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Mast cells: multitasked facilitators of protection against bacterial pathogens

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Abstract

Mast cells are crucial effector cells evoking immune responses against bacterial pathogens. The positioning of mast cells at the host–environment interface, and the multitude of pathogen-recognition receptors and preformed mediator granules make these cells potentially the earliest to respond to an invading pathogen. In this review, the authors summarize the receptors used by mast cells to recognize invading bacteria and discuss the function of immune mediators released by mast cells in control of bacterial infection. The interaction of mast cells with other immune cells, including macrophages, dendritic cells and T cells, to induce protective immunity is highlighted. The authors also discuss mast cell-based vaccine strategies and the potential application in control of bacterial disease.

Keywords

infection; mast cells; vaccine adjuvant

Mast cells (MCs) are multifunctional immune cells that are best known for mediating allergic reactions and association with host defenses against parasite infections (reviewed in [1]). However, recent studies have highlighted the substantial role of MCs in defense against bacterial pathogens (reviewed in [2–11]). Specifically, increased bacterial burdens of *Listeria monocytogenes*, *Klebsiella pneumoniae*, *Mycoplasma pulmonis* and *Salmonella typhimurium* were observed in MC-deficient/depleted mice, compared with that in wild-type (WT) mice, suggesting the important role of MCs in control of bacterial infection [12–15].

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MCs arise from hematopoietic stem cells, which enter the circulation and undergo maturation upon entering residential tissues (reviewed in [16]). MCs are present throughout the body, but are strategically located at host–environment interface areas, such as the skin, airways and the GI tract, where these cells function as sentinels equipped with a range of preformed mediators (reviewed in [5,17,18]). Thus, MCs are one of the first immune cells to encounter an invading pathogen and probably the fastest immune cells to respond to an infectious insult. An increase of MC populations at the infection site is often observed and may be the result of proliferation of the resident mature MCs (reviewed in [5]) and recruitment of new cells by responding to infection [19]. In this review, the authors have focused on the interaction of MCs with bacterial pathogens through pathogen-sensing receptors, followed by the functions of MCs as innate effector cells and the role in shaping the adaptive immune response. Finally, the authors have discussed the therapeutic uses of MCs against bacterial and viral infections.

Pathogen recognition by MCs

Being sentinel cells, MCs have an array of receptors to identify and react to invading bacterial pathogens. MCs recognize bacteria, bacterial products and immune components activated by bacterial infection through various surface receptors, and react with secretion of preformed and *de novo* synthesized effectors, such as TNF- α , IL-1 β , IL-4, IL-6, IL-8, proteases, cysteinyl leukotriene, histamine and heparin among others, to facilitate the control of bacterial infection. Recognition may occur directly or indirectly depending on the type of stimulus. Direct identification of the pathogen occurs through pathogen-recognition receptors (PRRs) such as Toll-like receptors (TLRs), FimH receptor CD48 and receptors for bacterial toxins. Indirect recognition involves receptors for components of the immune system such as the Fc receptors, which can bind pathogen-specific antibodies, complement receptor and the receptor for various inflammatory factors. A summary of pathogen-recognition receptors and ligands is listed in Table 1.

Direct recognition

TLRs, present in monocytes, macrophages, dendritic cells (DCs), B lymphocytes and MCs, are key cell-surface proteins that recognize a broad range of pathogen-associated molecular patterns. Binding of TLRs with ligands derived from bacterial pathogens can activate TLR signaling and lead to production of inflammatory cytokines, chemokines and costimulatory molecules contributing to host innate and adaptive immunity against bacterial infection. MCs have been shown to express most of the common TLRs including TLR-1–9 (reviewed in [20]). Experiments using different TLR-2 ligands, such as lipoteichoic acid, peptidoglycan and macrophage-activating lipopeptide, on murine and human MCs showed the production of distinct cytokines in response to these ligands [21]. Similarly, MC responses to different microbial stimuli may be distinct. Specifically, lipoteichoic acid has been shown to reduce Fc ϵ RI expression on MCs in contrast to Gram-negative lipopolysaccharide (LPS; a TLR-4 ligand), flagellin (TLR-5 ligand) and CpG oligodeoxynucleotide (TLR-9 ligand), which have not [22]. Moreover, it has been shown that human MC CD117 was upregulated by LPS, but down regulated by peptidoglycan stimulation [23]. Collectively, diversity in TLR species, signal adaptor molecules and

immune effectors allow multidimensional control of bacterial infection through the TLR signaling pathway. Among the 11–13 identified TLRs, TLR-2 is the most studied in MC activation. TLR-2 signaling has been shown to be critical for killing of *Francisella tularensis* in murine MCs [24]. TLR-2 is also required for the uptake of *Staphylococcus aureus* and subsequent MC activation, and treatment of MCs with TLR-2-neutralizing antibodies lowers the bacterial uptake [25]. In addition, comparison of immune responses between *Streptococcus equi* infected TLR-2-sufficient and -deficient bone marrow-derived mast cells (BMMCs) indicated that TLR-2 is essential for induction of various chemokines (CCL2, CCL7, CXCL2 and CCL5) and cytokines (IL-4, IL-6, IL-12, IL-13 and TNF- α) following infection by this organism [26]. Other TLR-mediated recognition and responses have been reported using ligands derived from bacteria. For example, both CpG (TLR-9 ligand) and flagellin (TLR-5 ligand) stimulate human cultured MCs to produce IL-1 β and TNF- α [27]. In addition to these two cytokines, CpG also leads to the production of IFN- α and cysteinyl leukotriene from human cultured MCs [27].

Other surface receptors in addition to TLRs are used by MCs to survey invading bacterial pathogens. For instance, CD48 (a type I fimbriae receptor) recognizes and binds to fimbriae-expressing bacteria, such as *Escherichia coli* [28]. Type I fimbriae expressed by *E. coli* trigger MCs to release histamine, which promotes bacterial clearance [29]. CD48 is also required for the interaction of MCs with *S. aureus* and *Mycobacterium tuberculosis* [25,30]. In addition to surface receptors, intracellular PRRs are involved in bacterial recognition by MCs. Signaling through NOD2 can cause release of IL-6, IL-8 and histamine upon phagocytosis of *S. aureus* [31]. MCs also can recognize toxins such as *E. coli* hemolysin. Hemolysin-producing *E. coli* strains cause the release of histamine, leukotrienes and proinflammatory cytokines in human intestinal MCs, whereas *E. coli* strains lacking hemolysin elicit no such response [32]. Streptolysin from *Streptococcus pyogenes* and α -toxin from *S. aureus* cause MC degranulation *in vivo*, measured by skin inflammation following intradermal injection, and *in vitro* determined by release of serotonin from toxin-incubated peritoneal mast cells (PMCs) [33].

Indirect recognition

Besides having a range of receptors to detect pathogens, MCs also have receptors to detect bacterial-activated immune components, such as complement receptors and the receptor for the Fc portion of antibody (FcR). Reaction of *L. monocytogenes* with MCs, mediated through an $\alpha 2\beta 1$ integrin, was demonstrated by Zutter's group [34]. The $\alpha 2\beta 1$ integrin, a well-known receptor for collagen, laminin and other non-matrix ligands involved in cell–matrix adhesion and cell–cell interaction, was expressed on PMCs [34]. Studies using MC-deficient mice, reconstituted with $\alpha 2\beta 1$ integrin-sufficient or -deficient MCs, strongly suggested that $\alpha 2\beta 1$ integrin was essential for PMC activation and inflammatory cytokine production in a *Listeria* peritonitis model [34]. Further studies by the same group found that complement component C1q, containing a collagen-like sequence, formed an immune complex with *L. monocytogenes* and interacted with PMC $\alpha 2\beta 1$ integrin to induce subsequent PMC activation and release of inflammatory effectors [35]. MCs also express multiple FcRs, which include the Fc γ R2 and the high-affinity receptor Fc ϵ RI for IgE [4,36]. Fc ϵ RI has been extensively studied in cases of allergy, asthma and certain parasitic

infections, but its role in bacterial infections has not been well defined [4,36]. The MC Fc γ RI has been identified to play a role in flagellin-induced inflammatory bowel disease [37]. Upon encounter with flagellated bacteria, the host can react by binding flagellin to cell surface TLR-5 for immune signaling activation and/or to generate flagellin-specific antibody. Indeed, a flagellin/flagellin-specific IgG/Fc γ RI complex was identified on colonic biopsy samples from inflammatory bowel disease patients using immunohistochemistry and coimmunoprecipitation [37]. Interestingly, this flagellin-IgG complex was costained with tryptase secreted by MCs. Binding of flagellin/flagellin-specific antibody to the MC surface Fc γ R was demonstrated in an *ex vivo* assay using human MCs derived from peripheral blood mononuclear cells of healthy volunteers. Furthermore, binding of flagellin-specific IgG to Fc γ RI-activated MCs leads to release of inflammatory mediators including histamine and TNF- α [37]. Flagellin-induced intestinal inflammation was lacking in MC-deficient mice, but restored to WT levels following reconstitution with WT BMMCs, suggesting the importance of MCs in inducing immune responses against intestinal bacterial pathogens [37].

Effector functions

MCs have a potent arsenal to combat bacterial infections ranging from antimicrobial peptides and proteases, for direct killing of pathogens or inhibiting growth, to secretion of chemokines and cytokines for recruitment and activation of other immune cells to facilitate control of infection. Some of these MC mediators are stored in preformed granules for fast release, others can be *de novo* synthesized and secreted upon activation by bacterial products through the receptors described earlier. Some of the best known preformed mediators are histamine, serotonin, dopamine, polyamines, lysosomal enzymes such as β -hexosaminidase, cathepsins, proteoglycans, proteases, several cytokines including TNF- α , IL-4, TGF- β , IL-15, VEGF and cathelicidin/LL-37 (reviewed in [38]).

MC antimicrobial peptides, capable of killing bacteria, include cathelicidin peptides that play a major role in defense against Group A Streptococcus (GAS) [39]. MCs prepared from cathelin-deficient mice (Cnlp^{-/-}, also referred to as Camp^{-/-}) showed a 50% reduction in GAS killing compared with WT MCs [40]. Furthermore, MC-deficient mice when reconstituted with WT MCs showed GAS erosive skin lesions, which were comparable with WT mice 48 h after bacterial injection; however, when they were reconstituted with cathelicidin-deficient MCs, the lesions were more severe and comparable with MC-deficient mice [39]. Cathelicidin/LL-37, which is capable of directly killing micro-organisms, is present in human MCs [40]. A novel way of controlling bacteria is through the formation of MC extracellular traps by dying MCs. Infection of HMC-1 (a human MC line) and BMMCs by *S. pyogenes* leads to formation of MC extracellular traps that are composed of DNA, histones, tryptase and antimicrobial peptide LL-37 to inhibit bacterial growth [41]. Extracellular traps are also formed in murine MCs and HMC-1 during *S. aureus* infection; however, *S. aureus* can subvert the extracellular antimicrobial activity by internalizing and persisting within these MCs, which may lead to chronic infection [42]. Apart from cytokines, MCs also have several enzymes used in host defense, such as MCP-6, which are stored in the MC granules and released upon infection [38,43]. MCP-6-null mice cannot efficiently clear *K. pneumoniae* from their peritoneal cavities, suggesting a crucial role for

MCP-6 in innate immunity [44]. Possible MC protease-mediated antibacterial mechanisms were highlighted in a report by Orinska *et al.* [45]. Results of their studies indicated that mRNA expression of MCP-2 (a MC chymase) was upregulated in the absence of IL-15, and the subsequent increase of protease activity contributed to bacterial clearance by enhancing microbiocidal activity. For example, increased protease activity could convert more inactive antimicrobial peptides precursors into the active form of antimicrobial peptides and recruit potent neutrophils to infection sites, probably by cleaving chemokine precursors to generate activated chemokines [45]. Antibacterial mediators, although not specifically identified, also play a critical role in anti-*Citrobacter rodentium* defense, as suggested by the observation of a greater than 90% killing rate within 1 h of incubation of cultured BMDCs with the bacteria [46].

Cytokines released by MCs upon activation include TNF- α , IL-6, IL-4 and IL-9. TNF- α secretion is crucial for early innate immune responses against *L. monocytogenes* [12]. Depletion of MCs with anti-c-kit antibody resulted in lower TNF- α production in the peritoneum following intraperitoneal *Listeria* injection, which correlated with impaired neutrophil recruitment and a 100-fold higher bacterial burden in the spleen and liver [12]. Intradermal *E. coli* bacterial challenge also lead to MC activation and subsequent release of TNF- α , which mediates T-cell recruitment to the draining lymph nodes, promoting interaction between recruited T cells and antigen-presenting cells, and facilitating the initiation of adaptive immunity [47]. IL-6 produced by MCs is important for reducing bacterial burdens and enhancing survival from *Klebsiella* peritonitis, but is not required in control of *Klebsiella* pneumonia, although IL-6 from other sources also seems to enhance neutrophil killing in the lungs [13]. This highlights the complexity and redundancy of the immune system in the control of infection.

MC IL-4 secretion is known to be important in allergic reactions and in the control of parasite infections. However, recent publications indicate that MC-secreted IL-4 also plays a role in antibacterial defense. IL-4 is a Th2 cytokine that binds to its high-affinity receptor (IL-4R) and plays a pivotal role in shaping the immune response (reviewed in [48]). The release of IL-4 is seen after infection of BMDCs by *F. tularensis* [19]. In this study, MC-derived IL-4 polarized macrophage activation towards the M2 phenotype, which resulted in effective control of intramacrophage *F. tularensis* replication *in vitro* (see following section for a more detailed review) [19]. IL-9 is a potent growth factor for both T cells and MCs. MCs have been shown to produce IL-9 upon activation by LPS, ionomycin/IL-1 or IgE-Ag complexes/IL-1 [49–51], which enhanced IL-4-mediated IgE and IgG production from human B cells [52]. IL-9 contributes to protection of mice against *Pseudomonas aeruginosa* in a intravenous injection/bacterial-shock model where survival correlated with the increase of anti-inflammatory IL-10 and a marked decrease of proinflammatory TNF- α and Th1 cytokine (IL-12, IFN- γ) production [53]. On the other hand, enhanced bacterial infection as a consequence of IL-9 has been reported for tuberculosis and leishmaniasis, possibly via promotion of detrimental Th2 responses by IL-9 [54, 55]. Collectively, IL-9 appears to be a Th2 cytokine that suppresses Th1 immunity, which is essential for control of many bacterial pathogens, leading to higher bacterial burdens. On the other hand, as IL-9 reduces uncontrolled inflammation, it prevents massive tissue damage and prolongs survival.

Other reports have shown that bacterial pathogens can stimulate MCs to produce various cytokines; however, the functions of these cytokines in control of the pathogens have not been elucidated. For example, infection of BMMC with *S. equi* lead to profound secretion of several cytokines including IL-4, IL-6, IL-12, IL-13 and TNF- α [26]. Infection of RBL-2H3 cell (a cell line similar to rat mucosal MCs) by *Mycoplasma pneumoniae* strains with P1 adhesin lead to degranulation and release of IL-4 [56]. The quorum sensing molecule (3OC₁₂-HSL) from *P. aeruginosa* causes production of IL-6 and release of histamine from P815 and HMC-1 cells, respectively [57]. Infection of cord blood derived mast cells by *S. aureus* lead to increased production of TNF- α and IL-8 [25]. Interestingly, some pathogens, such as *Streptococcus pneumoniae*, have been reported to cause rapid MC degranulation without release of the major cytokines such as TNF- α and IL-6 [58]. Thus, different cytokine profiles can be elicited in response to differing microbial stimuli.

Interaction of MCs with other immune cells

The host–environmental interface is residence for many different types of immune cells including MCs. So, the activation of one cell type will potentially influence the other. Interactions of MCs with other types of immune cells have been studied extensively, and it is known that upon bacterial infection, MCs may interact directly or indirectly with DCs, macrophages, T cells and B cells. These interactions may influence the innate immune response to infection and prime other cells for an adaptive immune response.

Interaction between MCs & macrophages

MC–macrophage interactions have been studied with reference to allergies and airway inflammation. Such interactions modulate the pathogenesis of inflammation. MCs have been shown to be a source of secretory phospholipase A₂, a family of enzymes that accumulates in patients with inflammatory, autoimmune and allergic diseases [59]. Secretory phospholipase A₂ targets macrophages and can modulate their role in the process of lung inflammation [59]. Moreover, MC granules from peritoneal lavage fluid enhance the respiratory burst activity in alveolar macrophages [60]. Apart from inflammatory diseases, MC–macrophage interactions have also been implicated in tumor biology. Mediators released from macrophages and MCs affect the production of collagenolytic enzymes by metastatic tumor cells, tumor-derived fibroblasts and stromal fibroblasts [61]. The principal mediator released by MCs, histamine, increases the production of β -glucuronidase and IL-6 in a dose-dependent manner through H1-receptor signaling from human lung macrophages [62].

While this information establishes that MCs can influence the functioning of macrophages, little is known about these interactions during bacterial infection. For instance, macrophages that engulf *S. aureus* release adenosine that can induce the production of inflammatory cytokines in MCs [63]. Our laboratory has studied the interactions between MCs and macrophages using the Gram-negative facultative intracellular bacterium *F. tularensis* as a model organism. It was observed that upon challenge of mice with *F. tularensis* live vaccine strain, a pathogen for mice, MCs infiltrated early at the sites of pulmonary infection, along with neutrophils and macrophages, which are the chief target cells for replication of *F.*

tularensis [19]. A MC–macrophage coculture system, established to assess the MC-mediated response in the control of *F. tularensis* replication within macrophages, showed that inhibition of bacterial replication was mediated by contact-dependent mechanisms between MCs and macrophages and also through the soluble mediator IL-4 released by MCs [19]. The authors observed that MCs physically contacted macrophages through a dendritic protrusion network; however, what cell components were being exchanged through the network between these two cell types remain to be elucidated [24]. *F. tularensis* infection activates MCs through TLR-2 signaling, resulting in upregulation of the hydrolytic enzyme cathepsin L, increase of MHC class II trafficking and LAMP2 and importantly, release of the Th2 cytokine IL-4 [24]. TLR-2 seems to be the major TLR involved in *F. tularensis*-mediated MC activation since TLR-2^{-/-}, but not TLR-4^{-/-}, MCs had 2 to 3 log higher bacterial replication and low levels of detectable IL-4 compared with WT MCs [24]. IL-4 secreted by MCs following *F. tularensis* infection binds to macrophage IL-4 receptor and activates STAT6 signaling to alternatively activate the macrophage. These activated macrophages had upregulated mannose receptor, which is important for recognition of *F. tularensis* and enhancing phagocytosis [64]. In addition, treatment of macrophages with IL-4 resulted in a marked increase of ATP production, which promoted acidification and phagosome–lysosome fusion, and lead to increased bacterial killing [64]. Results of a *F. tularensis* live vaccine strain challenge study showed a 40% decrease of survival when IL-4 was deficient, further confirming the importance of IL-4 in control of *F. tularensis* infection [64]. The interaction between MCs and macrophages during a *F. tularensis* infection is illustrated in Figure 1.

Interactions between MCs & DCs

DCs and MCs colocalize at host–environmental interface sites, which suggests that MC activation may influence DC maturation and migration. Upon infection, DCs are activated through surface PRRs and begin maturation processes. Mature DCs leave the site of infection and migrate to the draining lymph nodes to present antigens to T cells and activate them. MC mediators released after infection play an important role in this process. First, MCs are able to recruit DCs by various mechanisms. For example, in an *E. coli* infection model, MC-derived TNF- α upregulated E-selectin expression at local blood vessels to facilitate the recruitment of DCs [65]. Moreover, MCs were a requisite for the migration of plasmacytoid and CD8⁺ subsets of DCs into the draining lymph nodes after intradermal injection of *S. aureus* peptidoglycan [66]. Second, MCs mediate DC maturation. Coculture of MCs and DCs upregulated DC maturation markers such as CD80, CD86 and CD40, which are important costimulatory molecules for T-cell proliferation and cytokine production [67]. In addition, exosomes released by MCs also can be taken up and processed by the DCs and result in upregulation of costimulatory molecules on the DC surface [68]. Finally, MC-activated DCs induce T-cell differentiation and activation. MC prostaglandin D2 down regulates IL-12p40 and p70 production by DCs and leads to differentiation of CD4⁺ T cells into a Th2 response [69]. Histamine, another MC factor, has been shown to downregulate IL-12 and increase IL-10 in DCs, which resulted in decreased production of the Th1 cytokine IFN- γ and increased expression of the Th2 cytokine IL-4 *in vitro* [70]. MC-primed DCs not only induced CD4⁺ T cells to differentiate into Th2 cells, but Dudeck

et al. reported that PCMC-primed DCs stimulated CD4⁺ T cells to release increased levels of IFN- γ and IL-17, indicative of Th1 and Th17 responses, respectively [67].

Interactions between MCs & T cells

It should not be surprising that MCs can interact with T cells because of the presence of a wide spectrum of molecules on the MC surface that could possibly interact with T cells (reviewed in [71]). Moreover, MCs and T cells have been shown to colocalize in inflamed tissues such as seen with rheumatoid arthritis, asthma, allergy and parasitic infections [72,73]. Both MCs and T cells have the potential to activate each other by direct contact through surface ligand–receptor interactions and in concert enhance immune responses against pathogens. T-cell activation may occur via costimulation or by direct antigen presentation by MCs. The costimulatory molecule OX40L on human tonsil MCs can bind to T-cell surface OX40 receptors to stimulate T-cell proliferation [74]. Additional MC surface molecules interacting with T cells include CD80 and CD86, which can be upregulated by GM-CSF treatment [75]. However, contact-dependent mechanisms are not always required for optimal T-cell activation by MCs. For example, MC products such as TNF- α have been implicated in the recruitment, activation and functioning of T cells and MC-derived leukotriene B₄ causes chemotaxis of effector CD8⁺ T cells [71,76]. Treatment of MCs by LPS upregulated surface ICOSL expression, and LPS-treated MCs, when cocultured with CD4⁺ T cells, induced differentiation into IL-10-producing regulatory T cells [77].

MCs can also activate T cells via direct antigen presentation. These cells have been shown to present antigen to T cells via both MHC class I and MHC class II [78,79]. Rodent [80] and human [81,82] MCs expressing MHC class II were shown to activate T cells. It has recently been found that MCs can activate T cells via MC-derived exosomes (reviewed in [68]). The MC exosome is made up of immunologically relevant molecules such as MHC class II, CD86, LFA-1 and ICAM-1 [83]. MHC class II in MCs mainly exists in the intracellular compartment [84]. However, upon activation by various pathogens (e.g., *Francisella*) or bacterial derived products (LPS), MHC class II is upregulated and increasingly located on the cell surface to present antigens to CD4⁺ T cells [24,85]. The interactions between MCs and T cells are two-way events. As described earlier, MCs induce T-cell migration, proliferation and expansion; however, T cells also have the reciprocal potential to activate MCs. MCs cocultured with activated T cells release histamine, TNF- α and metalloproteinase 9 and increase expression of IL-4 mRNA (reviewed in [86]). The supernatants of MCs, incubated with membranes of activated T cells, can cause neutrophil chemotaxis [87]. In addition, anti-CD3mAb or PMA-activated T cells can cause degranulation and TNF- α release by MCs [88,89].

MC-based vaccination strategy

During bacterial infections MCs release a range of preformed mediators and also activate other immune cells to initiate an adaptive immune response. Such pathogen-specific responses depend on the communication between the cells present at the site of infection and cells in the draining lymph nodes. As discussed earlier, MCs can release mediators, which recruit other APCs (e.g., macrophages and DCs), activate these cells and facilitate migration

to draining lymph nodes, where the B cells and T cells are activated to generate humoral and cell-mediated responses. This establishes a role for MCs in bridging innate and adaptive immunity. Thus, immunization with an antigen in conjunction with MC-activating compounds should result in MC activation, leading to enhanced antigen-specific immune responses. Based on this concept, MC activators such as C48/80 have been tested as vaccine adjuvants for inducing enhanced pathogen-specific B- and T-cell responses [90]. For example, a powder formulation of MC activator C48/80 elicited enhanced PA (protective antigen of *Bacillus anthracis*) specific neutralizing antibody titers following rabbit intranasal vaccination [90]. Confirming the beneficial effect of MC-activating compounds in eliciting long-lasting humoral immune responses against protein antigens was the lack of this effect observed in W/W^v mice [91]. However, although intradermal and nasal administration of C48/80 seems to be safe in mice [91,92], it must be cautioned that anaphylactic shock in pigs and oxidative stress in rats upon administration of this MC activator have been reported [93,94]. Therefore, administration of MC activators needs to be carefully optimized to avoid deleterious effects on the host. A suitable alternative approach to MC-related vaccination may be to mimic the MC-derived granules as potent vaccine adjuvants and bypass the MC altogether. MC granules are protease–proteoglycan complexes consisting primarily of tryptase, heparin and a variety of immune mediators. With MC degranulation, particles are released from MCs to serve as a slow-release depot of immunomodulators to effectively induce host protective immune responses. Based on the granular property of MCs, St John *et al.* synthesized a heparin–chitosan microparticle, similar in size to released MC granules [95]. These microparticles with encapsulated TNF- α delivered together with influenza viral hemagglutinin induced a robust humoral response [95]. The flexibility of entrapping various immunomodulators broadens the application spectrum of this type of vaccine adjuvant to allow induction of desirable immune responses (Th1, Th2 and Th17) against the respective pathogen of interest. Hence, by either directly targeting MCs or by use of MC mediators, novel vaccination strategies may be developed.

Expert commentary & five-year view

In summary, a substantial body of literature has revealed the multiple talents of MCs and their critical contributions to immune defenses against bacterial pathogens. With an array of receptors for pathogen recognition, MCs are potentially among the earliest immune cells encountered by invading pathogens and possess the ability to directly kill microorganisms and/or influence other responding immune cells. The properties of MC mediator and activating compounds have recently been applied to novel vaccination strategies. A MC-based vaccine strategy for defense against bacterial infection is attractive and promising; however, the potential adverse effects of uncontrolled MC activation need to be taken into consideration if such activators are to be used in vaccine formulations. A greater understanding of the mechanisms of different classes of activators in mediating MC activation and subsequent immune responses would lead to better design of vaccine formulations against specific bacterial pathogens with minimal adverse consequence. As the mechanistic studies on MC effectors in control of bacterial pathogens press on, we should expect the development of future innovative strategies for preventive or therapeutic treatment against bacterial diseases.

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Key issues

- Mast cells have an array of surface and intracellular receptors to recognize bacterial pathogens.
- Mast cells can release mediators and effectively kill pathogens, promoting bacterial clearance.
- Mast cells can prime macrophages for effective control of *Francisella tularensis* via IL-4.
- Mast cells can stimulate dendritic cells and also present antigens directly to T cells to elicit an adaptive immune response.
- Mast cell activators and microparticles have potential therapeutic applications.

Figure 1. Mast cell-macrophage interactions during *Francisella tularensis* infection

MC recognition of *F. tularensis* via TLR-2 and MRs results in bacterial uptake and phagosome maturation with MHC class II and LAMP protein localization and acidification. MC signaling events lead to TNF- α release and IL-4 production that influence MAC IL-4 receptor, MR and MHC class II regulation. The ensuing IL-4 then promotes engulfment of bacteria with MRs, upregulates MAC ATP production and phagosome maturation, acidification with enhanced bacteria-killing potential. MAC: Macrophage; MC: Mast cell; MR: Mannose receptor; TLR: Toll-like receptor.

Table 1

Pathogen recognition by mast cells.

Receptors	Ligands/pathogen	Downstream effects	Ref.
<i>Direct recognition: bacteria or bacterial products</i>			
TLR-2	<i>Staphylococcus aureus</i>	Release of inflammatory cytokines such as TNF- α and IL-8	[25]
	<i>Francisella tularensis</i>	Secretion of IL-4, colocalization of MHC class II and LAMP 2 and killing of bacteria	[24]
	<i>Streptococcus equi</i>	Secretion of CCL2, CCL7, CXCL2, IL-4 IL-6, IL-12, IL-13 and TNF- α from BMMCs	[26]
TLR-4	LPS (Gram-negative bacteria)	Secretion of IL-6, IL-13, TNF- α , IL-5 and IL-10 from murine BMMCs	[96,97]
TLR-5	Flagellin (flagellated bacteria)	Secretion of IL-1 β and TNF- α from HCMCs	[27]
TLR-9	CpG-containing oligonucleotides	Secretion of IFN- α , IL-1 β , TNF- α and cysteinyl leukotriene from HCMCs	[27]
CD48	<i>Mycobacterium tuberculosis</i>	Release of histamine, β -hexosaminidase and synthesis of TNF- α and IL-6	[30]
	<i>Staphylococcus aureus</i>	Release of TNF- α and IL-8 from human CBMCs	[25]
	<i>Escherichia coli</i>	Release of TNF- α upon binding to FimH	[28]
NOD2	<i>Staphylococcus aureus</i>	Release of IL-6, IL-8 and histamine from P815 cells	[31]
Toxin receptors	<i>Escherichia coli</i>	Release of histamine, leukotrienes and proinflammatory cytokines from human intestinal mast cells	[32]
	<i>Streptococcus pyogenes</i>	Mast cell degranulation	[33]
	<i>Staphylococcus aureus</i>	Mast cell degranulation	[33]
<i>Indirect recognition</i>			
$\alpha 2\beta 1$ integrin	C1q and collectin	Mast cell activation and inflammatory response	[34]
Complement receptor	C5aR	Neutrophil recruitment to the site of infection	[98]
Fc receptors	Flagellin	Release of Th1-type inflammatory mediators	[37]
Fc γ RI			

BMMC: Bone marrow-derived mast cell; CBMC: Cord blood-derived mast cell; HCMC: Human cultured mast cell; LPS: Lipopolysaccharide; TLR: Toll-like receptor.