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Invited Review Article

Neuro-allergology: Mast cell–nerve cross-talk

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ABSTRACT

Mast cells (MCs) are derived from hematopoietic stem cells in the bone marrow, and their maturation is regulated by the tissue environment, such as the skin, lung and gut, leading to host defense. Peripheral nerve fibers located in various tissues are involved in diverse physiological and pathological processes. Anatomical relationships between MCs and nerve fibers were reported to have been observed in various organs. Moreover, MCs are positive for a large number of receptors for classical neurotransmitters (e.g., acetylcholine and corticotropin-releasing hormone) and neuropeptides (e.g., substance P, calcitonin gene-related peptides and hemokinin), and MC's functions are regulated by those nerve-derived factors. Also, histamine and proteases produced and released by MCs modulate nerve fiber functions. This functional cross-talk between MCs and nerve fibers can play physiological and pathological roles. MCs are key effector cells of allergic inflammation, such as atopic dermatitis, airway inflammation and food allergy. Here, we summarize and discuss the molecular mechanisms underlying the functional and anatomical cross-talk between MCs and nerve fibers in allergic inflamed tissues.

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Mast cells (MCs)

MCs were first reported as aniline-reactive cells by Paul Ehrlich in his 1878 doctoral thesis.¹ Over 140 years since his finding, accumulating evidence has revealed their origin, differentiation, and roles under physiological and pathological circumstances. The progenitor cells that give rise to MCs are located in the yolk sac and bone marrow and migrate into peripheral tissues such as the skin, lung and intestine via the blood circulation.^{2–5} Tissue-specific niche signals govern tissue-specific MCs' characters (e.g., transcriptome, proteases and cell surface molecules).^{3,6,7} Tissue-resident MCs play protective roles against parasites, viruses, protozoans and venoms,^{8–12} while they are conversely also involved in the pathogenesis of many diseases (e.g., autoimmune diseases, cancers, cardiovascular diseases, nonalcoholic fatty liver diseases and lung fibrosis).^{13–16} Although MCs have pivotal roles in regulation of our health and diseases, and it is well-established that they

act as the key effector cells in the pathogenesis of immunoglobulin E (IgE)-mediated allergic diseases, such as food allergy (FA), atopic dermatitis (AD) and asthma.^{17,18}

Role of MCs in IgE-mediated allergic disease

Allergen-specific IgE against foods, house dust and pollen synthesized by plasma cells bind to high-affinity IgE receptors (FcεRI) on the surface of murine and human MCs. When allergens invade our body and cause aggregation of FcεRI on MCs, the MCs release various bioactive substances into extracellular spaces, including biogenic amines (e.g., histamine and serotonin), cytokines (e.g., TNF-α, IL-4 and IL-5), MC-specific proteases (e.g., tryptase, chymase and carboxypeptidase A3), non-MC-specific proteases (cathepsin G, granzyme B and Renin), lipid mediators (e.g., leukotrienes, prostaglandins and sphingosine-1-phosphate) and extracellular vesicles (EVs [e.g., exosomes and microvesicles]). These bioactive substances regulate immune and non-immune cells.^{19–26} For instance, histamine from MCs increases vascular permeability and reduces the intrinsic tone of smooth muscle.²⁷ IL-4 produced by MCs activated with peanut and peanut-specific-IgE leads to a reprograms regulatory T cells toward a T helper 2 phenotype, followed by enhancement of a type 2 immune response against

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peanut.^{28,29} PGD₂ and miR103a-3p in EVs secreted by FcεRI-mediated activated MCs induce ILC2 migration and enhance ILC2s' IL-5 production, respectively.^{25,30} As described above, bioactive substances from MCs activated by allergen and allergen-specific IgE modulate functions of immune and nonimmune cells in IgE-mediated allergic inflammation, leading to a range of allergic symptoms.

It is well known that MC functions are also regulated by other immune cells in IgE-mediated allergic diseases. Mast cells' degranulation and cytokine production are regulated by regulatory T cells via TGF-β₁ or through OX40–OX40L interaction.^{31–33} IL-9 from CD4⁺ T cells (Th9 cells) induces accumulation of MCs in allergic inflamed tissues.^{34,35} Human airway epithelial cells enhance survival and PGD₂ secretion from human MCs stimulated with IgE and anti-IgE Abs via the SCF–Kit axis.³⁶ IL-4 from ILC2s causes intestinal MC expansion, leading to food anaphylaxis.³⁷ Thus, mutual interactions among MCs and other immune and/or non-immune cells are essential to the pathogenesis of allergic inflammation.

MCs and the nervous system

It is speculated that stress stimuli accentuate the inflammatory response to infections and are involved in episodes of autoimmunity. As a result of technical advances that enable assessment of the cross-talk between the immune and nervous systems, it has become clear that said cross-talk plays crucial roles in both physiological homeostasis and the pathogenesis of diseases.³⁸ Cross-talk between MCs and the central nervous system is one of the known

examples of neuroimmune interaction.³⁹ MCs are found in close proximity to the meninges and perivascular areas on the brain side of the blood–brain barrier, the preoptic area and the hippocampal and thalamic/hypothalamic regions. Those brain MCs have been suggested to play various roles in both physiological and pathological conditions, such as maintenance of the blood–brain barrier, determination of sexual and social behavior, neurodegeneration, vasculature growth and differentiation, the pathogenesis of Alzheimer's disease and the generation of migraine headaches.^{40–47} Anatomic and functional cross-talk between peripheral tissue MCs and nerves has also been reported in various tissues.^{39,48–51} This cross-talk in peripheral tissues modulates local inflammatory disease (e.g., airway hypersecretion, cough, irritable bowel syndrome and itch).^{52–54} MCs possess a diverse array of receptors for neurotransmitters and neuropeptides released from neurons (e.g., substance P [SP], hemokinin-1, acetylcholine, corticotropin-releasing hormone [CRH], calcitonin gene-related peptide [CGRP]), which regulate MC functions.^{39,55–58} Reciprocally, MC-derived histamine, proteases, neuropeptides and lipid mediators regulate nerves.^{54,59,60} MCs adhere directly to nerves via cell adhesion molecule I (CADM1).^{61,62} Clearly, the MC–nerve cross-talk found in different organs is pivotal for both health and disease.

MC–nerve loop cross-talk in skin of allergic inflammation

The skin acts as an immunological barrier between the host and pathogens such as bacteria, fungi, and viruses and works to induce optimal immune responses.⁶³ The anatomical relationship between MCs and neurons was observed in skin.⁶⁴ Glutamine derived from

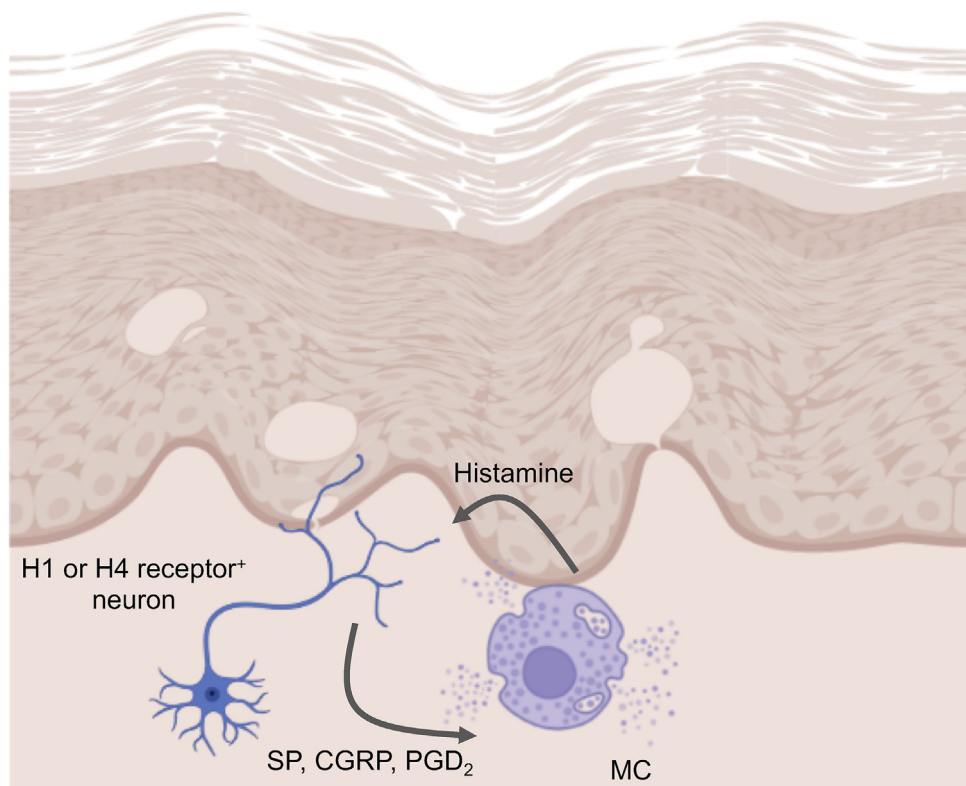


Fig. 1. MC–nerve loop in skin with allergic inflammation. Cross-talk between H1- or H4-receptor-expressing neurons and MCs promotes the pathogenesis of skin allergic inflammation. Exogenous stimuli activate neurons, causing release of neuropeptides and such lipid mediators as SP, CGRP and PGD₂, which in turn trigger degranulation of MCs. Moreover, histamine from these MCs activates neurons via H1 or H4 receptors, leading to secretion of SP and CGRP. MCs, mast cells; H1 or H4 receptor, histamine H1 or H4 receptor; SP, substance P; CGRP, calcitonin gene-related peptide; PGD₂, prostaglandin D₂.

MrgprD-expressing nonpeptidergic neurons (i.e., do not release neuropeptide) limits MCs' degranulation through the SP–MrgprB2 axis, thereby maintaining skin homeostasis.⁶⁵

MCs in the skin contribute to the pathogenesis of skin allergic inflammation such as in AD and urticaria. In AD, allergens and allergen-specific IgE and/or cytokines derived from epithelial cells, including IL-33 and thymic stromal lymphopoietin (TSLP), lead to degranulation and cytokine production by MCs.^{66–69} Histamine released from those cells reacts with C- and A-delta nerve fibers (non-myelinated and myelinated, respectively) via H1 and H4 receptors,⁷⁰ leading to induction of itch, which is the defining symptom of AD.⁷¹ Also, histamine activated those nerves to release neuropeptides, including SP and CGRP, which in turn elicit histamine and PGD₂ release from MCs via MrgprB2 or its human orthologue, MrgprX2, and CRTh2 or TRPV1 (receptor for PGD₂ metabolite, 15-deoxy-[12,14]-PGJ₂), respectively.^{20,56,72} Those findings suggest that the MC–nerve loop plays important roles in the pathogenesis of AD. In lesional sites of patients with AD, MC numbers and the density of cutaneous sensory nerve fibers were increased,^{73–77} and expression of the gene encoding SP (*Tac 1*) was significantly increased.⁷⁸ AD patients' plasma SP levels were increased, while CGRP levels were decreased, during exacerbation of AD.⁷⁹ These clinical studies further point to the importance of the MC–nerve loop in the pathogenesis of AD (Fig. 1).

Urticaria is recognized as an MC-driven disease, since patients with chronic urticaria can be treated with the anti-IgE monoclonal antibody, omalizumab.^{80,81} MC-derived mediators such as histamine and platelet-activating factor result in sensory nerve activation, vasodilation and plasma extravasation.^{82,83} Intradermal injection of some neuropeptides, such as SP and vasoactive

intestinal peptide (VIP), reportedly enhanced the wheal reaction in patients with urticaria.^{84,85} Our group showed that the number and percentage of MrgprX2-expressing skin MCs in patients with urticaria were significantly greater than in normal control (NC) subjects.⁵⁷ Thus, similarly to in AD, MC–nerve loops regulate the pathogenesis of urticaria. Also, we and others have shown that the serum hemokinin-1 level and the plasma VIP level in urticaria patients were significantly decreased compared with in NC subjects.^{58,86} Such imbalances of neuropeptides might affect the pathogenesis of skin allergic disorders.

MC–nerve loop cross-talk in lungs with allergic inflammation

Asthma is usually characterized by airway inflammation. It is a heterogeneous disease and is triggered mainly by type 2 immune responses to such environmental stimuli as house dust mite and fungi.⁸⁷ Many key airway characteristics (e.g., airway smooth muscle tone, mucus secretion and vascular permeability) are regulated via a large number of afferent cholinergic and adrenergic nerves.⁸⁸

Several research groups observed close anatomic proximity of MCs with SP-positive sensory neurons in physiological and asthmatic states.^{51,89,90} Sensory neurons also express the transient receptor potential vanilloid type 1 receptor (TRPV1) ion channel. In addition to transmitting afferent information waves, these neurons produce neuropeptides at local sites (by triggering an axon reflex). Inhaled irritants or endogenous stimuli, such as capsaicin, bradykinin and PM_{2.5}, coupled with tissue inflammation, cause secretion of pre-stored neuropeptides such as SP from TRPV1-positive neurons; those neuropeptides affect neighboring

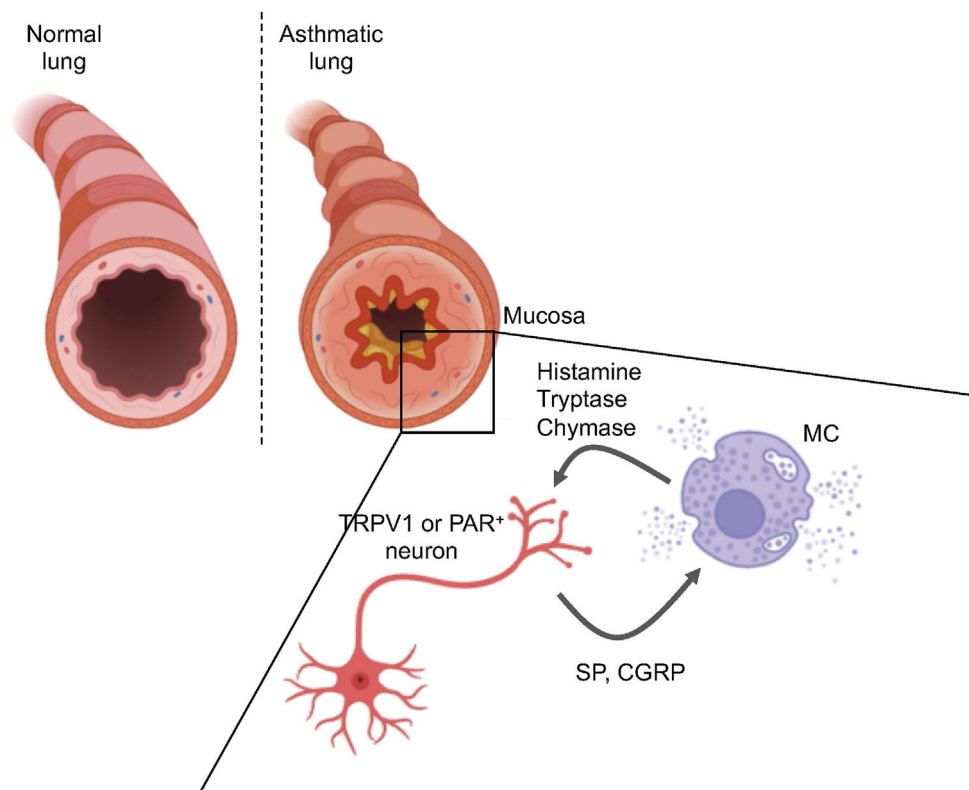


Fig. 2. MC–nerve loop in lung with allergic inflammation. TRPV-expressing neuron–MC cross-talk contributes to lung allergic diseases. Exogenous stimuli (e.g., house dust and fungi) activate neurons to release neuropeptides such as SP and CGRP, which in turn induce release of histamine and such proteases as tryptase and chymase from MCs. Moreover, these mediators from MCs activate neurons via H1 or H4 receptors and PAR, leading to secretion of SP and CGRP. MCs, mast cells; H1 or H4 receptor, histamine H1 or H4 receptor; SP, substance P; CGRP, calcitonin gene-related peptide; TRPV1, transient receptor potential vanilloid 1; PAR, protease-activated receptor.

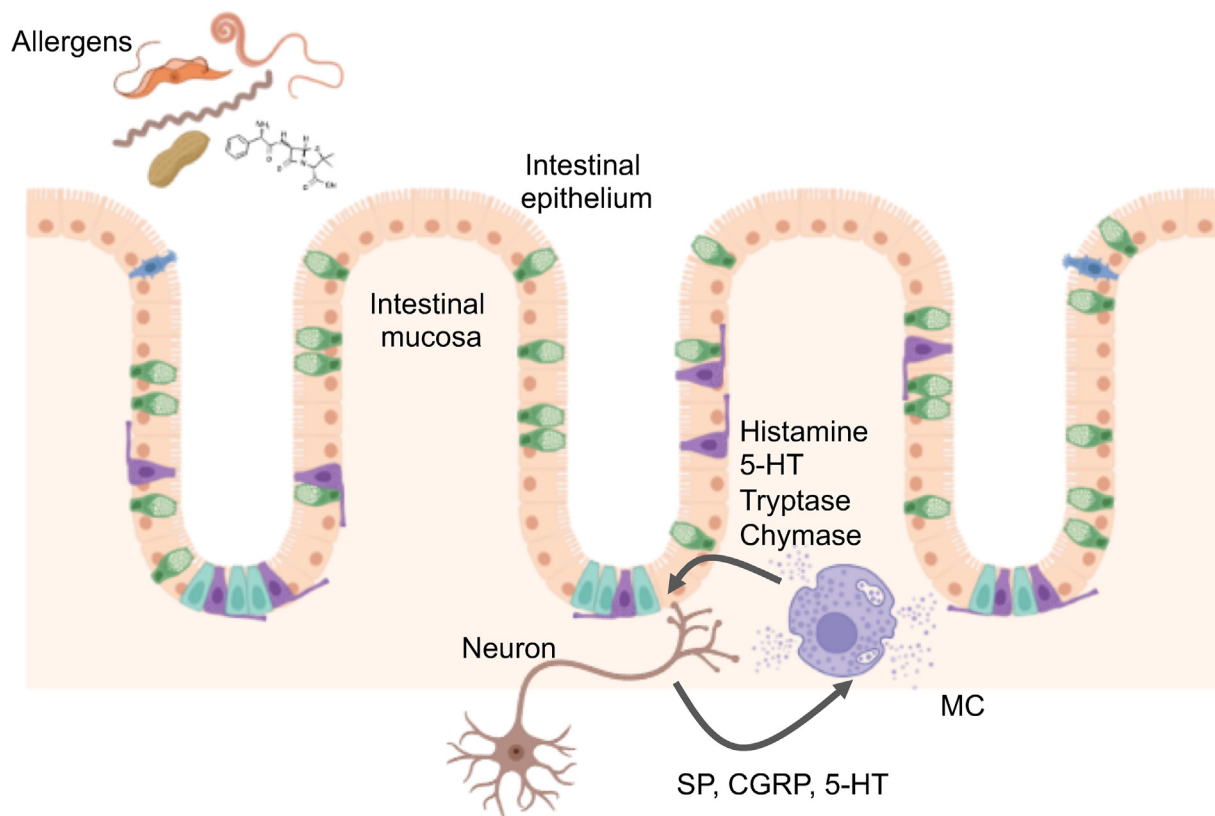


Fig. 3. MC–nerve loop in lung with allergic inflammation. TRPV-expressing neuron–MC cross-talk drives intestinal allergy. Allergens activate neurons to release neuropeptides such as SP, CGRP and 5-HT, which in turn induce MCs to release histamine, 5-HT and such proteases as tryptase and chymase. Moreover, these mediators from MCs activate neurons to secrete neurotransmitters and neuropeptides. MCs, mast cells; SP, substance P; CGRP, calcitonin gene-related peptide; 5-HT, serotonin.

cells, leading to bronchoconstriction, mucus secretion and recruitment of leukocytes.^{91–94}

SP levels are increased in the bronchoalveolar lavage fluid, sputum and plasma of asthmatics.^{95–98} MrgprX2–positive MCs are significantly more numerous in the lungs of asthmatics compared with non-asthmatics.⁹⁹ SP activates MCs through MrgprB2/X2 and NK1R, causing release of histamine and such proteases as tryptase and chymase.^{56,100–102} These mediators, in turn, cause SP or CGRP release from neurons that are close to MCs,^{51,70} leading to re-activation of MCs. Thus, these findings suggest that MC–nerve loops exacerbate airway inflammation (Fig. 2).

MC–nerve loop cross-talk regulates intestinal allergic inflammation

The intestine has the most kinds of immune cells (e.g., T cells, MCs, IgA⁺ B cells and macrophages) of all organs in our body and is continually exposed to foreign antigens such as dietary components, pollutants, harmful pathogens and commensal bacteria.^{103,104} To maintain intestinal homeostasis, mucosal immunity must distinguish between harmful and innocuous components.¹⁰⁵ Thus, mucosal immune responses are stringently regulated by several factors, including the nerves.¹⁰⁵ MCs and nerve fibers are co-localized in the colonic lamina propria surrounding mucosal crypts, and the frequency of these associations is significantly increased in the mucosa of patients with irritable bowel syndrome (IBS).⁵³ Moreover, the number of degranulated MCs in close proximity to colonic nerves correlated significantly with abdominal pain/discomfort.¹⁰⁶ Those findings suggest that MC–nerve interaction is a key modulator of intestinal inflammation. Immune

tolerance to innocuous dietary components, causes FA that can involve diarrhea and anaphylaxis.¹⁰⁴

MCs are well-known to contribute to the pathogenesis of FA.¹⁸ The number of MCs in proximity to enteric nerve fibers in the colonic mucosa is increased in FA mice compared with control mice.¹⁰⁷ These enteric nerve fibers release neurotransmitters, including CGRP, SP and serotonin,^{108,109} which induce release of histamine, serotonin and proteases (tryptase and chymase) from MCs. These MC mediators influence neurons by cleaving protease-activated receptors or GPCRs, which activates those receptors.¹¹⁰ On the other hand, Bosmans *et al.* showed that acetylcholine release upon vagus nerve stimulation suppresses the number of MCs and their release of proteases, leading to dampening of intestinal allergic inflammation.¹¹¹ These findings suggest that MC–nerve loops in the gut regulate gut allergic inflammation (Fig. 3).

Concluding remarks

Degranulation and proliferation of MCs are key steps in the causation of allergic inflammation in the skin, lung and intestine. These MC functions are triggered by various stimuli, including allergen-specific IgE plus allergen, cytokines and lipid mediators. Emerging evidence indicates that neurotransmitters and neuropeptides released from neurons cause MC degranulation, and that bioactive compounds (e.g., histamine, tryptase, chymase and SP) released from MCs then stimulate nerve-fiber functions. These MC–nerve loops in peripheral tissues are involved in the causation of allergic inflammation, meaning that they might be novel therapeutic targets for preventing/suppressing that inflammation. Our increased knowledge and awareness regarding the involvement of

the nervous system in allergic inflammation have opened up an exciting new research field: neuro-allergology.

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Conflict of interest

The authors have no conflict of interest to declare.

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