Published in final edited form as:

Mol Immunol. 2015 January ; 63(1): 74–79. doi:10.1016/j.molimm.2014.02.006.

Mast Cell Mediator Responses and Their Suppression by Pathogenic and Commensal Microorganisms

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Abstract

Mast cells (MCs) are selectively found at the host environment interface and are capable of secreting a wide array of pharmacologically active mediators, many of which are prepackaged in granules. Over the past two decades, it has become clear that these cells have the capacity to recognize a range of infectious agents allowing them to play a key role in initiating and modulating early immune responses to infectious agents. However, a number of pathogenic and commensal microbes appear to have evolved distinct mechanisms to suppress MC mediator release to avoid elimination in the host. Understanding how these microbes suppress MC functions may have significant therapeutic value to relieve inflammatory disorders mediated by MCs.

Keywords

Mast cells; Degranulation; Infection; Pathogen; Commensal; Mast Cell-Suppression; Antiinflammatory

1. Introduction

Although MCs are best known for their role in various harmful inflammatory disorders, they are increasingly recognized as powerful sentinel cells responsible for modulating the early immune responses to a wide range of infectious agents. This role is attributable in part to their preponderance at the host-environment interface and their innate capacity to rapidly release modulators of immune cell trafficking which promotes the early recruitment of

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pathogen-clearing immune cells from the blood. MCs possess on their surfaces a wide range of receptors that detect pathogens or their products and since they also express receptors for danger signals released by infected host cells, they can respond to distal microbial attack. In view of their pivotal role in immune surveillance it is not surprising that some virulent pathogens have evolved mechanisms directed at overcoming or neutralizing mast cell responses. Here, we discuss a recently described powerful mechanism of MCs suppression expressed by *Salmonella* and other pathogenic bacteria to impair MC degranulation without impairing other mast cell activities. Interestingly several opportunistic pathogens and commensal microorganisms appear to also have the capability to suppress MCs indicating that MC suppression may be advantageous, even for the endogenous flora. Understanding the basis of how pathogenic and commensal microbes suppress MC release of mediators may provide valuable clues for the development of novel strategies to temper these cells when they are involved in harmful inflammatory diseases.

2. Mast cell modulation of innate immune responses to infection

After heart diseases, microbial infections are the second most common cause of human death in the world [1]. MCs have several innate properties that make them uniquely able to contribute to immune surveillance against infections agents. These properties include their selective location in relatively large numbers immediately underneath the epithelial surface of the skin and the mucosa of the genitourinary tract and respiratory tract. Because these sites are typically where infections begin MCs appear strategically located to be one of the first immune cells that pathogens encounter after they have breached the epithelial barrier. MCs are also found in close proximity around peripheral blood and lymphatic vessels so they are also ideally positioned to recruit immune cells from blood vessels into infected tissue or coordinate movement of immune cells from infected sites into lymphatic vessels leading to the draining lymph nodes [2,3]. Recently, it was reported that MCs proximal to blood vessels constantly sample blood contents employing cytoplasmic protrusions [4] suggesting that these cells are also capable of detecting and interacting with blood borne pathogens.

MCs are highly specialized for the synthesis and secretion of a myriad of pharmacologically-active products. MC mediators have traditionally been divided into two major groups: those that are preformed, which include histamine, heparin, serine proteases, some select cytokines and chemokines such as TNF [5] and CXCL1/CXCL2 [6] and those that are synthesized *de novo* when the cells are activated, which include a wide range of cytokines and eicosanoids such as leukotrienes, prostaglandins and the thromboxanes [7]. The release of pre-packaged mediators into the surrounding tissue typically occur, beginning within seconds to minutes following stimulation, a strategy that gives MC-derived products a temporal advantage over those produced by other immune surveillance cells which take markedly longer. The prepackaged MC products can be released in explosive fashion or as piece meal.

The latter consists of a slow emptying of granule chambers in the absence of large scale intergranular fusion. Because of their longevity, MCs at sites of inflammation can undergo multiple cycles of degranulation followed by regranulation, in this way MCs are able to

sustain inflammatory responses to pathogens. Unlike degranulation response which is initiated within seconds of MC activation *de novo* synthesis of eicosinoids, cytokines and chemokines occurs significantly later which is comparable to when other immune cells secrete their mediators following activation. Many studies have shown that *de novo* production of these mediators by MCs can vary greatly depending on the stimulus and the experimental conditions.

Like other immune cells involved in immune surveillance, MC express a wide range of cell surface receptors that can directly bind pathogens, secreted toxins, or other microbial products. These receptors include most pattern recognition receptors (PRRs) as well as other receptors that specifically recognize microbial cell surface components. One of the best studied bacterial receptors on MCs is CD48 a GPI anchored protein that binds type 1 fimbriae on various enterobacteria and cell surface component on *Mycobacterium tuberculosis* [8,9]. Cross-linking of CD48 not only causes MC degranulation but also uptake of adherent bacteria. Additionally MCs also express on their cell surface, receptors for host proteins that coat pathogens such as complement fragments and antibodies [10]. Depending on the receptor that is engaged, their crosslinking can trigger extensive or piecemeal MC degranulation. For example, crosslinking of CD48 by type I fimbriated *E.coli* can result in extensive MC degranulation and release of a wide range of mediators whereas activation of TLR4 by lipopolysaccharides (LPS) results in significant secretion soluble mediators but little or no MC degranulation. Similarly, binding of cholera toxin to ganglioside GM1 results in significant secretion of IL-6 but no accompanying degranulation of MCs [11].

MC activation during infection is not always the result of contact with the infectious agent, their products or with opsonized microbes, many infected or otherwise stressed cells release danger signals or alarmins which serve as potent activators of MCs [12,13]. Therefore MCs do not have to be in immediate proximity to the site of infection to contribute to the immune response. The signaling agents released by stressed host cells range from antimicrobial peptides and ATP to IL-33 which are typically released when cells degrade [14]. Binding of any of these cellular products to MCs can trigger extensive MC degranulation.

In spite of the large body of information regarding immune recognition receptors for pathogens or their products on MCs, how they signal intracellularly leading to a secretory response remains largely unknown. Nevertheless, several of the key signaling events is likely to be shared with the well-characterized IgE signaling pathway triggered when allergens bind and crosslink IgE bound on high-affinity IgE receptor (FcεRI) on MCs [15]. When FcεRI receptors aggregate, they initiate a cascade of tyrosine phosphorylation events on multiple signaling molecules in the MC cytoplasm. Early on, activated Lyn kinase phosphorylates tyrosine residues at ITAMs (immunoreceptor tyrosine-based activation motifs) on the receptor subunits [15,16]. Subsequent amplification of tyrosine phosphorylation occurs through activation of Syk kinase, which phosphorylates another substrate LAT [17,18]. LAT phosphorylation activates PLCγ1, leading to cleavage of phosphatidylinositol into inositol trisphosphate (IP3) and diacylglycerol (DAG) [19,20]. DAG activates PKC and IP3 which in turn releases calcium from endoplasmic reticulum into the cytoplasm. This free calcium is utilized in the final stages of degranulation, for the direct fusion of granules into plasma membrane. For degranulation and extracellular release

of MC granules, fusion between granule membrane and plasma membrane is required to occur. The v-SNARE (VAMP8) on granule membrane and t-SNARE (SNAP-23) on plasma membrane form stable Trans-SNARE complexes to guide secretory vesicle into the plasma membrane [21,22]. Additionally, multiple accessory proteins are required to regulate cognate fusion processes and to assist in the formation of various protein complexes. As in the early signaling events that occur around the receptor, tyrosine phosphorylation is also important in regulating the final exocytic events. One of the accessory proteins of interest is NSF (N-ethylmaleimide-sensitive factor), which is an ATPase and vesicle-fusion regulator [23,24]. It is believed that timely dephosphorylation of tyrosine phosphorylated NSF helps to assemble and disassemble the SNARE fusion complexes, regulating the granule size and degranulation events. While many of these signaling substrates may be involved in the MC degranulation responses to antibody coated bacteria or type 1 fimbriated enterobacteria, only a portion of the substrates may be involved in the cytokine response to LPS, mediator release is not accompanied by degranulation.

Although MCs produce antimicrobial agents that directly reduce microbial burden in the body, for the most part the antimicrobial role of MCs appears to be mobilization of other immune cells to combat infection. The functional importance of MCs has been best studied following bacterial infections. The protective role of MCs and MC-derived TNF was first demonstrated close to two decades ago against *Klebsiella pneumoniae* infection [25] and against polymicrobial intra-abdominal sepsis [26]. Upon contact with bacteria, MCs release TNF which initiates early recruitment of neutrophil to clear the pathogen. MCs have been shown to play similar protective roles during *Pseudomonas aeruginosa* infections of the mouse peritoneum [27], *E. coli* infections of the peritoneum and urinary tract [28], *Citrobacter rodentium* [29] and *Helicobacter felis* [30] infections of the gastrointestinal tract, and *Haemophilus influenzae* infections of the ear [31]. MCs are equally effective against several Gram positive bacteria including *Streptococcus pyogenes*, *Mycoplasma pulmonis* [32], *Mycoplasma pneumonia* and *Listeria monocytogenes* [33]. MCs in peripheral tissue are activated upon contact with Dengue virus and in response they release diverse cytokines and chemokines NK and NK T cells to clear the virus [34-37]. It is not necessary for virus to infect MCs to activate them. Viral components such as protein Fv and synthetic viral dsRNA effectively activate MCs [38,39] and as a result can elicit the recruitment of CD8⁺ T cells [40]. Although it is unclear if MCs contribute to clearance of HIV, it appears that these cells become infected and serve as reservoirs contributing to persistent HIV infection [41-43]. MCs upon contact with cell surface components of various fungi *de novo* synthesize and secrete selected mediators without extensive degranulation [44]. During *Aspergillosis* [45] and *C. neoformans* infections [46] MC products promote significant anti-fungal innate immunity which mostly involves recruitment of phagocytic and other immune cells. A powerful MC mediated mechanism to reduce the burden of parasites in the gut such as *N. brasiliensis* [47], *Trichinella spiralis* and *Strongyloides* which is independent of immune cell recruitment is through the release of its proteases which triggers smooth muscle contraction.

3. Selective suppression of mast cell degranulation by *Salmonella*

Salmonella Typhimurium is a highly invasive pathogen and a leading cause of foodborne illness [48]. Global burden of nontyphoidal *Salmonella* on human health is as high as 93.8 million cases, but since many mild cases are not diagnosed, the number is likely much higher [49]. Most studies have associated *Salmonella*'s virulence to their capacity to invade and seek refuge in various host cells or their ability to disrupt major components of the adaptive immune system, including draining lymph nodes, the epicenter of the adaptive immune system [50]. However, these traits do not explain the capacity of *Salmonella* to disseminate widely in the body long before the adaptive immune develops. Food-borne *Salmonella* upon circumventing the gut rapidly reach the mesenteric lymph nodes from where they spread to the liver and other [51]. A recent study has revealed that *Salmonella* after penetrating the gut epithelium achieve their spread by avoiding a neutrophil response though inactivating local MCs. Employing their type III secretion system (T3SS) [52] *Salmonella* injected SptP (Salmonella Protein Tyrosine Phosphatase), a potent phosphatase into the MC cytosol [53]. MCs upon exposure to *Salmonella*, lost their capacity to degranulate even after exposure to potent stimulants such as IgE/antigen [54]. The *Salmonella* derived phosphatase was found to have multiple signaling targets in the MC including several previously implicated in MC degranulation. *Salmonella* SptP prevented the phosphorylation of Syk [15,55] which is important in conveying signals from the MC surface and also dephosphorylated Nethylmaleimide-sensitive factor (NSF) [23,24] a substrate important in the fusion events leading to MC degranulation. Interestingly, *Yersinia pestis*, a highly virulent pathogen responsible for the plague is also capable of MC suppression. This bacterium expresses YopH a phosphatase with a high level of structural homology with SptP [53], which is injected via T3SS [56] into MC. Thus, the spread of plague bacteria in the body may also involve MC suppression.

4. Mast cell suppression by other microbes

This capacity to suppress MC release of its inflammatory mediators is not exclusively a property of highly invasive bacteria but is seen in opportunistic pathogens and even in commensal microbes as MC suppression can benefit multiple lifestyles. Inactivation of local MCs can potentially prevent the host's immune system from being alerted thus enabling microbes to colonize that particular site and even spread to other regions. Although the specific bacterial factors involved remain elusive, several non-fimbriated commensal *E. coli* have been reported capable of inhibiting MC degranulation. In these cases, direct contact of MCs with large numbers of live *E. coli* is required. MCs exposed to these bacteria were found to no longer be responsive to potent activators including IgE mediated activation [57]. Many of the MC suppressing *E. coli* are commensal bacteria colonizing the gut. By suppressing MCs these otherwise innocuous bacteria could potentially contribute to the tolerant environment in the gut lumen [57]. Interestingly, several other commensal gut and mucosal microflora such as *Lactobacillus* and *Bifidobacteria* have been reported to inhibit MC degranulation through different modes of action [58-60]. The inhibitory activity of *Lactobacillus* appeared to reduce both MC degranulation and cytokine secretion through downregulating FcεRIα expression at the MC surface. Microarray analysis has revealed that upon exposure of MCs to *Lactobacillus*, expression of proinflammatory genes such as IL-8

and TNF- α are actively reduced whereas gene expression of anti-inflammatory cytokine (IL-10) is up-regulated [61]. *Bifidobacterium bifidum* has reportedly been shown to evoke similar inhibitory effects on IgE-mediated activation of MCs [62]. Pathogenic fungus such *Aspergillus fumigatus* produce a metabolite gliotoxin, with potent MC suppressive capacity [63]. This toxin inhibits not only MC degranulation but also lipid and cytokine secretion evoked by receptor or calcium ionophore mediated activation [63,64]. Several other fungal metabolites can suppress MC activities. This includes FK-506 purified from *Streptomyces tsukubaensis* [65] and cyclosporine A from *Tolypocladium inflatum* GAMS [66]. Since MC secreted proteases are especially effective in expelling parasite from infected mucosal sites, it is not surprising that some of these nematodes are equipped to block MC degranulation. The filarial nematodes secrete ES-62 block IgE mediated MC activation, eventually leads to inhibit the secretion of allergy related inflammatory mediators from MC [67]. This potent MC suppressor can selectively degrade protein kinase C- α (PKC- α), which is important for signaling cascade of MC activation. Although pathological contribution of MC inactivation has not been investigated, this study provides one important reason why frequency of onset of allergic disease in developing countries is much lower than one in developed countries. *Toxoplasma gondii* is also reported to inhibit MC degranulation during parasitic invasion. This parasitic infection significantly suppressed tyrosine kinase signaling cascade and its calcium cytoplasmic mobilization, which are important event during MC degranulation [68]. However, exact parasite-derived factors, inactivating MC degranulation, remain to be found.

Another way microbes may effectively inactivate MCs is by inducing them to lyse, as is the case of *Pseudomonas aeruginosa* which induce MC lysis through the secretion exotoxin A [69]. Since contents of MCs can be inflammatory it is not clear that this activity is as effective as MC suppressors in inhibiting or avoiding inflammation, as products of lysed MCs can be highly inflammatory.

5. Coopting mast cell suppressive properties of microbes for therapy

As indicated earlier, MCs can be prominent effectors of various harmful inflammatory disorders and as more is known regarding how different microbes suppress MCs, utilizing microbes or microbial products as therapy against some of these diseases may become more common. A diagrammatic illustration of how microbes suppress MC is shown in Figure 1. Although it is not because of their MC suppressing properties, some of the above mentioned agents are already being used clinically but when their MC suppressing property is also considered, they could have additional clinical uses. For example, the *Lactobacillus* and *Bifidobacterium* species are frequently being applied as probiotics in patients with inflammatory diseases in the gut [70]. In view of the capacity of probiotic bacteria in suppressing IgE mediated MCs responses, these bacteria or their products may potentially also be used to temper the pathology associated with allergic inflammation. The fungal metabolite Cyclosporin A is routinely used as a potent nonsteroidal immunosuppressive drug in patients following organ transplant, in view of its potent MC suppressing actions, this drug could be repurposed for the treatment of various inflammatory disorders where MCs play a key part.

6. Conclusion

As the role of MCs in mobilizing both innate and adaptive immune responses to microbes has become clear, there is also growing realization that certain microorganisms have evolved elaborate and powerful mechanisms either to inactivate MCs or avoid their activation. This property of MC suppression has been seen so far in parasites, bacteria and fungi. These microbes range from highly virulent pathogens to opportunistic pathogens and commensal bacteria that constitute the endogenous microflora at different body sites. By inactivating MCs these microbes are able to either spread widely without an accompanying neutrophil response as in the case of virulent *Salmonella* or remain invincible to the host's immune system in the gut as in the case of commensal bacteria. Studies aimed at identifying MC suppressing microbial moieties and elucidating their mechanism of action could provide new vaccine candidates against virulent pathogens on one hand and novel approaches to inactivate MCs during harmful inflammatory diseases on the other.

Acknowledgments

This work was funded by US National Institutes of Health grants U01-AI082107, R01-AI096305, R56-DK095198 and a block grant from Duke-NUS, Singapore.

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Highlights

1. Mast cells are important for modulating immunity against infectious agents
2. Mast cells modulate immunity through degranulation and mediator secretion
3. Invasive *Salmonella* bacteria can suppress mast cell degranulation through a phosphatase, SptP
4. The capacity to suppress mast cells is shared by select pathogens and commensal microbes

Figure 1. Suppression of mast cell degranulation by microbes

Various microbes employ distinct mechanisms to suppress MCs. SptP, injected by T3SS of *Salmonella*, dephosphorylates Syk and NSF to prevent MC degranulation. Dephosphorylation of NSF around MC granules causes homotypic fusion between the granules, which eventually blocks degranulation. Commensal *E.coli* utilize unknown mechanisms to inhibit MC degranulation and at the same time, decrease expression of proinflammatory cytokines (IL-8 and TNF- α) while increasing expression of antiinflammatory cytokines (IL-10). The ES-62 protein, secreted by nematodes, can degrade PKC- α in MCs inactivating MCs. *Toxoplasma* employing unknown factors suppress MC degranulation by inhibiting tyrosine phosphorylation signaling.