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Review

Mast cell secretome: Soluble and vesicular components

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ABSTRACT

Mast cells are multifunctional master cells implicated in both innate and adaptive immune responses. Their role has been best characterized in allergy and anaphylaxis; however, emerging evidences support their contribution to a wide variety of human diseases.

Mast cells, being capable of both degranulation and subsequent recovery, have recently attracted substantial attention as also being rich sources of secreted extracellular vesicles (including exosomes and microvesicles). Along with secreted *de novo* synthesized soluble molecules and secreted preformed granules, the membrane-enclosed extracellular vesicles represent a previously unexplored part of the mast cell secretome. In this review article we summarize available data regarding the different soluble molecules and membrane-enclosed structures secreted by mast cells. Furthermore, we provide an overview of the release mechanisms including degranulation, piecemeal degranulation, transgranulation, and secretion of different types of extracellular vesicles. Finally, we aim to give a summary of the known biological functions associated with the different mast cell-derived secretion products.

The increasingly recognized complexity of mast cell secretome may provide important novel clues to processes by which mast cells contribute to the development of different pathologies and are capable of orchestrating immune responses both in health and disease.

Contents

1. Introduction

Mast cells are bone marrow-derived hematopoietic innate immune cells. They are resident in various tissues particularly at sites which are exposed to environmental stimuli such as skin, gastrointestinal tract or airways [1]. Mast cells are typically classified into mucosal and connective tissue mast cell categories with different localization, phenotypes, molecular compositions and functions [2].

Mast cells are major components of protective immunity against various infectious agents including bacteria, viruses and parasites, however, they have been most intensively studied in the context of T-helper (Th) 2 immune responses. Mast cells express high

Abbreviations: CCL, chemokine (C—C motif) ligand; CTLR, C-type lectin receptors; ER, endoplasmic reticulum; EV, extracellular vesicle; EXO, exosome; HSV, Herpes simplex virus; ICAM, intercellular adhesion molecule; IFN, interferon; Ig, Immunoglobulin; IL, interleukin; ITAM, tyrosine-based activation motif; LFA, lymphocyte function-associated antigen; LPS, lipopolysaccharide; LT, leukotriene; MC_{CT}, chymase- and tryptase-positive mast cell; MC_T, tryptase-positive mast cell; MGL, macrophage galactose lectin; MHC, major histocompatibility complex; MR, mannose receptor; MV, microvesicle; PAF, platelet activating factor; PAI, plasminogen activator inhibitor; PAP, phosphatide phosphatase; PG, prostaglandin; PL, phospholipase; PMD, piecemeal degranulation; SNARE, soluble NSF attachment protein receptor; TGF, transforming growth factor; Th, T-helper; TLR, Toll like receptor; TNF, tumour necrosis factor; XCL, chemokine (C motif) ligand.

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affinity receptor FcεRI on their surface. In type I hypersensitivity reaction, following immunoglobulin (Ig) E-sensitization, they are activated by specific cross-linking antigens. As a consequence, they secrete various preformed and newly synthesized mediators like histamine, cytokines, and subsequently induce Th2 immune responses [3,4]. Although it is less known, mast cells also play a key role in the development of Th1 immune responses, and they are involved in Th1 immune diseases such as rheumatoid arthritis [5]. Mast cells express pathogen recognition receptors (PRRs) such as toll like receptors (TLRs) including TLR2, TLR3, TLR4, TLR6, TLR7 and TLR9 that recognize invading pathogens [5]. Following stimulation by a bacterial ligand, they secrete cytokines and express co-stimulatory molecules that promote pro-inflammatory Th1 immune responses [1,6–9]. Furthermore, mast cell-induced Th1 immune response is crucial in the clearance of protozoan and bacterial infections for instance by *Leishmania major* [10], *Escherichia coli* [11], *Pseudomonas aeruginosa* [12] or *Bordetella pertussis* [13,14].

The broad range of preformed and newly synthesized mediators allow mast cells to interact with both B and T cells and regulate the phenotype of other immune cells by which they can shape the host response. Expression of cell surface markers, adhesion molecules, co-stimulatory and co-inhibitory molecules are also important in direct cell-to-cell communication [15], although the exact mechanism is unclear yet [16,17].

Recent studies suggest that mast cells may communicate with other immune cells not only by releasing soluble mediators but also by secreted, membrane enclosed vesicles [18–20]. This review will focus on the possible mechanism of how mast cell-derived vesicles and soluble mediators participate in the orchestration of innate and adaptive immune responses.

2. Content of preformed mast cell granules

Preformed granules of mast cells contain proteoglycans, proteases, biogenic amines, lysosomal enzymes, cytokines and growth factors [21].

Mast cell glycosaminoglycans/proteoglycans include heparin, heparane sulfate [22] and serglycin [23], all responsible for the metachromatic staining of these cells [24]. Granular proteoglycans both mediate storage of granule components such as histamine [25] and regulate the release of secreted molecules [24]. After release into the extracellular space, granular proteoglycans exert both positive and negative effects on the enzymatic properties of mast cell proteases. They are known as anticoagulants regulating haemostasis [24]. Furthermore, serglycin of mast cell granules has been shown to promote apoptosis [26].

Best known examples of mast cell proteases are tryptase and chymase. Murine mucosal mast cells (homologues of human chymase+/tryptase+ mast cells, MC_{CT}s) are characterized by the expression of active tryptase and chymase. In contrast, connective tissue mast cells (corresponding to human tryptase+/chymase- mast cells, MC_{T}s) show tryptase activity only [2]. These enzymes are stored in mast cell granules [27], and may play important roles in inflammation and host defence [28]. In epithelial cells, tryptase upregulates interleukin (IL)-8, intercellular adhesion molecule (ICAM)-1 [29] and it has been suggested to play a role in the immune pathomechanism of psoriasis. Tryptase induces vascular relaxation [30] and activates sensory neurons (promoting secretion of substance P) inducing inflammation [31].This protease also activates other mast cells [32]. Chymase was shown to play a role in gut homeostasis, it regulates intestinal transport and has an effect on gastrointestinal smooth muscle cells [27].

From among lysosomal enzymes found in mast cells, β-hexosaminidase is generally used as a marker of mast cell degranulation [33]. However, the physiological and pathophysiological role of this enzyme remains unclear. It was shown that it can be found both in granules and in lysosomes, and it is essential for glycoprotein metabolism in the maintenance of cell homeostasis [34]. β-hexosaminidase has been also suggested to play a crucial role in eradication of bacterial infections by degrading bacterial cell wall peptidoglycans [34].

Biogenic amines (such as histamine, serotonine and dopamine) are probably the best known bioactive molecules stored in mast cell granules. From among the multitude of known effects of histamine, here we just mention a few examples such as increase in local blood flow and vascular permeability, effect on smooth muscle cells during inflammation and allergy (reviewed recently [21]). Also, it has been established that histamine regulates homeostasis in the body; it controls sleep-wake cycle [35], body temperature [36], gastrointestinal functions [37], and endocrine homeostasis [38].

Of note, studies on either histamine deficient histidine decarboxylase knock-out or serglycin knock-out mice suggest that both histamine and serglycin regulate granule maturation process [19].

Granules also contain cytokines and growth factors which are released during degranulation. These molecules are involved in i) the activation of other cell types, ii) induction of inflammation, iii) development of immune response during infection, iv) pathogenesis of allergy and v) development of autoimmune diseases [9,39,40].

3. Release of preformed granules (degranulation)

Mast cells are usually identified by the electron microscopic presence of electron dense lysosome-like secretory granules. These secretory granules are filled with various preformed molecules such as lysosomal proteins, histamine, heparin and β hexosaminidase among others [41]. Upon exposure to various stimuli such exposure to IgE and its antigenic ligands, complement components, peptides/neuropeptides, mast cells release the content of these granules within minutes by a process called degranulation. Of note, degranulation has been described not only in mast cells but also in eosinophils [42], basophils [43,44], neutophils [45], neuroendocrine cells and neurons [46].

In the past decades conventional degranulation of mast cells has been studied extensively. Mast cells express the high affinity receptor FcεRI on their surface. Upon cross-linking of the FcεRI-bound IgE by antigen, the receptors aggregate and induce a signalling pathway that involves phosphorylation of tyrosine-based activation motifs (ITAMs) and activation of FYN, LYN and SYK [47]. Soluble NSF attachment protein receptor (SNARE) proteins such as SNAP-23, syntaxin 4, VAMP7 and VAMP8 are involved in translocation of granules from the cytoplasm to the lysosomal compartment or to the internal surface of the plasma membrane. After docking at the plasma membrane, granules fuse with it and release their content to the extracellular milieu [21,48]. The exocytosis of granules is tightly controlled. It requires mobilization of Ca^{2+}, activation of protein kinase C, hydrolysis of adenosine triphosphate (ATP) and guanosin triphosphate (GTP) and reorganization of the actin cytoskeleton (reviewed recently by Wernersson and Pejler in 2014 [21]) (Fig. 1).

Once discussing degranulation, we must mention “piecemeal degranulation” (PMD) also (Fig. 1.). PMD was first recognized in basophils [49,50], mast cells [51,52] and eosinophils [53–55] as a selective release of a part of the granular content. Number of evidences support that it also occurs in neuroendocrine cells and neurons [46,56]. During PMD, vesicles, containing a given portion of the granular content, bud from the granule’s membrane. This is followed by transportation through the cytoplasm (without granule-to-granule fusion) leading to fusion with the plasma membrane and ultimate release of mediators [46,51]. Similarly to