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# Differential regulation of cutaneous immunity by sensory neuron subsets

Vincent Feuillet,<sup>1</sup> Sophie Ugolini ,<sup>1,\*</sup> and Ana Reynders<sup>2</sup>

The nervous and immune systems have classically been studied as separate entities, but there is now mounting evidence for bidirectional communication between them in various organs, including the skin. The skin is an epithelial tissue with important sensory and immune functions. The skin is highly innervated with specialized subclasses of primary sensory neurons (PSNs) that can be in contact with skin-resident innate and adaptive immune cells. Neuroimmune crosstalk in the skin, through interactions of PSNs with the immune system, has been shown to regulate host cutaneous defense, inflammation, and tissue repair. Here, we review current knowledge about the cellular and molecular mechanisms involved in this crosstalk, as depicted via mouse model studies. We highlight the ways in which different immune challenges engage specialized subsets of PSNs to produce mediators acting on immune cell subsets and modulating their function.

## The skin as a neuroimmune interface

Over the past decade, it has become increasingly clear that the nervous and immune systems interact closely, mutually influencing each other's activity in various organs, including the lung, gut, and skin [1]. The skin contains complex networks of adaptive and immune cells that are differentially distributed across the epidermis and the dermis and that provide a first line of immune protection against invading pathogens [2,3]. These immune cells include epidermal Langerhans cells (LCs) and subsets of T lymphocytes, as well as dermal dendritic cells (DCs), mast cells (MCs), granulocytes, innate lymphoid cells (ILCs), natural killer (NK) cells, and subsets of T lymphocytes [2,3] (Box 1). Moreover, the dermis is rich in blood and lymphatic vessels, facilitating the migration of immune cells into or out of the skin in response to tissue damage or infection [2,3]. The epidermis and the dermis are also densely innervated by multiple subsets of PSNs, specialized in the detection and transmission of highly diverse external and internal stimuli of different modalities (mechanical, thermal, and chemical) at various intensities and extending from pleasant to unpleasant/harmful [4–6]. As such, the skin represents an archetypal interface supporting neuroimmune interactions. Accordingly, growing evidence demonstrates that in addition to detecting and transmitting sensory information, cutaneous PSNs signal to immune cells, thereby actively influencing the outcome of cutaneous host defense, inflammation, and tissue repair [7]. One of the first lines of evidence in support of such a process was the discovery of neurogenic inflammation, in which the electrical stimulation of PSNs initiates a form of inflammation (redness, heat, swelling, pain) independently of other sources of immune activation [8]. It is now known that the underlying mechanisms involve activity-dependent local release of neuropeptides, such as substance P (SP) and calcitonin gene-related peptide (CGRP), from the PSNs and the action of these neuropeptides on blood vessel cells expressing cognate receptors, promoting vasodilation and immune cell extravasation [9]. Recent studies reveal that PSN-immune crosstalk extends beyond neurogenic inflammation [10]. Just as immune effectors modulate PSN activity, PSNs in turn engage in dialogue with immune cells via the release of neuropeptides, neurotransmitters, and

## Highlights

The skin is an epithelium densely innervated by various subsets of primary sensory neurons (PSNs) and containing large numbers of cutaneous immune cells. In addition to detecting a myriad of sensory stimuli, subsets of PSNs have been shown to be important regulators of cutaneous immunity.

Neuropeptide-producing PSNs are directly activated by microbes and, depending on the type of infection, can suppress or enhance the subsequent immune response. These neurons can also exacerbate inflammatory processes that occur in inflammatory diseases of the skin. Other subsets of PSNs, when activated, release neurotransmitters and neurokinins to control skin homeostasis and wound healing.

Clarifying the precise role of each subset of PSNs in response to specific pathological challenges will provide a deeper understanding of the mechanisms of cutaneous neuroimmune interactions.

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### Box 1. Skin-resident immune cells

Skin-resident innate immune cells include LCs, DCs, macrophages, MCs, eosinophils, NK cells, and ILCs. We provide here a brief description of some of these subsets [91–93]. LCs are the only antigen-presenting cells (APCs) of the epidermis; they provide immune surveillance. LC activation leads to inflammatory cytokine secretion and migration into the draining lymph node, promoting and shaping the adaptive immune response. DCs reside in the dermis, and, like LCs, they are professional APCs. There are several subsets of dermal DCs characterized by differential cell surface marker expression and differences in their ability to promote specific types of adaptive immune response. DCs play a critical role in inducing antigenic tolerance and maintaining homeostatic interactions with the skin microbiota. Skin macrophages are located in the dermis and are involved in removing cell debris at steady state. Through their capacity for phagocytosis and their ability to produce a broad spectrum of cytokines, they contribute to both the initiation and resolution of immune responses. MCs are found mainly in the dermis. They contain granules with preformed active molecules, such as histamine, serotonin, and tryptase, which are released in large amounts upon degranulation, contributing to allergic diseases. MC activation also results in the release of various immune mediators (IL-1 $\beta$ , tumor necrosis factor- $\alpha$ , leukotrienes) actively involved in host defense. Skin eosinophils are granular innate immune cells that, like MCs, rapidly release bioactive molecules (prostaglandins, leukotrienes). They play an important role in host defense but also in the pathogenesis of skin diseases, such as atopic dermatitis. NK cells and ILCs are innate lymphocytes involved in early immune responses and the maintenance of tissue homeostasis. Neutrophils, another type of innate immune cell, are not present in the skin at steady state but are recruited from the blood in large numbers during inflammation, a state that they amplify. They are actively involved in eliminating pathogens through phagocytosis and the formation of neutrophil extracellular traps.

T cells are the main adaptive immune cell subset resident in the epidermal and dermal layers of the skin.  $\alpha\beta$  T cells, including CD8<sup>+</sup> and CD4<sup>+</sup> cells, are skin-resident memory cells with antimicrobial, antitumor, or regulatory functions. The vast majority of  $\gamma\delta$  T cells reside in the epidermis, where they act as the main source of IL-17, thereby participating in host defenses against bacteria and fungi and playing an important role in inflammatory skin diseases.

neurokines, thereby influencing the nature, magnitude, and duration of cutaneous immune responses. In this review article, we discuss recent findings concerning the interaction of PSNs with cutaneous immune cells to modulate host defense, skin inflammation, and wound healing. Given the highly heterogeneous nature of PSNs, when examining PSN-mediated modulation of skin immunity alongside the ‘how?’ aspect, we attempt to address the question of ‘which’ PSNs are involved. Our discussions focus primarily on findings from mouse models, which have allowed refined, cell type-specific dissection of the molecular and cellular mechanisms involved in cutaneous neuroimmune interactions. Cross-species comparisons of the mechanisms identified in mice and testing their potential clinical relevance in humans remain important goals for future work.

### Heterogeneity of cutaneous Nav1.8-lineage PSNs

Like all tissue-innervating PSNs, cutaneous PSNs have their cell bodies in the dorsal root ganglia (DRGs) and trigeminal ganglia (TG) and are exclusively glutamatergic. PSNs convert sensory information detected in the periphery into action potentials, which are transmitted to the CNS, ultimately leading to conscious perception and appropriate behavioral responses [4,5]. To this end, they form synaptic connections with spinal cord interneurons, which are located in the dorsal horn and organized in a complex circuit. There, the information is first integrated before being transmitted to supraspinal centers via the activity of projection neurons [4]. Skin-innervating PSNs can be classified on the basis of morphological, anatomical (peripheral and central innervation), physiological, developmental, neurochemical (i.e., the ability to produce neuropeptides), molecular, and functional criteria (see [11] for a recent review). Briefly, cutaneous PSNs are divided into A $\beta$ , A $\delta$ , and C fibers, conducting action potentials with high, medium, and slow velocities, respectively [11]. The detection of innocuous stimuli, such as touch, is ensured by low-threshold mechanoreceptors (LTMRs), including A $\beta$ , A $\delta$ , and C-LTMRs [6]. Harmful stimuli provoking pain or itch are conveyed by different subsets of A $\delta$  and C nociceptors/pruriceptors, which are further subdivided into peptidergic (PEP) or nonpeptidergic (NP) [4,5,11]. Recent single-cell RNA-sequencing studies defined an extensive molecular and functional classification of PSN subsets across species, including mice, macaques, and humans [12–18]. On the basis of the

classification established by Usoskin *et al.* in mouse lumbar DRGs [13], we describe the PSN subsets that have been studied in the context of cutaneous neuroimmune interactions (Figure 1). These consist mainly of Nav1.8-expressing subsets of nociceptors and pruriceptors, as well as C-LTMRs [19,20]. Nociceptors/pruriceptors innervate both glabrous and hairy skin and are subdivided into several classes of TrkA-expressing peptidergic (PEP 1 and 2) and nonpeptidergic (NP1, NP2, and NP3) neurons [11,13] (Figure 1). The PEP1 subset contains C-fibers forming free nerve endings in the epidermis of glabrous and hairy skin. Because they coexpress *Tac1*, *Calca*, and *Trpv1* (SP-, CGRP-, and transient receptor potential vanilloid 1–encoding transcripts respectively), they are tuned to secrete CGRP and SP neuropeptides and are involved in thermal pain [21–23]. The PEP2 subset corresponds to Aδ fibers expressing *Calca* but not *Tac1* nor *Trpv1* [13,24]. They innervate hair follicles and convey acute mechanical pain elicited by hair pull [24]. NP1 nociceptors are C-fibers forming free nerve endings in the hairy and glabrous skin, selectively expressing Mas-related G protein–coupled receptor D (*Mrgprd*) and mediating acute mechanical pain and β-alanine itch [25,26] (Figure 1). NP2 C-pruriceptors form free nerve endings in the hairy skin and uniquely express *Mrgpra3* together with *Calca*/CGRP and *Trpv1* [13,27] (Figure 1). NP3 selectively expresses somatostatin (*Sst*), the interleukin receptor *Il31ra*, the natriuretic polypeptide b (*Nppb*), and also *Trpv1* [13,28] (Figure 1). The NP2 and NP3 populations are tuned to mediate preferentially chloroquine and inflammatory itch, respectively [13,27,29]. Finally, C-LTMRs

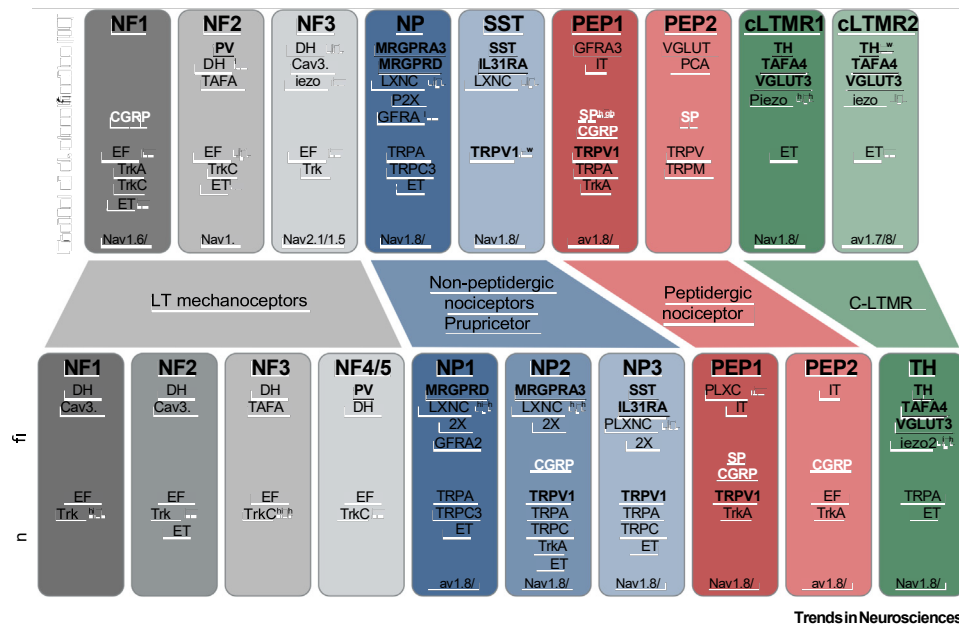


Figure 1. Next-generation single-nucleus/single-cell RNA-sequencing-based classification of lumbar primary sensory neurons (PSNs). Comparative representation of the PSN subsets identified by single-nucleus RNA-sequencing by Renthal *et al.* (upper part) and by single-cell RNA-sequencing Usoskin *et al.* (lower part) in mouse lumbar dorsal root ganglia [13,14]. The neuronal identity is defined by unique combinations of protein-encoding transcripts conferring functional properties on specialized PSNs. Renthal *et al.* described 9 subsets of lumbar PSNs [14] broadly corresponding to those described by Usoskin *et al.*, who classified lumbar PSNs into 11 distinct subsets, encompassing 5 subsets of myelinated low-threshold mechanoreceptors (LTMRs) (neurofilament-positive NF1-5), 3 subsets of nonpeptidergic unmyelinated nociceptors/pruriceptors (NP1-3), 2 subsets of peptidergic nociceptors (unmyelinated PEP1 and myelinated PEP2), and 1 subset of unmyelinated LTMRs (C-LTMRs) [13]. Some transcripts encode proteins present exclusively in one subset of neurons (in black, bold, and underscored), whereas others, such as the TRPV1 transcript (in black, bold), are expressed across many neuronal subsets (NP2, NP3, and PEP1). Of note, the expression of the canonical neuropeptides calcitonin gene-related peptide (CGRP) and substance P (SP) (in bold, white), is not restricted to the so-called peptidergic neurons. The figure depicts the distribution of protein products of corresponding transcripts identified in both studies. Figure created using [BioRender.com](https://BioRender.com).

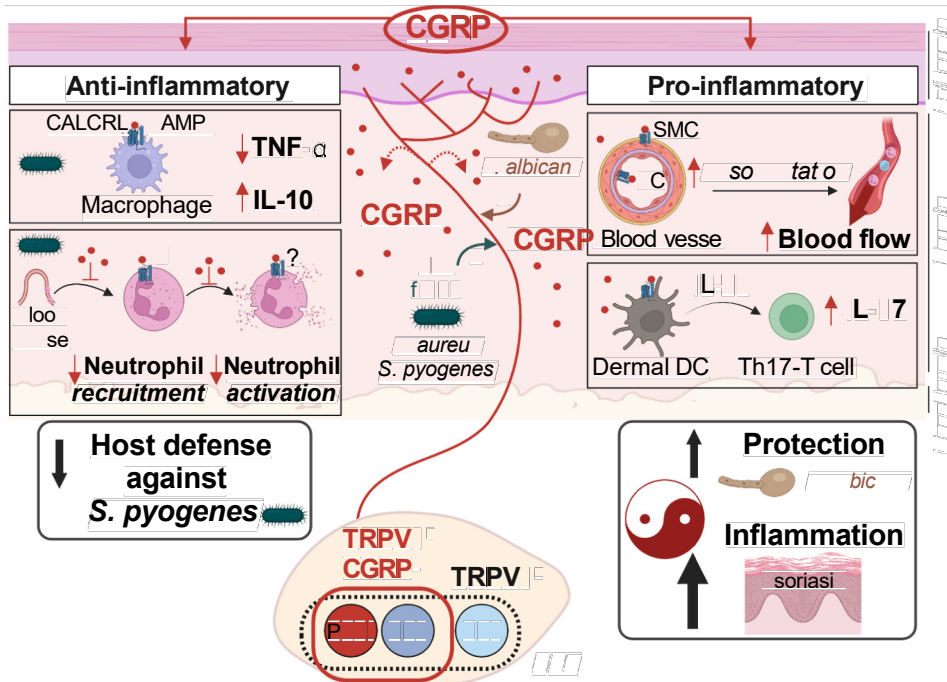
are defined as a homogeneous subset of neurons displaying specific expression of *Th*, *Slc17a8*, and *Fam19a4* (encoding tyrosine hydroxylase, the vesicular glutamate transporter VGLUT3, and the neurokinin TAF4A, respectively) [13,30–32] (Figure 1). They exclusively innervate hair follicles and uniquely convey affective aspects of touch at steady state [30,31,33]. Of note, others have found that the population of C-LTMRs contains two distinct subsets: the cLTMR1 neurons, corresponding to ‘canonical’ C-LTMRs as described by Usoskin *et al.* [13], and a defined cLTMR2 subset that expresses *Fam19a4/Slc17a8* transcripts but very low levels of *Th* [14,18] (Figure 1). This is consistent with previous findings demonstrating molecular and functional heterogeneity within mouse C-LTMRs subsets [30,34].

Additionally, PSNs are equipped to detect internal disturbances in their surrounding chemical environment. They express receptors for various inflammatory or inflammation-associated mediators produced by pathogens or by immune and nonimmune cells. These include receptors for microbial products, cytokines, nerve growth factors, lipids and lipid-derived mediators, extracellular ATP, protons, amines, peptides, and secreted enzymes [35]. The distribution of these receptors at steady state varies between neuronal subtypes, and a given combination of inflammatory mediators may therefore target specific PSN subtypes. Activation of these receptors by their respective ligands results in their direct activation or enhancement of PSN electrical activity, ultimately leading to hypersensitivity to external stimuli and amplification of pain or itch perception and responses [36]. Because distinct pathological contexts may have different distinct immune signatures, it is likely that the effects on the physiology of PSN subsets also vary, as discussed in the next sections.

## Towards an understanding of the PSN subset-specific modulation of cutaneous immunity

### PSNs regulate cutaneous immunity in response to microbial infection

Skin-innervating PSNs have been identified as direct detectors of microbes with an ability to modulate cutaneous host defense in response to bacterial, fungal, and viral infections [37]. In a foundational study, *Staphylococcus aureus* infection was observed to generate mechanical and heat hypersensitivity prior to eliciting tissue swelling [38]. This indicates that bacteria are able to activate PSNs directly, potentially affecting the immune response [38–40]. Consistently, *S. aureus* was found to elicit calcium transients, preferentially in capsaicin-responsive TRPV1<sup>+</sup> PSNs, via the secretion of pore-forming toxins. In addition, mice lacking Nav1.8<sup>+</sup> PSNs exhibit higher immune infiltration in the skin and draining lymph nodes, revealing a downregulation of the local inflammatory response by Nav1.8<sup>+</sup> PSNs in the context of *S. aureus* infection [38]. Furthermore, in follow-up studies on *Staphylococcus pyogenes* infection, it was found that, similarly to *S. aureus*, *S. pyogenes* produces pore-forming toxins that activate TRPV1<sup>+</sup> and, to a lesser extent, TRPV1<sup>-</sup> PSNs [39]. In this model, the local release of CGRP by TRPV1<sup>+</sup> nociceptors limits neutrophil recruitment and activation and reduces bacterial clearance [39] (Figure 2). Consequently, in the absence of TRPV1-lineage or TRPV1-expressing neurons, the bacterial load is lower and dermonecrosis is much milder, and the proportion of neutrophils infiltrating the lesioned skin is significantly higher [39]. Moreover, CGRP antagonism is sufficient to promote bacterial clearance, tissue healing, and neutrophil recruitment *in vivo* and to enhance neutrophil activity *in vitro* [39]. However, this immunosuppressive effect of TRPV1<sup>+</sup> neurons cannot be generalized to all bacterial infection contexts. In a model of bacterial infection with *Bacillus anthracis*, ablation of TRPV1<sup>+</sup> neurons has no effect on bacterial clearance and may even increase local inflammation and neutrophil influx into the skin [41]. The role of these neurons appears, therefore, to be highly dependent on the infection model. Along this line, TRPV1<sup>+</sup> PSNs enhance host immunity to cutaneous fungal infection with *Candida albicans* [42]. Efficient immunity to epicutaneous infection with *C. albicans* requires the release of interleukin (IL)-17A from  $\gamma\delta$  T cells [43]. The release of



**Figure 2. Contribution of the TRPV1<sup>+</sup>/CGRP<sup>+</sup> axis to the modulation of cutaneous immunity.** Mouse TRPV1<sup>+</sup>/CGRP<sup>+</sup> neurons, encompassing the PEP1 and NP2 subsets, may have pro- or anti-inflammatory functions, depending on the pathogenic context. Left: TRPV1<sup>+</sup> primary sensory neurons (PSNs) are directly activated by bacterial products following dermal infection with *Staphylococcus aureus* and *Staphylococcus pyogenes*, resulting in the production and release of calcitonin gene-related peptide (CGRP) [38,39]. In cutaneous *S. aureus* infection, nociceptive sensory neurons limit local immune infiltration (monocytes and neutrophils) and lymphadenopathy of the draining lymph node, a process that can be mimicked by CGRP injection [38]. In *S. pyogenes* infection, CGRP reduces neutrophil recruitment and activation, thereby decreasing the efficiency of bacterial elimination. It remains unclear whether the effects of CGRP on neutrophils is direct through engagement of the cognate receptor of this molecule [39]. Right: TRPV1<sup>+</sup>/CGRP<sup>+</sup> neurons can also activate the immune response. Optogenetic activation of TRPV1<sup>+</sup> fibers in mice results in the local release of CGRP, which acts on smooth muscle cells (SMCs) and endothelial cells (ECs) to promote vasodilation and elicit a Th17 immune response, which protects against *Candida albicans* [45]. *C. albicans*-derived molecules can also activate TRPV1<sup>+</sup> PSNs, driving the release of CGRP, which, by acting on dermal DCs, promotes their production of interleukin (IL)-23, which triggers IL-17 secretion by dermal T cells, resulting in more efficient fungal control [42]. This TRPV1<sup>+</sup>/CGRP<sup>+</sup>/IL-23<sup>+</sup>/IL-17<sup>+</sup> axis promotes host defense against *C. albicans* [42,45]. However, in mouse models of cutaneous inflammatory diseases, such as psoriasis, this axis contributes to the exacerbation of inflammation [58]. Figure created using BioRender.com. Abbreviations: DRG, dorsal root ganglia; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

this cytokine is dependent on IL-23 secretion by a subset of skin-resident CD301<sup>+</sup> DCs [42] (Boxes 1 and 2). The early upstream events triggering IL-23 production by CD301<sup>+</sup> DCs in response to *C. albicans* result from direct activation of TRPV1<sup>+</sup> neurons by fungal derivatives that may target dectin-1 receptors on PSNs, leading to local CGRP release [42,44] (Figure 2). Resiniferatoxin (RTX)-mediated depletion of TRPV1<sup>+</sup> neurons and CGRP antagonism *in vivo* hamper IL-23 production by CD301<sup>+</sup> DCs, resulting in decreased IL-17 secretion by  $\gamma\delta$  T cells and increased susceptibility to *C. albicans* infection [42]. Consistently, activation of TRPV1-lineage neurons by optogenetic stimulation in the absence of tissue damage or pathogen-associated products is sufficient to elicit a robust local inflammatory response and to promote an anticipatory type 17 immune response, which protects against subsequent *C. albicans* or *S. aureus* infection [45]. This response can be abolished by treating the mice with a CGRP receptor antagonist before

### Box 2. Modulation of immune cells activity by CGRP and SP

CGRP signals mainly through a heterodimeric receptor composed of the calcitonin-like receptor (CALCRL) and receptor activity modifier protein-1 (RAMP1) subunits, which have been demonstrated in various studies to be expressed on immune cells [94]. The proinflammatory role of CGRP is attributed largely to its ability to act on vascular cells and to promote neurogenic inflammation and immune-cell recruitment [95]. The immunosuppressive/immunomodulatory effects of CGRP on immune cells, including neutrophils, DCs, macrophages, and T cells, are well documented. For instance, CGRP limits neutrophil chemotaxis and activation [39,96–98], suppresses T-cell proliferation [99,100], and decreases proinflammatory cytokine production in macrophages while increasing the secretion of anti-inflammatory cytokines [101]. CGRP also plays an important immunomodulatory role [102–105]. CGRP restricts the ability of LCs to present antigen [104] and promotes the generation of Th2-type and Th17-type skewing LCs while decreasing the ability of these cells to generate Th1-type immunity [102,103].

SP is the other canonical molecule that induces neurogenic inflammation. SP was historically thought to bind exclusively to neurokinin receptors (NKRs), but studies from the past several years have revealed that it can also exert its functions by binding to MRGPRB2 and MRGPRA1 [74,76]. There are three known NKRs: NK1R, NK2R, and NK3R. NK1R has the highest affinity for SP and is the most studied of these receptors [106]. NK1R is widely expressed by vascular and immune cells, and the activation of this pathway generally enhances vasodilation and activates effector functions in various immune cell types [106]. Many studies have reported the functional expression of NKRs on immune cells [107–115]. Like CGRP, SP has multiple effects on various immune targets. For instance, it increases the production of IL-2 and interferon- $\gamma$  by T cells [107,116,117], it may promote the chemotaxis of neutrophils [114] and the degranulation and proinflammatory cytokine production by MC [76,77,79,118], and it supports the survival of DCs and the generation of Th1-type skewing DCs and LCs [109,119,120].

photostimulation [45]. Thus, this study provides an elegant proof for the existence of nerve-reflex arcs mediating CGRP-dependent neurogenic inflammation at secondary sites.

MRGPRD<sup>+</sup> neurons also have an impact on bacterial infection, decreasing host defense against intradermal *S. aureus* infection [46]. Genetic ablation of MRGPRD<sup>+</sup> neurons enhances MC responsiveness and improves bacterial clearance and resorption of skin lesions induced by *S. aureus* [46]. It remains unclear whether MRGPRD<sup>+</sup> fibers respond directly to *S. aureus* or are activated indirectly.

Finally, PSNs can also modulate antiviral immune responses. This was illustrated, for instance, in a study using a model of herpes simplex virus-1 (HSV-1) infection with a genetically modified virus able to replicate in keratinocytes but not in DRG neurons [47]. The authors showed that Nav1.8-lineage PSNs prevent excessive inflammation and enhance tissue repair by limiting the production of inflammatory cytokines and chemokines and the influx of neutrophils into the skin [47]. This control of skin inflammatory responses by PSNs is also required to promote the priming of antiviral CD8<sup>+</sup> T cells by DCs in the skin-draining lymph nodes [47]. Thus, PSNs control both innate and adaptive antiviral immune responses. Activation of TRPV1<sup>+</sup> nociceptor is also involved in the production of antiviral proteins after wounding via a CD301b<sup>+</sup> DC–IL-27–mediated pathway [48]. In addition, *in vitro* experiments revealed that Trpv1<sup>-/-</sup> skin explants are more susceptible to HSV-1 viral infection than wild-type skin, suggesting that TRPV1 loss sensitizes skin to HSV viral infection [48].

In summary, depending on the type of microbe, PSNs can suppress or enhance immune responses to skin pathogens, with opposite consequences for host protection. Strikingly, the release of CGRP by TRPV1<sup>+</sup> neurons can either promote or suppress inflammation and host resistance to infections. These different effects may be due to the specific action of different subsets of TRPV1<sup>+</sup>/CGRP<sup>+</sup> neurons and/or differential kinetics of activation related to the dynamics of the local immune response [7]. In line with the former scenario, TRPV1<sup>+</sup>/CGRP<sup>+</sup> neurons encompass PEP1 fibers innervating both hairy and glabrous epidermis and MRGPRA3<sup>+</sup> NP2 neurons, present only in glabrous epidermis (Figure 2). Moreover, different infection paradigms are

used across studies, with some injecting the microbes subcutaneously into the hind paw [38,39] and others performing epicutaneous injections into the shaved dorsal skin [42,45]. Together, this may lead to the activation of distinct microenvironments in which the very local release of CGRP may affect different immune compartments. In addition, it remains unclear if hair removal results in CGRP local release by TRPV1<sup>-</sup>CGRP<sup>+</sup> hair follicle–innervating A $\delta$  fibers, thereby priming the immune system [24]. In line with the latter scenario, CGRP is known for its multiple effects and numerous cellular targets (Box 2). Binding of CGRP to its cognate receptor initiates two main signaling pathways [49]. On the one hand, it leads to an increase in intracellular ATP and subsequent activation of the protein kinase A (PKA) pathway that rapidly upregulates the transcriptional repressor inducible cAMP repressor, dampening proinflammatory and enhancing anti-inflammatory cytokine production [50]. On the other hand, it can also activate phospholipase C cascade, which is critical for cytokine production by DCs, including IL-23 [51]. Therefore, intrinsic differences in downstream signaling pathways of the various cellular CGRP targets also contribute to the above-mentioned differences. The possible contribution of other cell types reported to express functional TRPV1, such as vascular smooth muscle cells, T cells, and keratinocytes, which may also be targeted with RTX, remains to be investigated [52–54].

#### PSNs regulate cutaneous inflammatory and allergic disorders

Psoriasis is a skin disease characterized by skin lesions resulting from deregulated interactions and complex feedback loops between the innate and adaptive immune systems [55]. Contribution of the nervous system to the disease has been suggested, because the density of SP- and CGRP-containing fibers is higher in psoriatic epidermis than in normal epidermis, and denervation improves or heals skin lesions [56,57]. Exacerbation of the IL-23/IL-17 immune axis plays a key role in the development of the disease [55]. In a mouse model of psoriasis triggered by application of the TLR7 agonist imiquimod (IMQ), Nav1.8<sup>+</sup> and TRPV1<sup>+</sup> PSNs were found to contribute to the pathogenesis of the disease by initiating IL-23 production in dermal DCs [58]. In this model, RTX-induced ablation of TRPV1<sup>+</sup> neurons and genetic ablation of Nav1.8 neurons attenuated psoriasiform inflammation, including IL-23 production by dermal DCs and subsequent release of IL-17A by  $\gamma\delta$  T cells [58]. Exposure to IMQ induces an increase in CGRP expression in PSNs, and CGRP plays a key role in driving IL-23 production and psoriasiform inflammation [59] (Figure 2). It has also been suggested that the TRPC4 channel expressed in a subset of TRPV1<sup>+</sup> PEP neurons mediates IMQ-induced psoriasiform scratching behavior and inflammation, probably through the local release of CGRP [60]. Local pharmacological TRPC4 blockade, however, has no effect on IL-23 production [60]. Because TRPC4 is expressed on various skin cells, such as immune cells, endothelial cells, and fibroblasts [61], further studies are required to decipher the selective contribution of PSN TRPC4 to the pathogenesis of psoriasis.

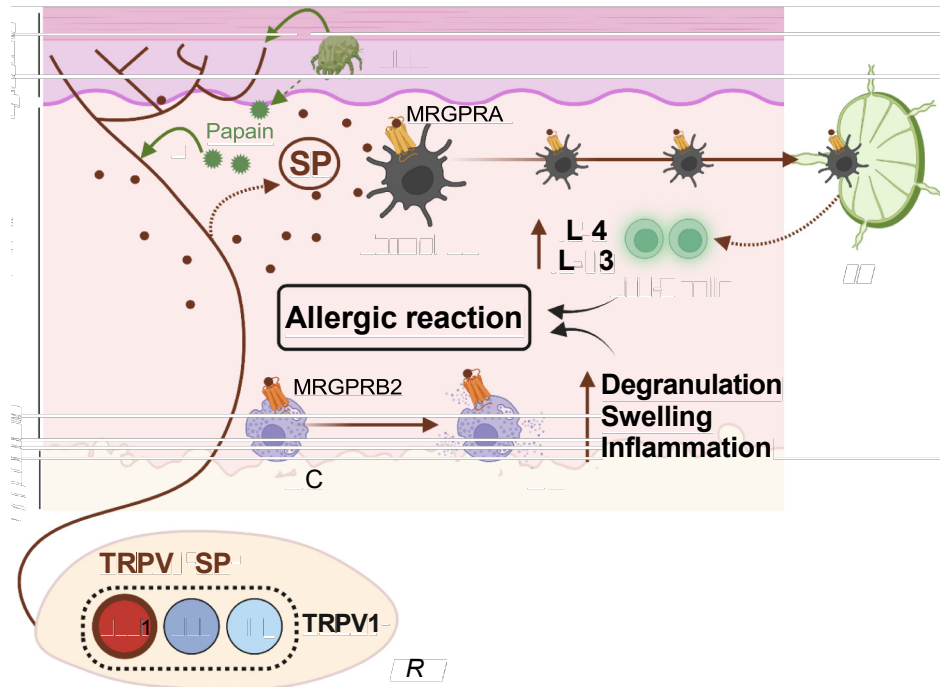
Atopic dermatitis (AD) is a chronic relapsing skin disorder characterized by chronic itching and excessive inflammation involving the production of excessive amounts of type 2 inflammatory cytokines (thymic stromal lymphopoietin or TSLP, IL-4, IL-13, IL-31, etc.) and the abnormal functioning of various cell types, including keratinocytes, immune cell subsets, and neurons [62]. AD weakens the skin epithelium, thereby increasing exposure to allergens and promoting the generation of allergen-specific IgE antibodies [62]. AD is accompanied by PSN remodeling. Increased nerve densities have been reported in patients with AD [63]. In addition, sensitization and/or overactivation of subsets of pruriceptor PSNs has been observed. This concerns mostly NP2 and NP3, which can be directly activated by type 2 cytokines and other pruritogens through binding on cognate receptors and which express or coexpress TRPV1, TRPA1, CGRP, and SP [13,29,64,65]. In mice, topical application of the vitamin D<sub>3</sub> analog calcipotriol (MC903) reproduces the principal feature of the human disease. Various immune cell subsets interact with



PSNs in different phases of scratching behavior. For instance, neutrophils are essential for the early initiation of itch behavior due to their production of CXCL10, which directly activates PSNs by binding to its cognate CXCR3 receptor [66]. The prototypical type 2 inflammatory initiator TSLP and associated effector molecules such as IL-4, IL-13, and IL-31 mediate itch in the chronic phase of the model [29,64–66]. Basophils were also recently found to play a key role in allergen-evoked, IgE-dependent acute flare-ups of itching in AD via the production of leukotriene 4, which directly activates the itch-dedicated NP3 subset by engaging its cognate receptor CysLTR2 [67,68]. Notably, the application of MC903 to the cheek induces the upregulation of several transcriptional modules in the TG, including genes associated with the identity and function of the itch-dedicated NP3 subset [66]. However, it remains unclear whether these genes are upregulated within NP3 neurons or whether they are also induced in other subsets of PSNs. Recently, it has been shown that overactivation of pruriceptor PSNs not only mediates excessive itching but also sustains the inflammatory immune response. Consistently, genetic silencing of Nav1.8-expressing neurons and silencing of PSN subsets with the lidocaine analog QX-314 attenuates MC903-induced inflammation, including excessive type 2 cytokine production, skin swelling, and scratching [69]. Of note, QX-314 is a membrane-impermeant blocker of voltage-gated sodium channels that penetrates neurons through the pores formed by activated large cationic channels [70]. Activation of TRPV1 and TRPA1 ion channels efficiently mediates the entry of QX-314 into neurons and leads to inhibition of firing [70,71]. However, other channels or coupled channels may convey this action [72]. Interestingly, in the aforementioned study, CGRP antagonism was sufficient to improve all symptoms of MC903-induced AD [69]. Moreover, a related study reported that TRPV1-lineage ablation and QX-314-mediated silencing of PSNs (including, but not exclusively, the NP3 subset) significantly decreased MC903-induced chronic inflammation and circulating IgE levels [73]. Finally, MRGPRD<sup>+</sup> fibers were found to be dispensable for these processes, highlighting the involvement of specific neuronal subsets in AD pathogenesis [46].

Other skin disorders include allergic responses to exogenous antigens that would not otherwise be immunogenic; these responses are mediated by excessive type 2 immune responses. TRPV1-lineage/TRPV1<sup>+</sup> neurons have been reported to initiate and maintain allergic responses by secreting SP and through the subsequent regulation of effector cells, including DCs and MCs [74,75] (Box 2). Like CGRP, SP also acts on immune cells by binding to cognate receptors, including the recently identified MRGPRB2 and MRGPRA1 [74,76] (Box 2).

MRGPRA1 has been detected in cutaneous DC subsets [74]. In response to papain, a protease present in many common allergens, SP is produced by TRPV1-lineage neurons and binds to the MRGPRA1 receptor expressed by CD301b<sup>+</sup> DCs, thereby promoting their migration into the draining lymph nodes and initiating type 2 allergic responses [74] (Figure 3). MRGPRB2 is highly expressed on MCs, and the SP–MRGPRB2 axis has been shown to be involved in neurogenic inflammation and to activate MC effector functions, including degranulation and the release of inflammatory mediators [76–79]. The finding that the SP–MRGPRB2 axis affects MC activity paved the way for investigations of the neuronal control of MC biology. In a model of skin allergy induced by exposure to house dust mites (HDMs), TRPV1<sup>+</sup> neurons were found to initiate the allergic response by producing SP, which activates MC by interacting with MRGPRB2, thereby promoting an allergic reaction [75] (Figure 3). HDMs directly elicit influx of calcium into TRPV1-expressing neurons, and RTX ablation of TRPV1<sup>+</sup> neurons attenuates skin inflammation [75] (Figure 3). By contrast to what has been observed for TRPV1<sup>+</sup> neurons, the nonoverlapping MRGPRD<sup>+</sup> NP1 subset of PSNs was found to decrease MC responsiveness in multiple disease models, including a model of allergic dermatitis [46]. The glutamate derived from MRGPRD<sup>+</sup> neurons acts on a metabotropic glutamate receptor expressed on MCs and controls their homeostatic activation by limiting the expression of *Mrgprb2* and proinflammatory cytokines [46] (Figure 4).



**Figure 3. Contribution of the TRPV1<sup>+</sup>/SP<sup>+</sup> axis to cutaneous allergic disorders.** Mouse TRPV1<sup>+</sup> primary sensory neurons (PSNs) are activated upon contact with house dust mites (HDMs) or HDM-derived molecules, such as papain, which causes them to release substance P (SP) [74,75]. SP binds to the MRGPRA1 receptor on dermal dendritic cells (DCs), promoting the migration of these cells to the draining lymph nodes (LNs), where they induce type 2 T (Th2) cell activation [74]. The interleukin (IL)-4 and IL-13 produced by activated Th2 cells are involved in allergic responses. SP can also bind to the MRGPRB2 receptor expressed on mast cells (MCs), which are in direct contact with sensory fibers [75]. This results in MC degranulation and the induction of tissue swelling and inflammation, thereby promoting an allergic reaction [75]. Figure created using [BioRender.com](https://www.biorender.com). Abbreviation: DRG, dorsal root ganglia.

### Regulation of cutaneous immune responses during wound healing

Wound healing is a biological process that enables injured tissues to recover full functionality. It involves the activation and recruitment of various cell types in specific programmed time frames. Abnormal wound healing often results in fibrosis, in which connective tissue replaces parenchymal tissue. Immune cells play an important role in wound healing through their actions during two important phases: the early inflammatory phase and the late tissue remodeling/repair phase. PSN signaling to immune cells has been shown to regulate the amplitude of the inflammatory immune responses in the early and repair phases [78,80,81]. In a mouse incisional wound model mimicking postoperative pain, the SP–MRGPRB2–MC axis was found to promote inflammation at very early stages and to amplify behavioral hypersensitivity [78]. In models of pathogen-free tissue lesions caused by the overexposure of the skin to UV light, the TRPV1<sup>+</sup> and GINIP<sup>+</sup> subsets of neurons have been reported to regulate immune cell composition, the inflammatory response, and tissue repair phases [80,81]. The pharmacological ablation of TRPV1<sup>+</sup> neurons and the genetic deletion of CGRP did not lead to immune changes in UV-exposed plantar skin during early phases of inflammation, but a transient increase in the numbers of DCs and αβ T cells was observed on day 5 after UV exposure [80]. In another model of sunburn based on the exposure of ear skin to UV light, it was shown that GINIP<sup>+</sup> PSNs play a crucial role in modulating the macrophage response, regulating inflammation, and promoting tissue repair. Exposure to UV triggered expression of neuronal damage-activated transcription factor ATF3 in GINIP<sup>+</sup> neurons,

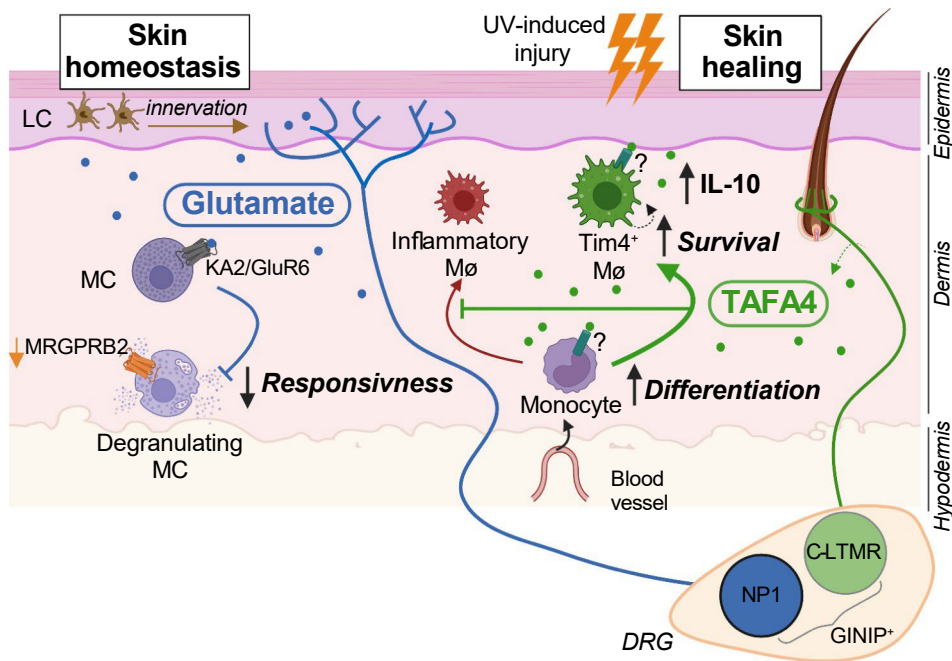


Figure 4. Role of glutamate produced by MRGPRD<sup>+</sup> neurons and TFAFA4 produced by unmyelinated low-threshold mechanoreceptors (C-LTMRs) in skin homeostasis and repair. Left: The innervation of the epidermis by MRGPRD<sup>+</sup> neurons requires at least partially Langerhans cells (LCs) [46]. MRGPRD<sup>+</sup> neurons release glutamate into the skin. This glutamate then binds to the kainite receptor (KA2/GluR6) expressed on mast cells (MCs), decreasing their responsiveness by decreasing the levels of MRGPRB2-encoding transcripts [46]. Right: Overexposure to UV radiation triggers skin inflammation and the activation of GINIP<sup>+</sup> primary sensory neurons (PSNs), including the MRGPRD<sup>+</sup> and C-LTMR subsets [81]. GINIP<sup>+</sup> PSNs decrease the infiltration of monocytes into injured skin and their differentiation into inflammatory macrophages (Mφ) while promoting the generation of prorepair Tim4<sup>+</sup> dermal Mφ [81]. C-LTMRs release the neurokinine TFAFA4, which binds to an as yet unknown receptor on Mφ, enhancing Tim4<sup>+</sup> Mφ survival and the release of interleukin (IL)-10 by these cells [81]. Figure created using [BioRender.com](https://www.biorender.com). Abbreviation: DRG, dorsal root ganglia.

and the genetic ablation of this neuronal subset resulted in abnormal skin repair and fibrosis [81]. GINIP<sup>+</sup> PSNs include the NP1/MRGPRD<sup>+</sup> subset and the C-LTMRs [82]. The local secretion of the neurokinine TFAFA4 by C-LTMRs plays a key role in the tissue repair process by promoting the survival and development of dermal Tim4<sup>+</sup> prorepair macrophages (Figure 4) [81]. Moreover, TFAFA4 can directly modulate macrophage functions by inducing their production of the anti-inflammatory cytokine IL-10 [81]. However, the mechanisms underlying the effects of TFAFA4 on macrophages remain to be determined. It has been suggested that FPR1 is TFAFA4 receptor on macrophages [83], but other studies have revealed that TFAFA4 can exert its effects independently of FPR1 [81,84]. These discrepancies could be due to the presence of several receptors with at least partially redundant activities. TFAFA4 also acts as a painkiller by modulating the activity of spinal cord neurons through its interaction with low-density lipoprotein receptor-related protein 1 [84]. It remains to be addressed whether the same pathway is involved in the modulation of macrophage functions by TFAFA4.

The ability of subsets of PSNs to promote a cutaneous Th17 immune response [42,45,58] has been shown to contribute to skin regeneration. In two skin wound models, it was demonstrated that applying IMQ- or allyl isothiocyanate-containing cream before and after wounding triggered the expansion of IL-17-producing γδ dermal T cells, which were essential for complete skin

regeneration [85]. Activation of TRPA1 but not TRPV1 on subsets of PSNs critically regulated this process [85]. TRPA1-expressing PSNs include nonpeptidergic nociceptors/pruriceptors NP1, NP2, and NP3 and C-LTMRs (Figure 1). Thus, whether any of these subsets is preferentially stimulated in this model remains to be determined [13,29,30,82]. It is also not known whether this process is mediated by CGRP, as suggested in a study applying a model of IMQ-induced psoriasis inflammation [58]. However, the 'homeostatic' level of IL-17-producing cutaneous  $\gamma\delta$  T cells may regulate the wound-healing ability of the skin [85]. Accordingly, another recent study has shown that cutaneous microbiota is able to regulate the pool of IL-17-secreting  $\gamma\delta$  T cells, thereby promoting wound healing, including skin reinnervation [86]. The underlying mechanisms require the upregulation of ATF3 and IL-17a receptor in injured PSNs [86].

#### Are functionally defined subsets of PSNs involved in different aspects of cutaneous immunity?

Just as sensory information may be encoded by one or several specialized subsets of PSNs, various aspects of cutaneous immunity may also be regulated by particular populations of PSNs.

The emerging and rapidly evolving field of neuroimmunology reveals a picture in which TRPV1/CGRP/SP-expressing PSNs would primarily regulate skin immunity against pathogens and allergens, whereas MRGPRD-positive and C-LTMRs would promote skin homeostasis and repair. But it is likely that this schematic view could be reconsidered and refined thanks to new approaches, including intersectional genetic approaches coupled with optogenetic or chemogenetic tools. In addition, it will be important to investigate how distinct pathological or immunological contexts affect different subsets of PSNs from a molecular and functional perspective. Indeed, pathological models exhibiting distinct immune signatures affect the neuroimmune dialogue differently, as shown by a recent study [87]. Another illustrative example is a recent study showing that subsets of PSNs completely lose their molecular signature after nerve injury and that the same lesion leads to different transcriptional responses in different PSN subsets [14].

#### Concluding remarks

In this review, we have described the growing body of evidence on direct interactions between the cutaneous nervous and immune systems. Skin PSNs can detect changes in the cutaneous microenvironment (including the presence of infectious microbes and allergens); activate immune responses accordingly; and influence the nature, amplitude, and duration of these immune responses. Current understanding of the underlying mechanisms mostly relates to the local release of CGRP and SP by TRPV1<sup>+</sup> PSNs and the well-documented ability of these neuropeptides to modulate immune cell functions. One key observation is that the net outcome of TRPV1<sup>+</sup> neuronal inputs in the immune system depends strongly on the pathological context. Cutaneous PSNs are highly heterogeneous and display a certain degree of functional specialization. Different subsets of PSNs also appear to have different influences on the immune system, as highlighted by the ability of MRGPRD<sup>+</sup> PSNs and TFAFA4<sup>+</sup> C-LTMRs to promote skin homeostasis and repair. Nevertheless, much work remains to be done to achieve a fuller understanding of the contributions of different PSN subsets to cutaneous immunity (see [Outstanding questions](#)). Moreover, the finding that lymph nodes are innervated by a unique subset of peptidergic PSNs [88] indicates another layer of complexity and highlights the technical challenges that will have to be overcome to reach deep understanding of the subtleties of cutaneous neuroimmune interactions. Finally, it should be noted that there is considerable evidence for sex-related differences in pain, with several studies demonstrating sex-specific neuroimmune regulation of pain [89]. In particular, the IL-23/IL-17/TRPV1<sup>+</sup> axis has been shown to generate pain in female but not male mice [90]. In many neuroimmunology studies on pain that involved subjects of both sexes, sex has not been included as a biological variable in the analysis. We advocate that it be considered in more detail in future studies.

#### Outstanding questions

Cutaneous PSNs are heterogeneous in nature and exhibit functional specialization in the transmission of particular types of sensory stimuli. How does this diversity affect the regulation of skin immunity?

The effect of defined subsets of PSNs on particular cutaneous immune cells appears to substantially depend on the nature of the pathological context of the skin. How do different inflammatory or infectious challenges modify PSN subsets, and what are the consequences for skin immunity?

The recognition that pain is an essential sign of inflammation provided the basis for investigating the role of nociceptors in the regulation of cutaneous immunity. Recent data show that other subsets of non-nociceptive PSNs also have immunoregulatory capabilities. For example, C-LTMRs promote wound healing by producing the neurokinine TFAFA4. Could other subsets of non-nociceptive PSNs also be involved in controlling skin immunity? What would be the underlying mechanisms?

There is ample evidence of sex differences in pain, and studies suggest sex-specific neuroimmune regulation of pain. There are also inherent differences in the immune systems of males and females. How does sex contribute to the neural regulation of cutaneous immunity, and what mechanisms would underlie sex-related differences in this context?

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## Declaration of interests

The authors declare no conflict of interest.

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