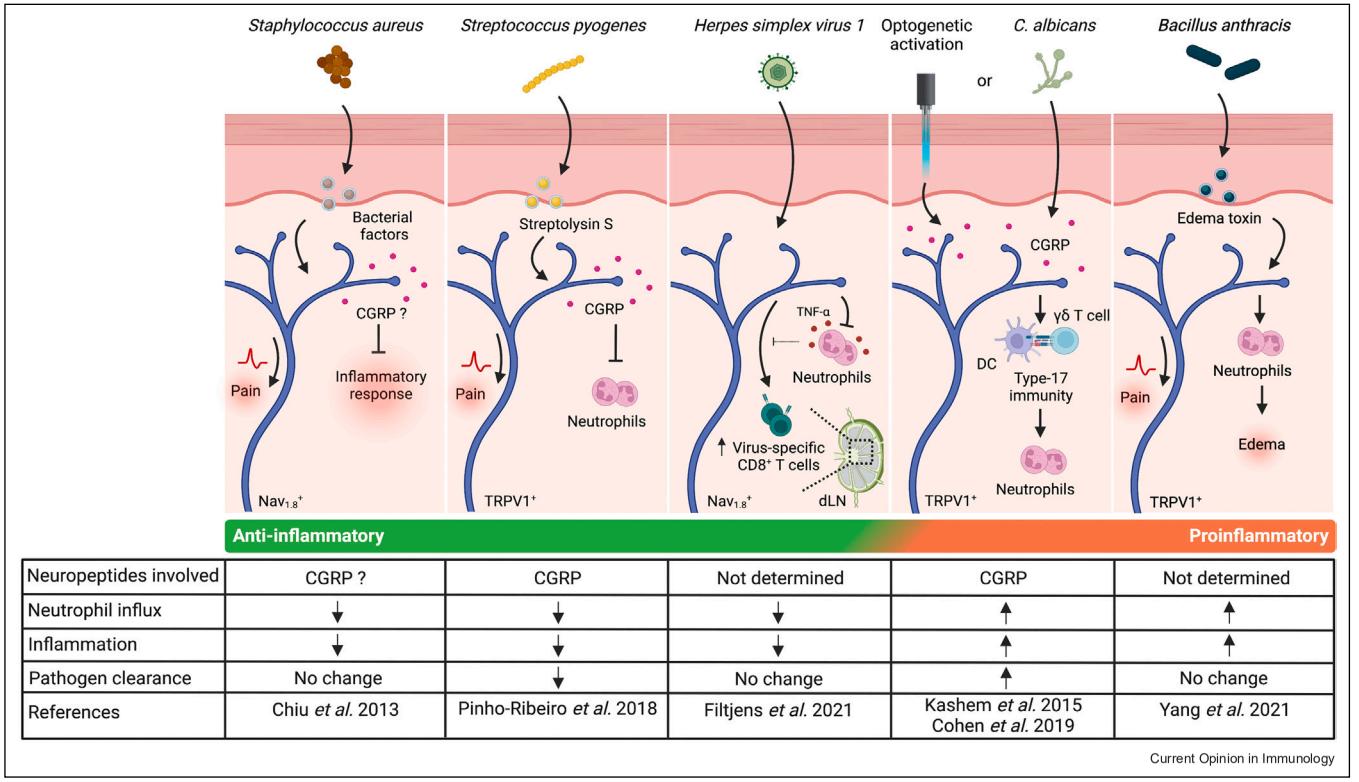
Nociceptive sensory fiber activation can also drive cutaneous antifungal immunity. Kashem et al. revealed that $TRPV1^+$ sensory neurons detect *Candida albicans* (*C. albicans*) and release CGRP, driving IL-23 production by dermal $CD301b^+$ DCs, which promotes protective IL-17 production by γδ T cells [27]. This group also found that the optogenetic activation of cutaneous $TRPV1^+$ neurons was sufficient to induce immune-cell recruitment and to elicit inflammatory cytokine (TNF-α, IL-6, IL-23, IL-17, and IL-22) production, thereby increasing local host defenses against pathogens such as *C. albicans* and *S. aureus* [28]. CGRP release is required for this $TRPV1^+$ neuron-induced type-17 inflammation. Another recent study suggested that, following skin injury in mice, $TRPV1^+$ neurons may enhance the antiviral host response by inducing the production of proteins with antiviral properties, such as Oas2, Oasl2, and Isg15 [29]. These studies show that the contribution of skin sensory neurons to host defense is highly context-dependent.

Neuroimmune interactions in skin allergic and inflammatory diseases

Some skin disorders, such as atopic dermatitis (AD), allergic contact dermatitis (ACD), and psoriasis, are associated with immune dysregulation and inflammation. Cutaneous denervation experiments have highlighted the importance of neuroimmune interactions in a model of psoriasis [30]. Skin exposure to imiquimod induces IL-23-dependent psoriasis-like inflammation in mice. Riol-Blanco et al. showed in this model that $TRPV1^+$ $Nav_{1.8}^+$ neurons are essential drivers of this inflammatory response, through promotion of an IL-23/IL-17 pathway initiated by dermal DC activation [31] (Figure 3). Thus, this pathway is beneficial in fungal-infection contexts [27,28], but detrimental in the context of psoriasis. The TRPC4 cation channel expressed by $CGRP^+$ sensory neurons is also involved in the development of skin inflammation and chronic itch in a model of psoriasis-like inflammation [32] (Figure 3). Immune-cell infiltration, particularly with mast cells and T cells, is reduced in imiquimod-treated skin from *Trpv1*-KO mice, suggesting a role for the receptor itself [33]. However, TRPV1 is expressed by immune-cell subsets in addition to neurons [34], rendering the underlying mechanisms more difficult to understand.

Skin exposure to allergens, such as house dust mites, can directly activate $TRPV1^+$ peptidergic nociceptors, leading to SP release in the skin [35•]. This neuropeptide acts on MRGPRB2, a receptor specifically expressed by mast cells, leading to mast-cell degranulation and promoting an allergic reaction [35•,36••]. The role of SP in skin inflammation has also been described in a model of allergy induced by the cysteine protease papain [37•]. This study involving the genetic ablation of $TRPV1^+$ nociceptors and mice deficient for the SP gene revealed

Figure 2

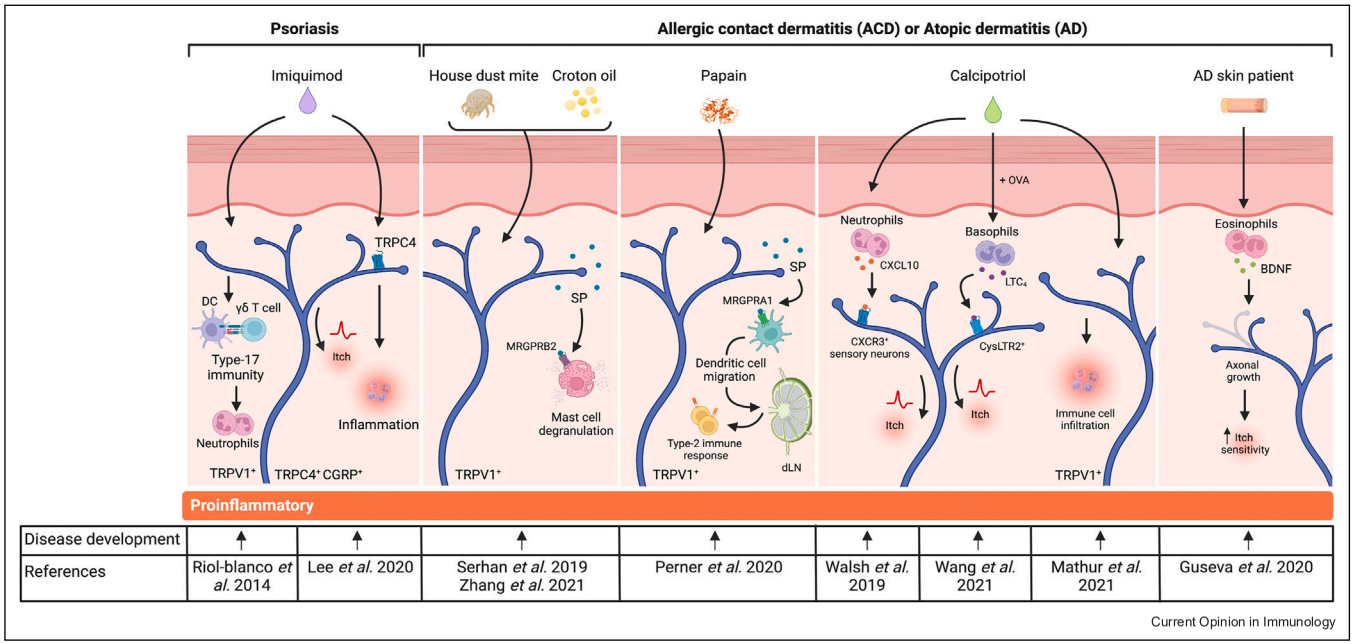


Neuropeptides involved	CGRP ?	CGRP	Not determined	CGRP	Not determined
Neutrophil influx	↓	↓	↓	↑	↑
Inflammation	↓	↓	↓	↑	↑
Pathogen clearance	No change	↓	No change	↑	No change
References	Chiu *et al.* 2013	Pinho-Ribeiro *et al.* 2018	Filtjens *et al.* 2021	Kashem *et al.* 2015 Cohen *et al.* 2019	Yang *et al.* 2021

Current Opinion in Immunology

Neuroimmune crosstalk during skin microbial infections. Neuroimmune regulation in infectious diseases can be pro- or anti-inflammatory, depending on the pathological context. The neuropeptide CGRP, produced by $Nav_{1.8}^+$ $TRPV1^+$ sensory neurons, acts on immune responses with opposite outcomes on the clearance of different pathogens. In infections with *S. pyogenes*, this pathway limits inflammation and pathogen elimination, whereas, in infections with *C. albicans*, it promotes pathogen clearance by inducing a type-17 response elicited by DC and γδ T cells. During infection with HSV-1, $Nav_{1.8}^+$ sensory neurons promote the resolution of inflammation by controlling the recruitment of neutrophils, thereby limiting tissue damage. This regulation is required for the induction of a virus-specific CD8 T-cell response by DCs in the dLNs. By contrast, in response to *B. anthracis* infection, the neutrophil infiltration induced by $TRPV1^+$ neurons increases edema and immunopathology without affecting bacteria elimination. The precise molecular basis behind these differences in regulation remains unclear. This figure was created with BioRender.com.

Figure 3



Neuroimmune interactions in skin allergic and inflammatory diseases. Somatosensory neurons play a pro-inflammatory role and are actively involved in the development of some skin inflammatory diseases. $TRPV1^+$ sensory neurons promote an inflammatory response or initiate a type-17 immune response in a model of imiquimod-induced psoriasis. These neurons, through their production of SP, can also act on receptors expressed on mast cells or DCs in models of ACD induced by house dust mite or croton oil and papain, promoting mast-cell degranulation and DC migration, respectively. In models of AD induced by calcipotriol, immune cells, including neutrophils and basophils, release mediators, such as CXCL10 and leukotriene C4 (LTC_4), respectively, which act directly on sensory neurons, inducing itching. Observations in patients with AD have suggested that the production of BNDF by eosinophils plays a key role in the activation and axonal growth of itch neurons. This figure was created with BioRender.com.

that allergen-activated neurons promote DC migration into LNs, thereby initiating type-2 immune responses to allergens. In this model, SP acts through the MRGPRA1 on CD301b$^+$ DCs, promoting the migration of these cells [37•] (Figure 3).

AD is characterized by itching, granulocyte activation, type-2 inflammatory cytokine production, and high serum IgE levels [38]. Topical application of the vitamin-D3 analog calcipotriol (or MC903) can induce AD-like symptoms in mice. Transcriptomic analysis of the TG revealed that calcipotriol modulates the expression of genes involved in itch-neuron excitability [39]. Calcipotriol also triggers immune-cell infiltration in skin, leading to an onset of itch behaviors induced by neutrophil activation due to the production of CXCL10, a CXCR3 ligand expressed by sensory neurons in these conditions (Figure 3). In addition, the immune-cell infiltration in TG in this model and transcriptional changes in the spinal cord suggest that itching may also be centrally modulated. During MC903-induced AD, the pharmacological inhibition or genetic depletion of TRPV1$^+$ sensory neurons reduces skin immune-cell infiltration and blood IgE levels [40]. In another model of AD combining MC903 application and ovalbumin sensitization, basophils close to sensory neurons have been shown to release leukotriene C4, which directly activates the sensory neurons, triggering itching [41]. Finally, the itching observed in humans with AD may result not only from the activation of sensory fibers, but also from an increase in their axonal growth in the upper dermis [42]. These morphological changes may be due to brain-derived neurotrophic factor (BDNF) production by eosinophils, which is observed only in AD patients (Figure 3).

In these models of skin inflammation, sensory neurons have mostly proinflammatory functions. However, they may also have anti-inflammatory properties in some circumstances. TRPV1 channels are required to trigger spontaneous scratching in a mouse model of ACD induced by the topical application of squaric acid dibutyl ester. Ablation of the *Trpv1* gene or pharmacological ablation of TRPV1$^+$ sensory neurons promotes cutaneous inflammation in this model, consistent with an anti-inflammatory role [43].

Neuroimmune crosstalk in skin homeostasis and repair

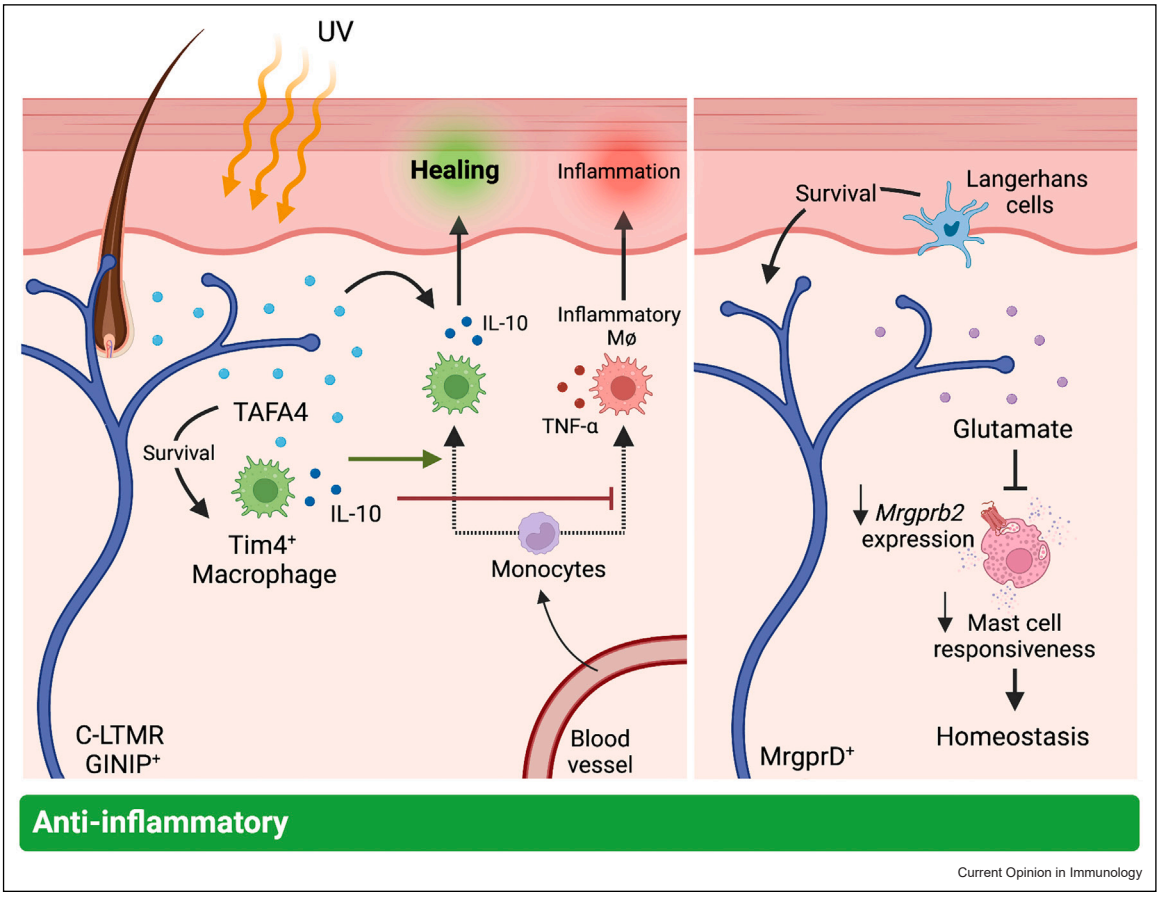
Mechanical injury or exposure to ultraviolet (UV) radiation can also cause skin damage in the absence of pathogens, inducing an inflammatory reaction. The healing process depends on the amplitude of the inflammatory response, which must be tightly controlled, to restore skin homeostasis and integrity. Skin-repair processes are orchestrated by various immune cells, mostly macrophages, and nonimmune cells, such as fibroblasts [44]. Tissue damage induces pain, and wound healing is often associated with itching, which has led to further studies of the role of the sensory nervous system in regulating tissue repair.

The multifunctional cytokine transforming growth factor β plays a key role in scar formation and skin repair [45]. It has been shown to be required for IL-31 production by dermal DCs during healing after full-thickness incisional wounds [46]. TRPV1$^+$ nociceptors expressing IL-31 receptors are also activated and sensitized, resulting in the transmission of an itch signal and scratching behavior. In this model, IL-31-deficient mice display less scratching during the repair process, with no significant effect on wound healing.

Most studies on the neural regulation of skin immune responses have focused on the role of $Nav_{1.8}^+$ TRPV1$^+$ neurons and their production of CGRP and SP [17]. $Nav_{1.8}^+$ GINIP$^+$ nonpeptidergic sensory neurons have also recently been shown to have a regulatory role [47••]. There are two main subsets of GINIP$^+$ neurons: MrgprD-expressing C-fibers, which innervate the interfollicular region of the epidermis as free nerve endings, and nonnoxious C-low-threshold mechanoreceptors (C-LTMRs) expressing tyrosine hydroxylase (TH), TAFA4, and VGLUT3, which innervate hair follicles. MrgprD$^+$ neurons mediate noxious mechanical information, whereas C-LTMRs convey pleasant touch sensations at steady state. C-LTMRs have also been implicated in injury-induced mechanical pain modulation, probably through TAFA4 production [48,49]. In a model of sunburn induced by skin overexposure to UV light, Hoeffel et al. revealed a major anti-inflammatory, prorepair role of GINIP$^+$ sensory neurons [47••]. In this model, epidermis destruction and the resulting inflammation activate GINIP$^+$ neurons, including C-LTMR, triggering TAFA4 production by these neurons in the skin. Mice lacking GINIP$^+$ neurons or the *Tafa4* gene present an unbalanced macrophage response and higher cutaneous levels of inflammatory cytokines, leading to repair defects and fibrosis. TAFA4 modulates the inflammatory profile of dermal macrophages, inducing expression of the anti-inflammatory cytokine IL-10. This TAFA4/IL-10 pathway also promotes the development and survival of Tim4$^+$ prorepair macrophages, which play a crucial role in restoring homeostasis, promoting healing, and preventing fibrosis (Figure 4). In addition to its anti-inflammatory role, TAFA4 has also been reported to have strong analgesic effects [48,49].

An immunoregulatory role has recently been described for another subset of nonpeptidergic GINIP$^+$ nociceptors expressing MrgprD. Zhang et al. found that glutamate release from these neurons limits the expression of genes, such as *Mrgprb2*, involved in mast-cell

Figure 4



Neuroimmune crosstalk promotes skin homeostasis and repair. In a model of sunburn based on skin overexposure to UV light, nonpeptidergic GINIP$^+$ neurons promote skin repair and inhibit fibrosis. This regulation is mediated by the production of TAFA4 protein by C-LTMR, a subset of GINIP$^+$ neurons innervating hair follicles. TAFA4 promotes the survival of Tim4$^+$ skin-resident macrophages (Mø), and their production of anti-inflammatory cytokines. This TAFA4/IL-10 pathway also controls the nature of the macrophages developing from monocytes recruited from the blood. TAFA4 promotes the development of prorepair Tim4$^+$ macrophages at the expense of inflammatory TNF-α-producing macrophages, promoting tissue repair and preventing fibrosis. Another subpopulation of MrgprD$^+$ nonpeptidergic sensory neurons is crucial to maintain skin homeostasis. These glutamate-producing neurons decrease *Mrgprb2* expression in mast cells, suppressing mast-cell inflammatory responses in various contexts. Moreover, the number of epidermal nerve endings of these MrgprD$^+$ sensory neurons is decreased by the absence of LC, highlighting the important role of neuroimmune interactions in homeostatic conditions too. This figure was created with BioRender.com

responsiveness, reducing inflammatory responses [36••]. Glutamate release is increased by MrgprD agonism, which also attenuates mast-cell degranulation and reduces inflammation in multiple skin-disease models. The authors also revealed that epidermal MrgprD$^+$ GFRα2 nonpeptidergic nerve endings are reduced by long-term LC ablation (Figure 4). Neuroimmune interactions are therefore essential for the maintenance and restoration of skin homeostasis.

Conclusion

The neuroimmunology field has expanded considerably over the last decade. However, our comprehension of the molecular mechanisms governing interactions between the nervous and immune systems remains limited. We now need to understand the heterogeneity of sensory neuron populations and their responses in different pathological contexts. Transcriptomic analyses have revealed considerable diversity in skin sensory neurons at steady state [10–12]. Furthermore, the transcriptomic profiles of these cells undergo a major reprogramming after axonal injury [11•]. More detailed characterizations of activated neurons and the mediators produced by nerve endings in the skin in specific disease contexts are required. However, the detection and quantification of neuron-derived molecules in tissues are technically challenging due to the very small amounts produced and their action in the microenvironment of nerve endings. Moreover, different combinations of neurons of different natures may be activated simultaneously, in specific inflammatory contexts, generating a series of different molecules that can act in an additive, synergistic, or antagonistic manner. Moreover,

the depletion of some neuronal subpopulations may induce compensatory mechanisms, leading to interpretation bias.

Receptors for neuron-derived molecules, including CGRP, SP, TAFA4, galanin, somatostatin, and glutamate, are expressed by immune-cell subsets. However, depending on the inflammatory/infectious context, these molecules may have proinflammatory or anti-inflammatory effects, with beneficial or deleterious consequences for host defense. CGRP, for example, may activate or inhibit different cell types, as a function of the cutaneous pathological condition [50]. Its divergent effects, depending on the context, could be explained by the differential expression of CGRP receptors on different cell types or by the time window for CGRP production. Indeed, CGRP receptors are expressed on monocytes, macrophages, neutrophils, ILC2, and in epidermal cells, such as keratinocytes, melanocytes, and LCs [50]. Genetic studies targeting the receptors for these neuron-derived mediators in specific cell types will facilitate dissection of the precise mechanisms involved and provide promising new therapeutic targets.

Finally, it will also be important to understand the contribution of the pain perceived by the central nervous system to immune-response regulation in the skin and in other peripheral tissues, such as the lung and the gut [51].

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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- • of special interest
- •• of outstanding interest

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