

Mast cells within cellular networks

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Mast cells are highly versatile in terms of their mode of activation by a host of stimuli and their ability to flexibly release a plethora of biologically highly active mediators. Within the immune system, mast cells can best be designated as an active nexus interlinking innate and adaptive immunity. Here we try to draw an arc from initiation of acute inflammatory reactions to microbial pathogens to development of adaptive immunity and allergies. This multifaceted nature of mast cells is made possible by interaction with multiple cell types of immunologic and nonimmunologic origin. Examples for the former include neutrophils, eosinophils, T cells, and professional antigen-presenting cells. These interactions allow mast cells to orchestrate inflammatory innate reactions and complex adaptive immunity, including the pathogenesis of allergies. Important partners of nonimmunologic origin include cells of the sensory neuronal system. The intimate association between mast cells and sensory nerve fibers allows bidirectional communication, leading to neurogenic inflammation. Evidence is accumulating that this mast cell/nerve crosstalk is of pathophysiologic relevance in patients with allergic diseases, such as asthma. (J Allergy Clin Immunol 2019;■■■:■■■-■■■.)

Key words: Mast cells, neutrophils, eosinophils, T cells, asthma, murine cytomegalovirus infection, vaccination, substance P, sensory nerves, neurogenic inflammation

Neutrophils comprise 50% to 70% of human leukocytes in peripheral blood, and 1 to 2×10^{11} cells per day are continuously generated in the bone marrow. A key step of an acute inflammatory response is the rapid recruitment of neutrophils from the blood to the infected tissue, where they can set up a first line of defense as effector cells against microbial invaders.^{1,2} There is ample evidence that both recruitment of neutrophils and some

Abbreviations used

APC:	Antigen-presenting cell
CGRP:	Calcitonin gene-related peptide
mCMV:	Murine cytomegalovirus
MC _{TC} :	Human tryptase- and chymase-positive mast cell
MHCII:	MHC class II
MRGPRX2:	Mas-related G protein-coupled receptor
NGF:	Nerve growth factor
NK1R:	Neurokinin-1 receptor
SP:	Substance P
TLR:	Toll-like receptor
TRPV1:	Transient receptor potential vanilloid type 1

of their effector functions can be promoted by activated mast cells. Initially, it was shown in several murine models for acute inflammation that mast cells are able to initiate recruitment of neutrophils.³⁻⁹ A cornerstone in this context was the observation that mast cells trigger the life-saving influx of neutrophils in murine models for acute bacterial infection.¹⁰⁻¹² With regard to the underlying mechanisms, mast cell-derived TNF, which can be stored within secretory granules and released on demand,¹³ plays a prominent role in attracting neutrophils. Additionally, mast cell-derived TNF was reported to be critical for neutrophil recruitment in patients with late-phase cutaneous anaphylaxis,¹⁴ contact hypersensitivity reactions,^{15,16} T_H17 cell-dependent lung inflammation,¹⁷ formation of cutaneous granulomas,¹⁸ IL-33-induced peritonitis,¹⁹ and experimental autoimmune encephalomyelitis.²⁰ Of note, this latter finding was not reproduced by using a Kit-independent strain of mast cell-deficient mice that avoids the pleiotropic effects of Kit mutations across a variety of cells beyond the mast cell itself.²¹

In general, there is ample evidence that the nature of the mutation resulting in mast cell deficiency, the strain background of mice, and the protocol to induce an experimental phenotype can all contribute to generation of contradictory results when comparing different mast cell-deficient mouse strains. A detailed review of this subject can be found in several previous publications.²²⁻²⁵

In addition to TNF, mast cell-derived leukotrienes, human tryptase, mouse tryptase mast cell protease 6, and macrophage inflammatory protein 2 are critical for the protective influx of neutrophils.²⁶⁻³⁰ In a murine contact hypersensitivity reaction model, it was reported that recruitment of neutrophils is driven by mast cell-derived TNF acting on endothelial cells expressing TNF receptor 1.³¹ Taken together, there is ample evidence that neutrophil attraction, as an important step in a variety of acute inflammatory reactions, can be mediated by mast cell mediators, including TNF.

Part of our own work focused on the effect of mast cell mediators on activation of murine neutrophil effector functions.³² Cocultures of IgE/antigen-activated murine bone marrow-derived mast cells

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and neutrophils freshly isolated from bone marrow revealed that activated mast cells strongly modulate expression of neutrophil activation markers (ie, decrease of CD62L and increase of CD11b) on the neutrophil surface. Furthermore, activated bone marrow–derived mast cells initiate generation of reactive oxygen species in neutrophils, enhance their phagocytosis, and promote neutrophil survival *in vitro*. Mechanistically, all these phenomena depend in part on the mast cell–derived cytokines TNF and, to an even greater extent, GM-CSF and do not require cell-cell contact.

In an LPS-driven murine model for acute lung inflammation, we demonstrated that neutrophil phagocytosis is impaired in mast cell–deficient *Kit^{W-sh}/Kit^{W-sh}* mice. Consequently, phagocytosis can be restored on engraftment with wild type–derived but not with GM-CSF–deficient mast cells, corroborating our *in vitro* findings.³² Thus mast cells can contribute to both local activation of critical neutrophil effector functions and their prolonged survival, which can be facilitated by close cell-cell contact.³³ It is tempting to speculate that neutrophils can also have an effect on mast cell activation in a bidirectional communication between these cell types, yet this deserves further investigation.

In this context more information has been gathered on interactions between mast cells and eosinophils. Infiltrating eosinophils have been detected in close proximity to mast cells in allergic inflamed tissue and in patients with several other diseases.^{34,35} This led to the hypothesis that mast cells and eosinophils form an “allergic effector unit.”^{36–38} Within this allergic effector unit, both cell types are suggested to have soluble and physical crosstalk that enhances cellular functions, amplifying the late phase of allergic inflammation. Mast cell–derived soluble factors able to modulate eosinophil function include IL-5, GM-CSF, and IL-3, among others. Interestingly, cocultures of eosinophils and mast cells prolonged the otherwise poor survival of the former in the presence of dexamethasone. This effect might play a role in patients with corticosteroid-resistant asthma.³⁶ On the other hand, eosinophils are able to release a variety of factors able to promote activation of mast cells, including platelet-activating factor, stem cell factor, nerve growth factor (NGF), eosinophil major basic protein, eosinophil cationic protein, and eosinophil peroxidase.³⁴ Furthermore, eosinophils enhanced mast cell mediator release through physical contact involving interaction between CD48 expressed on mast cells and 2B4 expressed on eosinophils.³⁸ Taken together, these paracrine and physical interactions between both cell types might be relevant in patients with allergic diseases and also in those with several inflammatory and neoplastic disorders.³⁵ However, in addition to interactions with cells from the innate part of the immune system, mast cells are also able to communicate with cells from the adaptive immune system, as outlined in the following 2 sections.

CROSSTALK BETWEEN EFFECTOR T CELLS AND MAST CELLS

Close proximity between mast cells and T cells in inflamed tissues led to the suggestion of a bidirectional relationship between these cell populations.^{39,40} In general, interactions of T cells and mast cells can be cell-to-cell, cytokine, and exosome mediated.⁴¹ In the absence of soluble mediators, direct contact between human and murine mast cells and activated T cells was reported to induce mediator release and activation of mast cells, causing release of stored mediators and production of cytokines,

including TNF, IL-4, IL-6, and IL-8.^{42–46} Interactions between intercellular adhesion molecule 1 and lymphotoxin- β receptor with their respective ligands was reported to be responsible for T cell–induced mast cell activation.⁴² Activation of mast cells could also be accomplished on incubation with cell membranes derived from activated T cells.^{43,47} Additionally, surface molecules on membrane vesicles secreted by T cells were also shown to activate mast cells.⁴⁸ The latter phenomenon might allow distant activation of mast cells.

For stimulation of effector T cells by mast cells, the ability of the latter to present antigens and express costimulatory molecules is of central importance. A combination of LPS and IFN- γ was shown to induce expression of both MHC class II molecules and costimulatory CD80/CD86 molecules on mast cells.^{49,50} Inducible expression of MHC class II (MHCII) and processing and presentation of antigenic peptides on mast cells leads to expansion of previously activated CD4⁺ effector T cells and also of CD4⁺CD25⁺ regulatory T cells. Moreover, activated mast cells can promote T-cell activation by soluble TNF,⁵¹ by triggering the costimulatory molecule OX40,⁵² and through release of exosomes carrying MHCII molecules and CD86.⁵³ Synapse-like contacts between dendritic cells and mast cells initiated by inflammatory conditions lead to transfer of MHCII complexes, enabling the latter to prime allogeneic T cells.⁵⁴ In the human system mast cells primed with IFN- γ are able to induce superantigen-specific T-cell responses and antigen-specific T_H1 recall responses.⁵⁵ However, mast cells should not be regarded as professional antigen-presenting cells (APCs) able to activate naive T cells, although they can function as nonprofessional or atypical APCs.⁵⁶

Evidence has accumulated suggesting a protective role for mast cells in antiviral immune responses.^{57–59} In this context we have shown that mast cells degranulate on infection of mice with murine cytomegalovirus (mCMV) involving Toll-like receptor (TLR) 3/TRIF–dependent and independent mechanisms.⁶⁰ On infection, mast cells are also critical for the recruitment of mCMV-specific CD8 T cells to the lungs.⁶¹ The lungs are a predilection site for mCMV infections, and accordingly, interstitial pneumonia is the most dreaded manifestation of CMV disease in immunocompromised patients. In mast cell–deficient *Kit^{W-sh}* mice, CD8 T cells were recruited less efficiently to the lungs, correlating with strongly enhanced viral replication and delayed clearance of virus. Both phenomena were restored on reconstitution of mast cell–deficient mice with mast cells generated *in vitro*.^{61,62}

Most likely, a wave of mast cell–derived CCL5 in the sera of infected mice contributes to the recruitment of mCMV-specific CD8⁺ T cells, which is in agreement with published findings.⁶³ However, in the mCMV model mast cell deficiency does not affect the functionality and expansion of virus-specific CD8⁺ T cells.⁶¹

EFFECT OF MAST CELLS ON PROFESSIONAL APCs IN MODELS FOR VACCINATION AND ALLERGIC AIRWAY DISEASE

Initially, it was shown that mast cells are able to trigger migration of professional APCs in several murine models.^{64–68} Concomitantly, mast cells enhance expression of costimulatory molecules on APCs (CD80, CD86, and CD40), thereby also promoting their maturation.⁶⁹ Thus, by influencing both migration

and maturation of APCs, mast cells are well suited to modulate APC-driven immune responses, acting at the interface of innate and adaptive immunity.

This property of mast cells as a nexus linking innate and adaptive responses makes them an attractive target in vaccination models using adjuvant in combination with antigen. In this context we demonstrated that mast cells are critical for development of a variety of phenomena after topical application of the TLR7 ligand imiquimod in combination with a cytotoxic T-lymphocyte antigenic peptide (ie, a murine model for transcutaneous immunization).⁷⁰ Mast cells expressing TLR7 and the mast cell–derived cytokines IL-1 β and TNF are critical to mount a rapid and full-blown inflammatory response on application of adjuvant that was mainly characterized by the influx of neutrophils.^{70,71} Additionally, hypertrophy of draining lymph nodes is driven by mast cell–derived TNF in agreement with published data.^{16,72,73} Emigration of Langerhans cells as professional APCs from the epidermis to the draining lymph nodes is partly dependent on mast cell–derived IL-1 after topical application of imiquimod.

Finally, expansion and function of peptide-specific cytotoxic CD8⁺ T cells are severely impaired in this model in the absence of mast cells.⁷⁰ In line with this, the mast cell activator compound 48/80 was also shown to exert a mucosal⁷⁴ and intradermal⁷⁵ adjuvant function and to enhance protective humoral immunity. Of note, adjuvant effects of compound 48/80 applied either intradermally or through the mucosal route were recently shown to be independent of mast cells by using Kit-independent mast cell–deficient mouse strains.⁷⁶

Murine inflammatory airway disease based on sensitization to antigens and subsequent provocation is often used as a model for the pathogenesis of human asthma, including inflammation of the airways, overproduction of mucus, and hyperreactivity to bronchoconstrictors.⁷⁷ Mast cells have been linked to induction of allergic airway disease in mice, although this was shown to depend on the experimental model.^{78–80} In this context we were able to demonstrate that in previously sensitized mice mast cells can promote migration of antigen-laden APCs from the lung to the draining lymph nodes on intranasal antigen challenge.⁶⁷ Accordingly, in the absence of mast cells, airway inflammation, mucus production, and airway hyperreactivity were all decreased. Interestingly, the phenotype seen in mast cell–deficient mice could be restored after transfer of antigen-laden APCs to sensitized mice before airway challenge. Taken together, this study suggests that interaction between mast cells and APCs can be critical for development of airway disease.

However, we were able to show that the contribution of mast cells to development of murine allergic airway disease strongly depends on the genetic background.⁸¹ Regarding the latter, identification of a traceable polymorphism closely linked to the *Kit*^{W-sh} allele allowed us to generate congenic mast cell–deficient mice on a BALB/c background, which is termed C.B6-*Kit*^{W-sh}.⁸¹ Unexpectedly and in sharp contrast to their C57BL/6-*Kit*^{W-sh} mast cell–deficient counterparts, C.B6-*Kit*^{W-sh} mice show all the signs of allergic airway disease despite the absence of mast cells. This phenomenon might, at least in part, reflect the complexity seen in human disease. In the next section we will shed some light on mast cell/nerve interactions and how they contribute to physiologic and pathophysiologic responses, with a focus on allergic inflammation.

MAST CELL INTERACTIONS WITH THE SENSORY NEURONAL SYSTEM IN PATIENTS WITH CHRONIC INFLAMMATORY DISEASES

Microlocalization is a fundamental organizing principle of inflammatory responses because many neuronal and inflammatory mediators are rapidly inactivated. The functional communication between mast cells and nerves depends on membrane-membrane contacts mediated by cell adhesion molecule 1.^{82,83} This intimate association was shown by the presence of dense core vesicles at the points of contact.⁸⁴ Close anatomic proximity and functional communication of mast cells with sensory nerves has been suggested in different organs, such as the gut,⁸⁵ skin,⁸⁶ and respiratory tract.^{87–90} In patients with chronic skin diseases, including psoriasis and atopic dermatitis, contacts between mast cells and sensory nerves are increased in number.⁸⁶ Many inflammatory diseases of the skin and intestine are accompanied by mast cell hyperplasia in the inflamed mucosal epithelium and in adjacent smooth muscle.^{91,92} Therefore mast cell/nerve communication in smooth muscle might be enhanced.

Human skin mast cells have shown immunoreactivity to the neuropeptide substance P (SP). Using electron microscopy, Toyoda et al⁹³ demonstrated that SP was localized within the mast cell secretory granules. Interestingly, mast cells positive to SP and the amount of SP within mast cells were increased in lesional skin from atopic patients. This suggests that SP could be synthesized as a newly generated mediator when inflammation prevails. *In vivo* experiments using human skin have shown that intradermal injection of SP provokes wheal, flare, and itch responses. These responses are mainly mediated by mast cell degranulation, followed by increased vascular permeability and marked infiltration of eosinophils and neutrophils, and can be blocked on depletion of peripheral nerve neuropeptide content.^{94–96}

Moreover, Stoyanova and Gulubova⁹⁷ described a population of mast cells in the human intestine that were immunopositive for both tryptase and SP. These cells were found in greater frequencies in biopsy specimens from patients with chronic ulcerative colitis compared with control specimens.⁹⁷ In biopsy specimens from the guts of patients with inflammatory bowel disease but not in biopsy specimens from noninflamed tissue, SP treatment induces secretion of histamine.⁹⁸

In our group we analyzed the distribution and localization of mast cells and sensory nerve fibers in cross-sectioned small airways by using human precision-cut lung slices. We showed a close anatomic localization of mast cells with sensory nerves, especially with mast cells containing the neuropeptide SP (Fig 1). These observations indicate that an inflammatory environment increases the frequencies of SP and tryptase double-positive mast cells. Nevertheless, whether human mast cells produce SP has to be confirmed at the mRNA level.

Indeed, several lines of evidence point out that functional communication between mast cells and sensory nerves is involved in the pathogenesis of chronic inflammatory disease.

Vagal sensory neurons represent a dominant afferent innervation to the airways and lungs.^{99,100} C-fibers are a nonmyelinated subset of afferent nerves that have been shown to be involved in the pathophysiology of asthma, including airway hyperreactivity.^{100–102} C-fibers are characterized by coexpression of the transient receptor potential vanilloid type 1 receptor (TRPV1) ion channel and sensory neuropeptides, such as SP.¹⁰³ Interestingly,

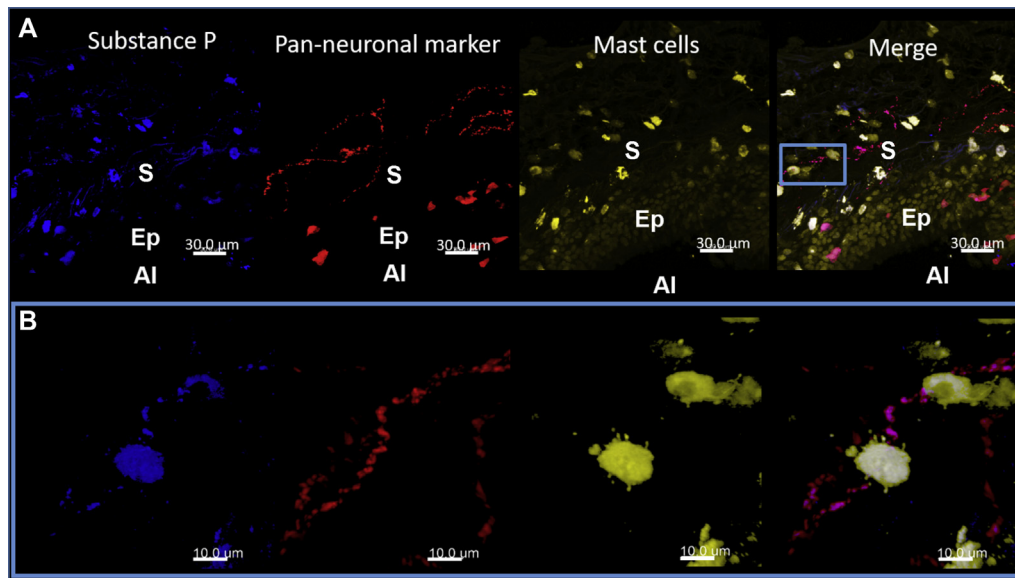


FIG 1. Distribution and localization of mast cells and sensory nerve fibers in cross-sectioned small airways of human precision-cut lung slices. Human lung material was cut into 300- μ m-thick viable precision-cut lung slices, including cross-sectioned small airways. Nerves were immunostained with the panneuronal marker PGP9.5 (red), mast cells were visualized with anti-human tryptase antibody (yellow), and SP was localized with an anti-SP antibody (blue). Lung tissue autofluorescence was used to illustrate lung structure. **A**, Representative image illustrating the airway lumen (Al), epithelium (Ep), and submucosa (S) in a cross-sectioned small airway shows distribution of peripheral nerves (red), mast cells (yellow), and the neuropeptide SP (blue). SP-positive sensory nerves (pink) were observed in proximity to SP-positive mast cells (white). Three-dimensional images are shown. Scale bar = 30 μ m. **B**, Zoom of the indicated rectangular area in Fig 1, A, showing subepithelial mast cell/nerve interactions including sensory nerves and SP and tryptase double-positive mast cells. Scale bar = 10 μ m.

they serve not only as afferent information wires but also have a strong local effector function through release of neuropeptides at the site of stimulation (axon reflex). On stimulation with inhaled irritants or endogenous signals associated with tissue inflammation, C-fibers release neuropeptides through the axon-reflex mechanism, leading to neurogenic inflammation. In this setting neuropeptides affect neighboring effector cells, leading to bronchoconstriction, protein extravasation, mucus secretion, and recruitment of leukocytes.¹⁰⁴ The neuropeptide SP is known as one of the most important mediators of neurogenic inflammation. Increased levels of SP have been detected in bronchoalveolar lavage fluid,¹⁰⁵ sputum,^{106,107} and plasma¹⁰⁸ from asthmatic patients, and increased levels of SP have also been found on allergen challenge.

SP is an effective constrictor of airways, and this has been demonstrated in *in vitro* and *in vivo* experiments by using different animal and human airways.^{109–112} SP has a high affinity for the neurokinin-1 receptor (NK1R), and it also binds, although with lower affinity, to the other tachykinin receptors, neurokinin-2 receptor and neurokinin-3 receptor.¹¹³ In addition, the direct effect of SP on NK1R on airway smooth muscle cells, several studies have suggested that the SP/NK1R route can contribute to airway constriction indirectly through mast cell activation.^{109,114}

The theory that NK1R expression has a functional significance for asthma symptoms and affects the sensitivity of mast cells to SP under allergic conditions was challenged by the failure of several NK1R antagonists in clinical studies.^{115,116} This was explained by the limited pharmacologic properties of the antagonists and the complexity of the neuropeptide system, including redundant

neuropeptides and receptors and alternative receptor pathways. Regarding the latter, it was demonstrated that SP activates murine mast cells and human tryptase- and chymase-positive mast cells (MC_{TC}s) through Mas-related G protein-coupled receptor X2 (MRGPRX2).^{117–119} Most MC_{TC}s were found in human connective tissue, such as the skin.^{120,121}

Brightling et al¹²² showed in bronchial biopsy specimens that infiltration of the airway smooth muscle cell layer with mast cells is associated with airway disorders. In a subgroup of asthmatic patients, these mast cells were tryptase and chymase positive.¹²² Increased frequencies of MC_{TC}s and MRGPRX2-positive mast cells in the lungs of asthmatic patients indicate that an MRGPRX2-expressing MC_{TC} subpopulation might influence asthma pathology.^{123,124} However, the exclusive expression of MRGPRX2 on MC_{TC}s in the lung and its function in airway hyperresponsiveness has to be proved. Other studies demonstrated that intraepithelial mast cells in patients with T_H2-high asthma have a different phenotype containing high levels of tryptase and carboxypeptidase 3 but low chymase levels and predict responsiveness to inhaled corticosteroids.¹²⁵ These studies demonstrate the plasticity of mast cell phenotypes that can change under pathologic conditions according to the specific microenvironment.¹²⁶

In our own work (unpublished) we showed that challenge of sensory nerve endings leads to an axon-reflex response that activates mast cells through SP. Ultimately, this causes enhanced airway constriction in passively sensitized human lung tissue. Enhanced airway constriction was inhibited by the NK1R-specific antagonist fosaprepitant (Ivemend).¹²⁷ Expression of

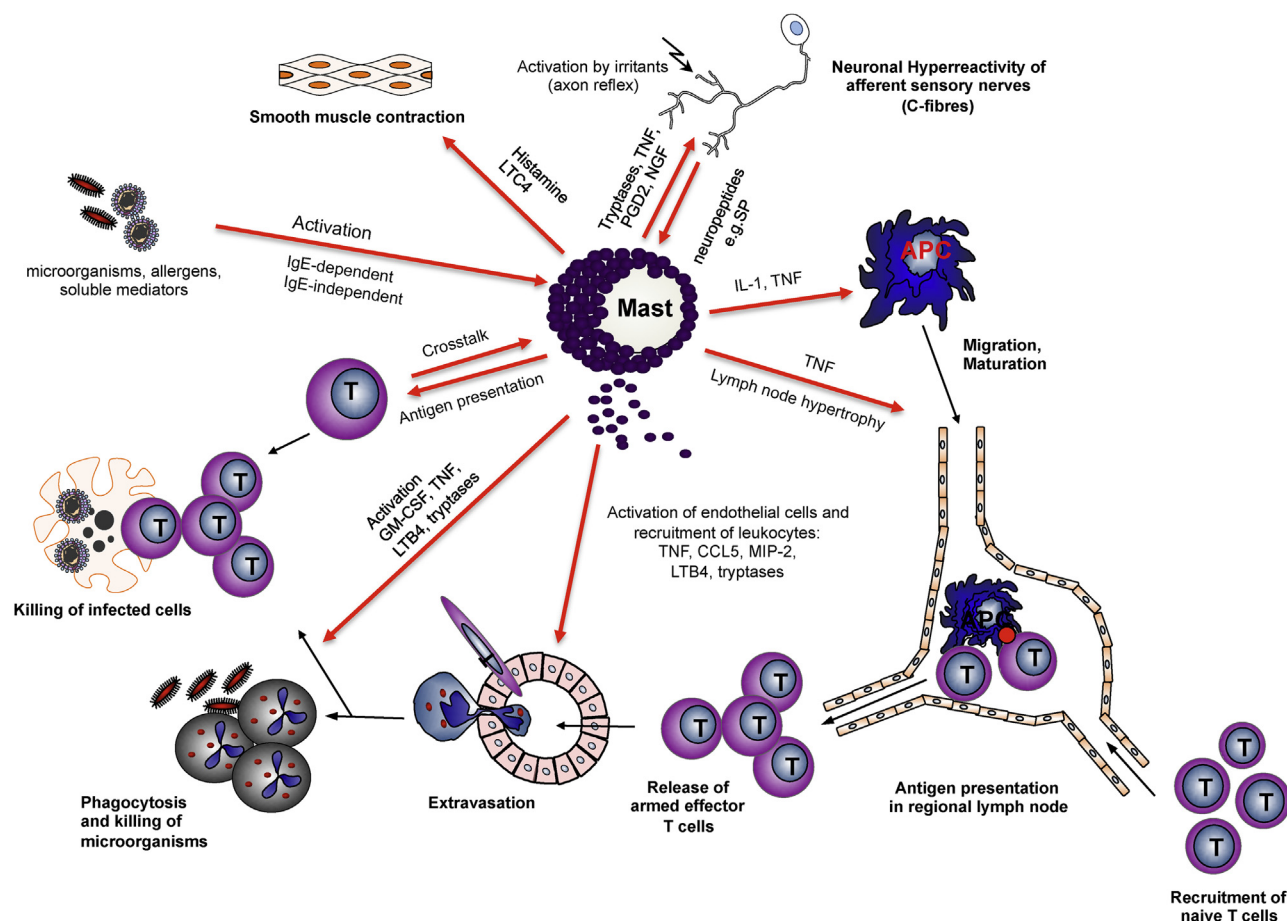


FIG 2. The networking mast cell. Afferent sensory nerves (C-fibers) can be activated by exogenous or endogenous stimuli. This sets up an axon-reflex mechanism leading to neurogenic inflammation. Secreted neuropeptides, such as SP, released through the axon-reflex mechanism activate mast cells by binding to NK receptors or MRGPRX2 to release mediators (histamine and leukotriene C₄), promoting smooth muscle cell contraction. *Vice versa*, activation of afferent neurons by mast cell-derived mediators (tryptase, histamine, cysteinyl leukotrienes, and neurotrophins) causes neuronal hyperreactivity and thus a vicious circle of neuroinflammation. Mast cells activated by IgE or IgE-independent signals are able to promote migration of antigen-laden professional APCs to the draining lymph nodes, where they initiate expansion of antigen-specific T cells. Additional signals, including mast cell-derived TNF, are required to facilitate this initiating event in development of the adaptive immune response. Therefore it is very likely that mast cells have an effect on the magnitude of the immune response. Mast cell mediators, such as CCL5/RANTES, have a role in recruitment of CD8⁺ T cells to sites of viral infection. Activation of effector T cells and mast cells can also be triggered by intercellular crosstalk. In this context mast cells can function as nonprofessional APCs. Additionally, mast cells are able to activate endothelial cells, leading to attraction of neutrophils as a critical event in many acute inflammatory reactions. Moreover, mast cells also boost neutrophil activation.

NK1R on mast cells seems to be regulated by IgE binding to FcεRI, as shown in several studies with *in vitro* cultures and confirmed by our group.¹²⁸⁻¹³⁰ Using fresh human lung tissue, we showed that anti-IgE antibody treatment (omalizumab) during passive sensitization of lung tissue leads to a significant decrease of neurally induced bronchoconstriction. These data emphasize that IgE binding to mast cells positively affects the expression of NK1R on mast cells and thus their sensibility to SP. However, SP was shown to induce mast cell degranulation¹³⁰⁻¹³² and histamine release from a variety of mast cell types, including human mast cells isolated from bronchoalveolar lavage fluid,^{133,134} skin,¹³⁵ and inflamed gut mucosa.⁹⁸ However, the presence of NK1R and MRGPRX2 on mast cells suggests both autocrine and paracrine mechanisms. For instance, it has been reported that SP induces release of cytokines in human mast cells.¹³⁰

It must be mentioned that neuropeptides also have anti-inflammatory and protective functions. It should be recalled that mast cell degranulation and inflammation can also be negatively regulated, such as through the calcitonin gene-related peptide (CGRP) or vasoactive intestinal peptide/pituitary adenylate cyclase-activating peptide family, which often colocalize with SP.^{136,137} In a murine model of allergic asthma, CGRP inhibits dendritic cell maturation and allergen-specific T-cell responses, which affects the outcome of allergic airway inflammation *in vivo*. In the gut the neuropeptide CGRP exhibits protective effects on gastric mucosa injury after cerebral ischemia reperfusion in rats.¹³⁸ A regulatory interaction between SP and CGRP was shown when injection of CGRP with SP into human skin converted the long-lasting vasodilation induced by CGRP into a transient response. Vasodilation

was regulated by the action of proteases from mast cells stimulated by SP.¹³⁹

Mast cells synthesize and release a variety of molecules that, in turn, influence neuronal activity. Mast cell mediators, including TNF, tryptase, NGF, prostaglandin D₂, and adenosine, can enhance the sensitivity of TRPV1 or decrease its threshold for activation.¹⁰² Therefore allergic reactions in the airways can increase the excitability of sensory fibers and promote a feedback between mast cells and terminal nerves.¹⁰¹ Moreover, this effect can increase parasympathetic tone in the airways by increasing central and peripheral reflex arcs.⁸⁹ Indeed, increasing evidence indicates that TRP receptors, such as the TRPV1 channel, are relevant in the development of several aspects of airway hyper-sensitivity.¹⁰² Thus mast cells and nerves mutually influence each other in different pathologies, including psoriasis, inflammatory bowel disease, and asthma.

NGFs seem to play a special role in the mast cell/nerve interaction, especially in setting the sensitivity of the interaction and inducing hyperreactivity in pathophysiologic conditions. Neurotrophins have been shown to promote differentiation and survival of mast cells, which in turn represent a major source of neurotrophins. In patients with diseases like mastocytosis, the neurotrophin system is highly upregulated. In combination with increased neurotrophin levels, increased expression of several isoforms of tropomyosin-related kinase receptors on mast cells contributes to the pathophysiology of mastocytosis in autocrine and paracrine loops.¹⁴⁰ In the skin mast cells act as a “power-house” by releasing algogenic and pruritogenic mediators, which initiate a reciprocal communication with specific nociceptors on sensory nerve fibers. Consequently, nerve fibers release inflammatory and vasoactive neuropeptides, which in turn activate mast cells in a feedback mechanism, thus promoting a vicious cycle of mast cell and nociceptor activation leading to neurogenic inflammation and pain/pruritus.¹⁴¹ In this context we were able to show in a rat asthma model that the mast cell-dependent early-phase response can be blocked by anti-NGF treatment.¹⁴²

Interaction between mast cells and sensory nerves occurs preferentially in organs with direct contact to the environment, such as the skin, lung, and gut. For instance, in the lung these interactions are of pathophysiologic relevance in patients with allergic diseases, such as asthma. However, the underlying mechanisms are not completely resolved.

CONCLUSIONS

With the advent of mast cell-deficient mouse strains and their widespread use, mast cell functions have been considered to be much broader than their original role in IgE-driven immediate-type reactions. However, caveats have been raised about mast cell-deficient Kit mutant mice and their reconstitution with mast cells generated *in vitro*.

Ideally, Kit-dependent and independent strains deliver consistent results that are corroborated by findings derived from human mast cells *ex vivo* or *in vitro*. In the future, mouse strains that allow efficient development of human mast cells from hematopoietic stem cells can be extremely useful tools for investigation of mast cell biology and as preclinical models.¹⁴³

In different studies it has become apparent that mast cells can be critical for the rapid recruitment and activation of neutrophils (ie, for induction of an acute inflammatory response; Fig 2). Furthermore, there is ample evidence that mast cells can promote

induction of adaptive immune responses in different ways. First, mast cells can support migration and maturation of professional APCs to the draining lymph nodes. Second, mast cells can directly interact with T cells. In this context mast cells can act as nonprofessional APCs by presenting antigen to preactivated T cells, either after uptake and processing of antigen or after receiving MHCII from professional APCs on cell-to-cell interaction.

Intimate interactions between peripheral sensory neurons and mast cells form a microenvironment for communication resembling synaptic junctions. Emerging evidence indicates that mast cell mediators can act on neurites and *vice versa*. The axon-reflex mechanism allows activation of mast cells by neuropeptides, leading to neurogenic inflammation, including contraction of smooth muscle cells, mucus secretion, and recruitment of leukocytes in patients with chronic inflammatory diseases. By using novel and more specific models, it will be fascinating to further unravel the manifold functions and interactions of mast cells with immune and nonimmune cells.

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