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New roles and controls of mast cells

Eric Espinosa and Salvatore Valitutti

Mast cells are innate immune cells implicated in immune surveillance and defense. They are filled with secretory granules where a vast array of molecules endowed with multiple biological activities are stored. The process of granule secretion, named degranulation, is a tightly controlled biological phenomenon that allows mast cells to rapidly and efficiently release bioactive mediators in response to extracellular stimuli. MC degranulation allows fighting pathogens, limiting envenomation and contributes to tissue homeostasis. However, it is also a potentially harmful response that plays a key role in the development of allergy and inflammatory diseases.Recent findings revealed that MC degranulation is a complex modular process that can be controlled at multiple levels. First, mast cells can decode different activation stimuli into two main patterns of degranulation that differently impact inflammatory responses. Second, mast cells in contact with antibody-opsonized cells or parasites form antibody-dependent degranulatory synapse for dedicated secretion and defense. Third, IL-33 fine-tunes FcR-mediated degranulation at the single cell level. Together these recent findings show how mast cells adapt their degranulation responses to environmental cues and highlight the remarkable functional plasticity of these cells.

Address
Centre de Physiopathologie de Toulouse Purpan (CPTP), Université de Toulouse, CNRS, INSERM, UPS, France

Corresponding author: Espinosa, Eric (eric.espinosa@inserm.fr)

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Introduction

Mast cells (MCs) belong to an unique cellular lineage of the innate immune system [1••]. They are located in virtually all tissues and are noticeably abundant in tissues at the host–environment interface such as skin and mucosa. For instance, MCs represent about 10% of the immune cells in the skin [1••] and about 5% in the intestine [2]. They constitute a tissue resident population in close vicinity to blood vessels and terminal nerve endings. Being strategically located, MCs are among the first immune cells to encounter antigens or incoming pathogens [3,4,5].

Based on their tissue location and granule content, murine MCs are typically classified as either connective tissue (CTMC) or mucosal-type mast cells (MMC) [6,7]. Their human counterparts are defined according to the proteases they produce: MC_{TC}, expressing tryptase and chymase and MC_T, expressing tryptase only. It should be noted that this classification is simplistic since MC phenotypes and roles are profoundly molded by the tissues environment where they mature. MCs are indeed endowed with a high degree of plasticity [7].

Upon stimulation, MC can release a vast array of powerful biological mediators that can dramatically affect the extracellular milieu. MC cytoplasm is filled with hundreds of secretory lysosomes, named secretory granules (SGs) where a huge panel of mediators is stored (such as histamine, heparin, tryptases, chymase, carboxypeptidase A3, TNF, *etc.*) [8]. These mediators can be swiftly released upon degranulation allowing MC to impact tissue homeostasis (vascular permeability, vasomotricity, matrix remodeling, *etc.*), to participate in inflammatory processes and to fight pathogens. Several proteases are embedded within SG proteoglycan matrix (tryptases, chymase, carboxypeptidase A, *etc.*)[8]. Upon degranulation, these proteases are released and can affect the function of a variety of proteins (ex: activation, inhibition or degradation of cytokines, receptor shedding, venom degradation, *etc.*)[8,9]. Upon appropriate stimulation, MC can also release neo-synthetized mediators such as eicosanoids and a large array of cytokines and chemokines [8]. Although MC function and SG release are involved in physiologic tissue homeostasis, excessive MC activation plays a crucial role in the pathogenesis of allergy and of organ-specific inflammatory disorders such as psoriasis or inflammatory bowel diseases [10,11].

MC degranulation has been extensively studied in the context of allergy and is classically seen as a rapid process, triggered by the aggregation of high-affinity IgE receptors by soluble ligands. In this review, we discuss recent results showing that MCs are capable of setting up several degranulation modalities. These findings extend our knowledge on how MC sense signals derived from extracellular milieu and provide adapted responses.

Triggering of secretory granule release: multiple secretory pathways in response to multifaceted stimuli

Secretory pathways

The release of the mediators stored in SGs, is a complex and tightly regulated process that has been extensively studied, but is still incompletely understood [12,13]. In simple terms, SG exocytosis consists in the fusion of SG membrane with cell plasma membrane followed by the release of the SG matrix into the extracellular space. Beyond individual granule exocytosis, other patterns of SG content release have been described. 'Kiss-and-run' exocytosis allows partial release of the SG cargo through the formation of a transient fusion pore with the plasma membrane. 'Piecemeal exocytosis' is a mechanism by which shuttle vesicles move cargos of SG stored mediators to the plasma membrane. Finally, 'compound exocytosis' (also named anaphylactic degranulation) is based on intracellular homotypic SG-SG fusion leading to the formation of degranulation chambers, whereupon these multi-granular structures fuse with the plasma membrane to deliver their content [12,13,14,15]. While compound exocytosis allows MCs to swiftly and massively release their SG content, piecemeal degranulation allows surgical delivery of chosen SG components.

Triggering stimuli

MC degranulation is efficiently triggered by two main classes of receptors: i) Fc receptors (FcRs) that allow MCs to specifically respond to antibody-targeted antigens and ii) G-protein-coupled receptors (GPCR) that allow MCs to degranulate in response to soluble mediators (Table 1).

Most FcRs are ITAM-containing activating receptors that signal upon aggregation induced by Ig-bound antigens [16]. All MCs express the high affinity IgE receptor (FcεRI) that allows them to participate to IgE-dependent allergic processes. Skin human MCs also constitutively express the low affinity IgG receptor FcγRIIA. Moreover, human MCs can express the IFN-γ inducible high affinity IgG receptor FcγRI (CD64) [17]. Murine MCs express the low affinity IgG receptor FcγRIIIA and the inhibitory receptor FcγRIIB that tightly controls their activation [16].

Besides FcR, other receptors can induce MC degranulation (Table 1). We focus here on the newly described Mas-related G-protein-coupled receptor X2 in human (MRGX2 or MGRPRX2) and in rodent (Mrgprb2, the mouse orthologue of MRGPRX2) [18,19••]. These GPCR bind to various basic cationic molecules collectively called basic secretagogues, such as neuropeptides (Substance P and neuropeptide Y) and antimicrobial peptides (LL37 and human β-defensins) [19••,20,21]. Several drugs involved in pseudoallergic reactions, such as morphine, Icatibant or Cetrorelix have been identified as MRGPRX2 agonists [19••]. Beside small-diameter neurons in the dorsal-root and trigeminal ganglia, connective tissue MCs are the unique immune cells that

Table 1

Receptors that trigger MC degranulation.

Receptor	Stimulus	References
FcR		
FcεRI	IgE/multivalent antigen	[29]
FcγRIIA(human)/FcγRIIIa(mouse)	IgG immune complexes	[30,31]
FcγRI*	IgG/multivalent antigen	[17]
GPCR		
C5aR (CD88)	C5a	[32,33]
C3aR	C3a	[34]
MRGPRX2(human)/MrgprB2(mouse)	Large array of basic secretagogues:	[19••,20,21]
	-Neuropeptides: Substance P, VIP, Cortistatin 14	[18,22,35••]
	-Compound 48/80	[19••]
	-Opiates: morphine, dynorphin	[21]
	-Several cationic drugs (Cetrorelix, Icatibant . . .)	[21,36]
	-AMPs: LL37, hBD2	[23,24,37]
	-Eosinophil granule proteins (MBP, EPO)	[22]
	- Wasp peptide toxins : mastoparans	[19••]
ET-A**	Endothelin-1	[38,39]
	Snake venom sarafotoxins	[27]
Others		
P2X7R	ATP	[40,41,42]
TLR2	Peptidoglycan	[43]
CD48	FimH	[44]
	2B4	[45]

AMP, antimicrobial peptide; VIP, Vasoactive intestinal polypeptide; MBP, Major basic protein; EPO, eosinophil peroxidase.
* FcγRI is inducible in human MC but is not expressed on mouse MC.
** ET-A was reported to be expressed on rodent CTMC.