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Mast cells as effector cells of innate immunity and regulators of adaptive immunity

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ABSTRACT

Mast cells are widely distributed in human organs and tissues and they are particularly abundant at major body interfaces with the external environment such as the skin, the lung and the gastrointestinal tract. Moreover, mast cells are located around blood vessels and are highly represented within central and peripheral lymphoid organs. The strategic distribution of mast cells closely reflects the primary role of these cells in providing first-line defense against environmental dangers, in regulating local and systemic inflammatory reactions and in shaping innate and adaptive immune responses. Human mast cells have pleiotropic and multivalent functions that make them highly versatile cells able to rapidly adapt responses to microenvironmental changes. They express a wide variety of surface receptors including immunoglobulin receptors, pathogen-associated molecular pattern receptors and danger signal receptors. The abundance of these receptors makes mast cells unique and effective surveillance cells able to detect promptly aggression by viral, bacterial and parasitic agents. In addition, mast cells express multiple receptors for cytokines and chemokines that confer them the capacity of being recruited and activated at sites of inflammation. Once activated by immunological or nonimmunological stimuli mast cells secrete a wide spectrum of preformed (early) and de novo synthesized (late) mediators. Preformed mediators are stored within granules and are rapidly released in the extracellular environment to provide a fast vascular response that promotes inflammation and local recruitment of other innate immunity cells such as neutrophils, eosinophils, basophils and monocyte/macrophages. Later on, delayed release of multiple cytokines and chemokines from mast cells further induce modulation of cells of adaptive immunity and regulates tissue injury and, eventually, resolution of inflammation. Finally, mast cells express several costimulatory and inhibitory surface molecules that can finely tune activities of T cells, B cells and regulatory cells by cognate interactions within lymphoid organs. The multivalent capacity to recognize and to react to internal and external dangers together with their ability to cross-talk with other immunocompetent cells make mast cells a unique effector cell of innate responses and a main bridge between innate and adaptive immunity.

1. Introduction

Mast cells (MC) are widely distributed within the majority of human tissues and are considered as main components of the immune system. These cells were discovered by Paul Ehrlich in 1879 and since then they have been implicated in a variety of human diseases including allergic, autoinflammatory and autoimmune diseases and cancer. The role of MC in protective immunity came out later when they were found to be one of the main cells involved in the response to parasitic infections. However, it was only after the discovery of IgE and the finding that MC express the high affinity receptor for this class of immunoglobulins that the functions of MC as major players of innate immune response became to be fully appreciated.

2. Mast cell development and biological functions

MC originate from a multipotent hematopoietic progenitor in the bone marrow and migrate, through blood, to peripheral tissues where they undergo the final stages of differentiation and maturation [1]. Maturation of MC depends on several molecules, such as Stem Cell Factor (SCF), that binds to Kit receptor on MC surface, and other cytokines like IL-3, IL-4, IL-6, IL-9 and IL-10 [2]. The majority

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of MC are located at all major surfaces between the body and the external environment, including the skin, airways, gastrointestinal and urogenital tract. Due to their strategic location, MC are among the first cells to interact with antigens, and, thus, they are key cells in immunological surveillance against infections. Moreover, MC are abundant around blood vessels where their mediators exert rapid vasoactive effects. MC are endowed with a large repertoire of surface receptors allowing them to detect efficiently pathogens and to promote their clearance [3] (Fig. 1). Upon activation, MC release within seconds a unique panel of soluble mediators that modulate the recruitment, survival, proliferation and activation of other leukocytes [4]. Depending on the stimuli and on the type, intensity and combination of receptors activated, MC secrete different types and amounts of biologically active mediators with pro-inflammatory, anti-inflammatory and/or immunosuppressive properties [5]. MC response is biphasic: an immediate release of preformed mediators, such as histamine, proteoglycans, serotonin, neutral proteases (chymase and tryptase), of lipid mediators (PGD2, LTC and PAF), and pre-stored cytokines, such as tumor necrosis factor-alpha (TNF-α) followed by a slower secretion of newly synthesized mediators including cytokines (IL-1,IL-3,IL-4, IL-5, IL-6, IL-8, IL-9, IL 10, IL-13, GM-CSF, TGF-β), chemokines (CCL1, CCL2, CCL3, CCL4, CCL5, CXCL2) and growth and angiogenic factors [6]. Mediators released by MC can act at various levels of inflammatory cascade: they can regulate vascular flow and permeability (histamine and lipid mediators), promote the cellular recruitment at sites of inflammation (TNF), release products with killing activity (cathelicidin) [7]. Under certain circumstances, MC may also inhibit inflammatory responses by releasing IL-10 and TGF-β that restore homeostasis and limit tissue injury [8].

The best known mechanism of MC activation is dependent on antigenic stimulation through the cross-linking of IgE bound to their high affinity receptor (FcεRI). MC express other receptors, including Fcγ receptors, receptors for pathogen-associated molecular patterns (PAMPs), for complement components, as well as cytokine, chemokine and hormone receptors [9]. Pattern recognition receptors (PRR) expressed on human MC include Toll-like receptors (TLRs), Nod-like receptors (NLRs) and CD48. Most of the surface and intracellular TLR (TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9) are expressed on MC. Engagement of the different TLR induces graded and differentiated responses that range from just priming of MC (without mediator release) to secretion limited to cytokines or to full activation with release of preformed mediators and of the full panel of cytokines and chemokines [10–12]. NLRs, that interact with cytoplasmic microbial products, promote inflammation and cytokine secretion (IL-1β), through the activation of inflammasome (NLRP) [13]. Cryopyrin-associated periodic syndrome (CAPS) is a disease associated with mutations of NLRP3 in which MC are constitutively activated and continuously secrete their proinflammatory cytokines [14]. Finally, MC express several costimulatory molecules (CD40L, OX40L, CD86, CD80) that finely tune T and B cells by either enhancing or inhibiting their responses [15].

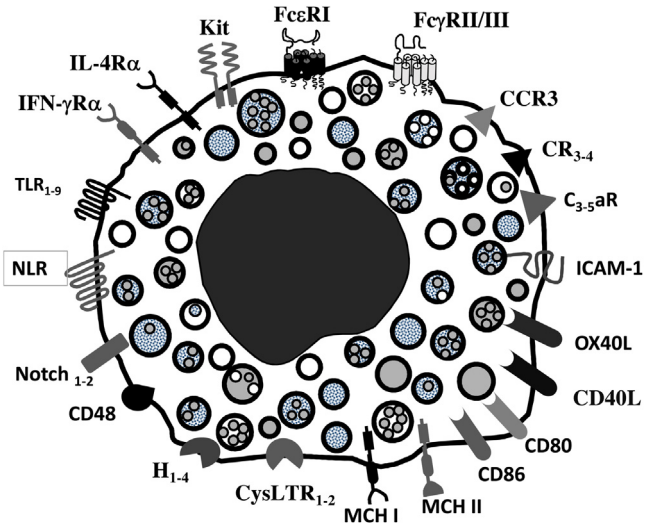

Fig. 1. *Main receptors expressed on human mast cells* Mast cells express multiple receptors involved in the recognition of bacterial, viral and fungal products, receptors for immunoglobulins and complement components as well as receptors for several cytokines and chemokines. These receptors are crucial for proper homing and recruitment of mast cells within peripheral tissues and to ensure appropriate activation of mast cells during infections. Mast cells also express costimulatory molecules that mediate cognate interactions with cells of adaptive immunity in peripheral lymphoid organs. $C_{3\text{-}5A}R$: $C_{3\text{-}5}$ anaphylatoxin chemotactic receptor; CCR3: C–C chemokine receptor type 3; $CR_{3\text{-}4}$: Complement receptor type 3–4; CysLTR: Cysteinyl leukotriene receptor; H: Histamine receptor; MHC: Major Histocompatibility Complex; NLR: NOD-like receptors; TLR: Toll-like receptors.

Overall, MC interfere with all components of immunity by participating to innate responses and by modulating antigen presentation and development of adaptive responses. MC exert these pleiotropic effects by either secreting soluble molecules (mediators, cytokines and chemokines) or by establishing cognate (cell-to-cell) interactions (Table 1). It is important to point out that all types of interactions between MC and other immune cells are always bidirectional. While MC control several functions of innate and adaptive immune responses, many immune cells, including T cells, B cells and T reg cells, simultaneously modulate MC responses.

3. Direct effector functions of MC in innate immune responses

The protective role of MC in bacterial and viral infections has been clearly demonstrated over the years. Several studies have shown that MC-deficient mice are more susceptible to septic shock and suffer increased mortality upon infection with different strains of bacteria [16]. For instance, mast cells were able to kill opsonized bacteria upon binding to complement or IgG Fc receptors, and endocytosis was observed via both oxidative and nonoxidative pathways [17]. As reported above, MC express multiple classes of PRRs that, once activated, induce the secretion of molecules with direct killing activity and mediators that recruit further inflammatory and immunocompetent cells. Human MC release a variety of antimicrobial peptides such as cathelicidins and proteases [18,19]. Enzymes with antibacterial capacities are stored within MC granules and include tryptase, cathepsin G and secreted phospholipases A_2 ($sPLA_2$) [20,21]. Moreover, to promote the physical removal of pathogens and to counteract their diffusion, MC release mediators that increase mucus production in the lung and gastrointestinal tract and enhance gut motility that favor parasite expulsion [11,22].

Table 1
MC-derived mediators and their target cells of innate and adaptive immunity.

Mediators	Target cells
CXCL8, CXCL10, TNFα, GM-CSF	Neutrophils
CCL5, CCL11, LTC_4, PAF, $sPLA_2$	Eosinophils
Histamine, GM-CSF, IL-4, $sPLA_2$	Macrophages
CCL3, CCL4, CXCL9, CXCL10	Th1 $CD4^+$ cells
CCL5, CCL11	Th2 $CD4^+$ cells
CCL2, CCL20	Th17 $CD4^+$ cells
CCL4, CCL5, CXCL10, LTB_4	$CD8^+$ cells
Histamine, TGF-β1	Regulatory T cells

Legend:
LTC_4: Cysteinyl leukotriene C_4.
PAF: Platelet-Activating Factor.
$sPLA_2$: secreted phospholipase A_2.