



Mast cell–neuron axis in allergy

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The peripheral nervous system and the immune system are virtually distributed in all organs in mouse and human. They act in concert to constitute an exceptional sensory system capable of sensing threatening stimuli, including allergens, and triggering appropriate biological responses. Recent advances in the field have revealed that tissue-resident mast cells and nearby sensory neurons could form functional neuroimmune clusters driven by bidirectional interactions and predisposed to significantly influence major allergic conditions. In this review, we highlight recent discoveries that paved the way toward a better understanding of how mast cells and sensory neurons can communicate to regulate basic features of allergic disorders in different organs.

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Abbreviations: IgE, Immunoglobulin E; FcεRI, Fc Epsilon Receptor I; CGRP, Calcitonin Gene Related Peptide; FDA, Food and Drug Administration; TRPV1, Transient Receptor Potential Vanilloid 1

Current Opinion in Immunology 2022, 77:102213

This review comes from a themed issue on **Special Section Neuroimmunology**

Edited by **Roland Liblau** and **Isaac Chiu**

<https://doi.org/10.1016/j.coi.2022.102213>

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Introduction

Allergies and mast cells

Allergies are exacerbated immune responses against a broad panel of innocuous environmental antigens commonly named ‘allergens’. The allergic inflammation is elicited upon development of an allergen-specific type-2 immune response, leading to the production of allergen-specific IgE antibodies [1]. Allergies affect 20–30% of the population and can, under certain circumstances,

lead to severe and life-threatening anaphylactic reactions. Mast cells are tissue-resident innate immune cells found in multiple organs, including the skin and the gastrointestinal tract, and often in contact with peripheral nerve fibers [2–4]. They have been historically characterized as co-expressing c-kit (i.e. CD117, the receptor for the stem cell factor) and the high-affinity receptor for IgE (i.e. FcεRI). They are activated in response to multiple signals, including the liaison of allergens to FcεRI-bound IgE that are specific for such allergens [5], which position them as key players in allergic responses.

The peripheral nervous system

The peripheral nervous system (PNS) is composed of neurons that innervate peripheral organs, outside the central nervous system. Thanks to this peculiar anatomy, the main function of the PNS is to detect a wide diversity of stimuli and to trigger an appropriate behavioral response. Among different neurons of the PNS, nociceptive sensory neurons (i.e. nociceptors) have drawn a lot of attention in the past decade, and can be subdivided into two main populations: peptidergic and nonpeptidergic nociceptors [6]. In addition to their main role in the transduction of sensory signals, sensory neurons have been recently shown to participate in the regulation of immune responses and associated inflammations, mainly through the secretion of a broad range of immunomodulatory neuropeptides (e.g. substance P, CGRP, vasoactive intestinal peptide (VIP), and somatostatin). Such neuroimmune interactions have been shown to play major roles in intestinal-tract homeostasis, host defense against pathogens, and various chronic inflammatory conditions such as psoriasis, rheumatoid arthritis, and allergic disorders such as asthma, atopic dermatitis, and allergic-contact dermatitis [7–10]. Among all immune cells, mast cells express receptors that can bind multiple neuropeptides, allowing them to become privileged cellular partners in biological processes in which sensory neurons play an important role, including allergy.

Mast cell MrgprB2/X2, pseudoallergy, and integration of neuron-derived signals

Mass-related G-protein-coupled receptor (Mrgpr) family is a large family of G-protein-coupled receptors composed of approximately 50 members across several species among which are mouse and human [11,12]. The vast majority of Mrgprs have been reported to be expressed by small-diameter sensory neurons of the

peripheral nervous system. In 2015, McNeil et al. [13] reported that the MrgprB2 was a mast-cell-specific receptor and the mouse ortholog of MRGPRX2. They showed that MrgprB2 was specifically expressed *in vivo* by skin and peritoneal/digestive-cavity mast cells, which represents, until now, the most specific marker described to identify mast cells in these two tissues. This observation raised important biological questions that will be further discussed in the ‘Future perspectives’ section below.

MrgprB2 and MRGPRX2 can both be activated by many cationic molecules and efficiently trigger mast-cell degranulation *in vivo* and *in vitro*. Unfortunately, various FDA-approved drugs that share similar basic properties can activate MRGPRX2 and are responsible for mast-cell-dependent, but IgE-independent, immediate ‘pseudo-allergy’ at the site of injection and commonly named injection-site reactions [14,15].

A broad panel of natural ligands of MrgprB2 has been reported, such as neuropeptides (e.g. substance P, vasoactive intestinal peptide), host-defense peptides (e.g. cathelicidin, β -defensin), venom-derived peptides (e.g. wasp mastoparan), and bacteria-derived products (e.g. quorum-sensing molecules) [15]. Such capacity to ‘sense’ different exogenous and endogenous molecules strongly suggests that mast cell MrgprB2 could be involved in various physiological and host-defense processes such as communication with nearby neurons, venom detoxification, and bacteria elimination [16,17].

Previous studies have contributed to demonstrate that mast cells could sense and differentially integrate signals to further regulate their secretion strategy [18]. Aggregation of the high-affinity IgE receptor (FcεRI) was associated with a sustained increase in intracellular calcium levels, followed by a delay, and the exteriorization of large and irregularly fused granular aggregates. This phenomenon often triggered a systemic and sustained inflammatory response. Conversely, substance-P-mediated MrgprB2/X2 activation elicited a fast intracellular calcium spike followed by the immediate release of small and individual granules. Such a fast mode of degranulation led to the development of a moderate and quickly resolving skin inflammation.

Whether mast-cell activation via FcεRI or MrgprB2/X2 could eventually result in distinct qualitative and quantitative release of granule-associated mediators is still not completely understood. However, recent findings strongly suggested that cross-linking of FcεRI could lead to preferential release of histamine and serotonin than observed upon engagement of MrgprB2/X2 [19]. Further work will be needed to better understand the subtlety of the molecular mechanisms governing different mast-cell secretory programs. It is interesting to speculate that, at

least in the skin, the release of small and labile granules observed upon activation of mast cell MrgprB2/X2 could favor local communication with nearby peripheral neurons and mimic a ‘synapse-like’ communication strategy [18]. Interestingly, other *in vitro* evidence seems to point out a role for MrgprB2/X2 not only as a receptor for substance P but also other neuropeptides such as the VIP, somatostatin, or cortistatin [20]. It would thus be very interesting to compare the *in vivo* response of MrgprB2/X2-expressing mast cells to these different neuropeptides, and evaluate if different neuropeptides might differentially regulate mast-cell responses.

The sensory neuron — MrgprB2+ mast-cell axis in health and disease

In 2019, three independent articles demonstrated a functional crosstalk between MrgprB2-expressing mast cells and sensory neurons *in vivo*, which regulated atopic dermatitis-like inflammation, itch, and pain. Green et al. [21] investigated the role of neuron–mast-cell interactions in the development of the so-called ‘neurogenic inflammation’, a pathological context thought to regulate pain sensation. Using two complementary mouse models of postsurgical incision and complete Freund’s adjuvant that mimic human inflammatory pain, the authors showed that mast-cell expression of MrgprB2 was required for the full development of pathological features, including swelling, innate immune-cell recruitment, and pain hypersensitivity. In these experimental settings, MrgprB2-mediated mast-cell activation was found to be correlated with sensory neuron injury and mice that lack MrgprB2 showed significant reduction of nerve injury compared with MrgprB2-sufficient mice. The authors further reported that neuron-derived substance P was required for MrgprB2-dependent mast-cell activation *in vivo* and *in vitro*. These results identified MrgprB2/X2 as a potential target for treating inflammatory pain and paved the way toward additional important discoveries on the physiological and pathological role of the substance-P–MrgprB2/X2 mast-cell axis.

Importantly, substance-P-mediated mast-cell activation was independent of the neurokinin-1 receptor (NK-1R), confirming again that MrgprB2/X2 is the mast-cell receptor for substance P. These data are in line with previous observations that NK-1R antagonists (L733060 and aprepitant) failed to demonstrate efficacy in patients with asthma [22], severe migraine [23], and anti-histamine-refractory chronic pruritus in chronic nodular prurigo [24]. These clinical pitfalls could be explained, at least in part, by the fact that NK-1R antagonists can also bind and block the mouse MrgprB2, but do not prevent activation of the human MrgprX2 [25].

Atopic dermatitis is a chronic, relapsing skin inflammatory disorder that affects 20% of children and

characterized by severe pruritus and pain. In a recent study, Serhan, Basso et al. [26] investigated the role of mast cells and peptidergic sensory neurons in the development of pathological features associated with a relevant model of type-2 skin inflammation that uses epicutaneous exposures to house dust mites (i.e. very common domestic allergens) and *S. aureus* toxins to recapitulate aspects of the human condition, including the dependency in IL-4 and IL-13 for full development. They reported that house dust mites could directly activate TRPV1⁺ *Tac1*⁺ (i.e. substance-P-producing) sensory neurons via their cysteine-protease activity. Such neurons then secreted substance P and activated MrgprB2-expressing mast cells to degranulate in the tissue and kick-start the development of the pathology. In support of these findings, mice deficient in *Tac1* (i.e. that lack the substance-P precursor), TRPV1⁺ neurons, mast cells, or *Mrgprb2* were almost protected from the development of the pathology. These data indicated that, after exposure to allergens, activation of TRPV1⁺*Tac1*⁺ nociceptor–MrgprB2⁺ mas-cell sensory clusters could represent a key early event in the control of type-2 immune response and subsequent allergic skin reactions. In line with these findings, another study reported that allergen-induced substance-P release by TRPV1⁺ sensory neurons triggered MrgprA1-dependent dendritic cell migration to the lymph node where they initiated the allergic immune response [27].

It is now well accepted that the communication between skin sensory neurons and mast cells can occur in both directions. Meixiong et al. [19] investigated the role of MrgprB2-mediated mast-cell activation in the context of nonhistaminergic itch, a frequent condition for which the molecular mechanisms are not well understood. They found that, compared with classical FcεRI-mediated activation, MrgprB2-mediated skin mast-cell degranulation resulted in the preferential release of more tryptase but less histamine, which then triggered the broad excitation of Mrgprd⁺, Mrgpra3⁺, and 5ht1f⁺ sensory neurons, three subpopulations of well-defined nonpeptidergic pruriceptors. These experimental findings are in line with clinical observations that chronic itch conditions associated with atopic dermatitis or allergic-contact dermatitis are refractory to histamine antagonists [28,29]. Using three independent models of allergic skin inflammation, the authors reported that Mrgprb2-deficient mice exhibited significantly less itch compared with MrgprB2-sufficient animals.

Based on these studies, it is now clear that targeting neuroimmune interactions in the context of allergic skin inflammation, including atopic dermatitis, could represent

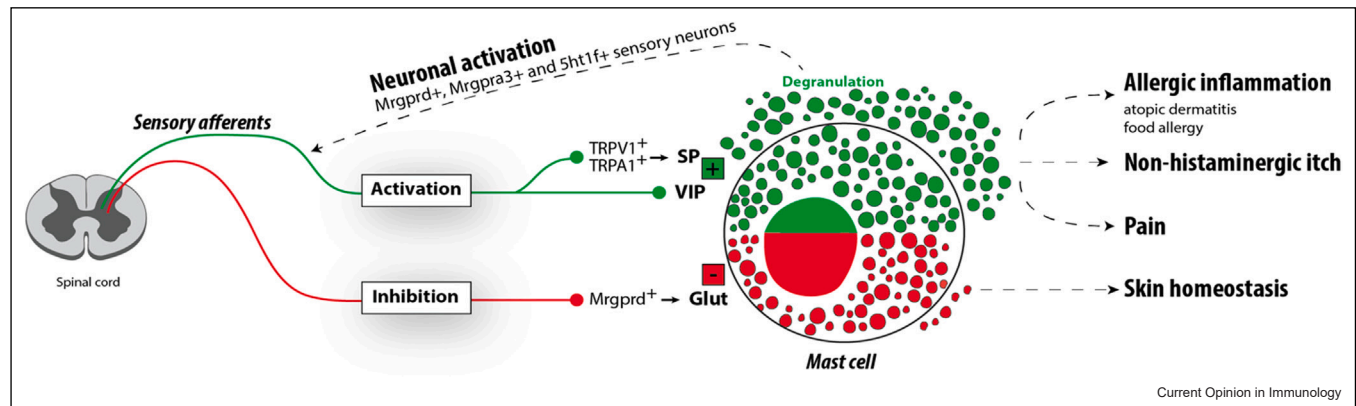
a new therapeutic intervention to prevent not only the production of pathogenic type-2 cytokines, but also the severe itch condition associated with the pathology.

Suppression of skin mast-cell response by nonpeptidergic neurons

The skin is composed of a meshwork of sensory nerves, some of them belong to the above-described family of peptidergic neurons (i.e. including substance-P-secreting nociceptors), but others belong to a non-peptidergic group of neurons such as those expressing the receptor MrgprD. While peptidergic neurons can positively regulate mast-cell activation, a recent study by Zhang et al. [30] showed that epidermal nonpeptidergic MrgprD-expressing neurons can, on the contrary, negatively regulate their activation. The authors first described that epidermal nerve endings from a subset of nonpeptidergic MrgprD⁺ neurons were reduced in the absence of Langerhans cells. Combining different transgenic mouse models of cell-specific depletion, they demonstrated that ablation of either Langerhans cells or MrgprD⁺ neurons amplified the expression of mast-cell-associated genes, including *MrgprB2*, *Mcp4*, *Cma1*, and *Tpsab1*, increased mast-cell degranulation, and pathological features associated with different models of skin inflammation. In line with these observations, exogenous administration of the MrgprD agonist, β-alanine, well known to enhance the excitability of MrgprD⁺ neurons and their production of glutamate [31–33], reduced the expression of mast-cell-associated genes and dampened mast-cell response. Finally, the authors showed that inhibition of glutamate release or glutamate-receptor binding also led to enhancement of mast-cell activation and associated genes. These data indicated that MrgprD⁺ neuron-derived glutamate could represent a natural endogenous mechanism that continuously dampens skin mast-cell activation status and maintains optimal tissue homeostasis.

Given the high number of mast cells in the skin and the amount of pro-inflammatory mediators prestored within their granules, it is understandable that mast-cell activation status must be tightly regulated to avoid the development of an excessive inflammatory response and/or anaphylactic-like reaction. Additional studies will be needed to better understand whether such neuroimmune-inhibitory mechanisms also happen in other organs in which mast cells are known to play an important role, such as the lungs or the gastrointestinal tract, and if they can be leveraged to inhibit mast-cell-dependent reactions. The neuropeptide CGRP has also been described to inhibit mast-cell degranulation [34]; however, the majority of studies have been done *in vitro* [35] and only scarce

Figure 1



Bidirectional interactions between mast cells and sensory neurons.

evidence has been shown to date that this interaction might be relevant *in vivo* [36].

Local activation of gut sensory afferent by mucosal mast cells sensitized with food-allergen-specific IgE

In the gut, the vast majority of mast cells are found in close proximity with the intestinal lumen and have been shown to participate in the pathophysiology of gastrointestinal disorders. In mice, these mast cells are characterized by their expression of the chymase Mcpt1, and their degranulation is thought to be implicated in various pathologies [37]. The irritable-bowel syndrome (IBS) is a common functional gastrointestinal disease characterized by abdominal pain and altered the frequency and consistency of stool. Mast cells have been suggested to be active players in the pathophysiology of IBS as an increased number of degranulated mast cells was reported in mucosal biopsies from IBS patients compared with healthy controls [38]. In such biopsies, mast cells were found in close proximity with nerve fibers and the distance between mast cells and nerve fibers correlated with the intensity of symptoms reported in patients. Even if conflicting results have been obtained since, recent meta-analysis seems to confirm the potential role of mast cells in IBS [39].

Finding the full spectrum of stimuli that activate mast cells in the context of IBS is still an ongoing challenge. A recent study by Aguilera-Lizarraga et al. [40] described that a breakdown of immune tolerance to food antigens during bacterial infection in mice could induce the production of dietary antigen-specific IgE locally within the intestine. Subsequent ingestion of these antigens triggered mast-cell activation through an IgE-dependent mechanism, leading to the release of histamine and the

sensitization of visceral sensory neuron afferents that conveyed the sensation of pain. Importantly, injection of food-derived antigens in the gut mucosa of IBS patients induced an immediate histamine-dependent swelling of the mucosa. These results clearly showed that IgE-induced local mast-cell degranulation might be an important trigger of abdominal pain in post-infectious IBS, arguing for a localized IgE-dependent allergic response to food allergen in IBS patients. The reported findings are independent of the expression of MrgprB2/X2 by gut mast cells and it is still elusive whether other stimuli other than IgE could be responsible for additional pathological features associated with IBS. Is any food derivative/additive capable of activating mast cells via other receptors? Are those mast cells in the gut expressing MrgprB2/X2? Are they sensitive to neuropeptides secreted by afferent fibers in the gut mucosa? These are still open questions and thrilling future areas of investigations.

Future perspectives

The discovery of MrgprB2/X2 opened new perspectives on the role played by mast cells in health and disease and enabled to functionally demonstrate their capacity to integrate common neuron-derived signals and to finely tune neuron excitation (Figure 1). Until now, neuron–mast-cell functional units have been found to be involved in pathological conditions via the regulation of itch, pain, and allergic skin inflammation. Experimental data demonstrating a beneficial role of such interaction are still missing in the literature. In addition, fewer pieces of evidence have suggested that mast cells could also communicate with sympathetic and parasympathetic fibers to regulate physiological processes [41,42], while additional work will be needed to better

explore these observations, it is a promising area of future investigations.

Tissue-resident macrophages, including those found in the gut, have been shown to exhibit precise tissue-support functions [43–47]. Given the embryonic ontogeny of mast cells [48,49] and the fact that they are also found deeply embedded in various tissues, it would be interesting to understand whether they can also have a function of tissue support rather than a classical function of immune defense via their interaction with nearby neurons.

Several questions are still opened in the field and constitute vast areas of investigations. Notably, it would be very informative to understand the full distribution of MrgprB2/X2 across organs and if they are associated with niche-specific functions. It is interesting to speculate that depending on the organ and the neuronal micro-environment in it, mast cells could have developed specific neuroimmune-interaction patterns that could be translated into specialized cellular functions. It is a true exciting time for the field of mast-cell biology, as it now emerges as key cellular components of the body capable of bridging the gap between the immune and nervous systems.

CRedit authorship contribution statement

NG and LB wrote the paper.

Conflict of interest statement

N.G. is chief scientific officer and board member at Genoskin SAS & Inc. He is a member of the scientific advisory board for MaxiVAX. He has served as consultant or received honorarium for Boehringer Ingelheim, GlaxoSmithKline, Escient Pharmaceuticals, Genentech, and Novartis. He has a patent pending for the treatment of type-2 inflammation and mast-cell-dependent disorders.

Acknowledgements

We thank Nadine Serhan for assisting with graphical representations. This work was supported by grants from the Société Française de Dermatologie (SFD), France, the Société Française d'Allergologie (SFA), France, the Agence National pour la Recherche (ANR), France, the ACTERIA Foundation, Switzerland, and the European Research Council (ERC-2018-STG #802041, Europe).

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