Mast cells (MCs) are particularly abundant at host-environment interfaces, such as skin and intestinal mucosa. Because of their location, it has been hypothesized that MCs can act as sentinel cells that sense microbial attacks and initiate a protective immune response. Several studies have suggested that animals deficient in MCs exhibit a worsened pathology in various experimental models of bacterial infection. However, other studies have indicated that MCs under certain circumstances may have a detrimental impact on bacterial disease, and there are also recent studies indicating that MCs are dispensable for the clearance of bacterial pathogens. Herein, we review the current knowledge of the role of MCs in bacterial infection.

Mast cells (MCs) originate from pluripotent hematopoietic stem cells of the bone marrow. Having egressed from the bone marrow, they circulate as immature precursors in the blood, after which they home to most tissues of the body and there mature under the influence by local growth factors, such as stem cell factor and IL-3. When MCs mature, they acquire an abundance of secretory granules that gradually become filled with a variety of compounds, including biogenic amines, such as histamine and serotonin, certain preformed cytokines [eg, tumor necrosis factor (TNF) and IL-4], growth factors (eg, basic fibroblast growth factor and vascular endothelial growth factor), proteoglycans of serglycin type, lysosomal hydrolases, and several MC-restricted proteases [chymases, tryptases, and carboxypeptidase A3 (CPA3)].

When MCs are activated, they may undergo degranulation, a process in which the contents of their secretory granules are released to the exterior. The best-characterized mechanism of MC activation involves the binding of specific antigen to IgE molecules bound to their high-affinity receptor, FcεRI, on the MC surface, causing receptor cross-linking and subsequent signaling events, eventually triggering degranulation. However, MCs can be activated in response to numerous additional stimuli, such as complement components, IgG, neuropeptides, pathogen-derived peptides, and various cell wall products of bacteria. More important, in addition to causing secretion of mediators from preformed stores, MC activation induces de novo synthesis of a large panel of additional inflammatory mediators, including various lipid-derived compounds, such as leukotrienes, platelet-activating factor, and prostaglandins, and transcription and release of a multitude of cytokines and chemokines. Altogether, MC activation can thus result in the release of a wide spectrum of proinflammatory compounds, which together can produce an exceptionally powerful inflammatory response.

MCs are without doubt best known for their detrimental impact on allergic and other inflammatory diseases, but there is also evidence that MCs can be beneficial to their host. The latter notion is supported by many lines of evidence. For example, the strategic localization of MCs at host-environment interfaces, such as skin and intestinal mucosa, makes it attractive to propose that MCs can act as sentinel cells that orchestrate the first line of defense toward invading bacterial and other pathogens. In further support for this scenario, MCs express a wide variety of pattern recognition receptors, such as Toll-like receptors, and it has been shown that activation of MCs by either live bacteria or purified bacterial cell-wall products causes up-regulation of expression and release of numerous proinflammatory factors with important roles in antibacterial responses.


Disclosures: None declared.
On the basis of these notions, research efforts conducted over the past decades have explored the possibility that MCs may have a role in the protection toward bacterial pathogens. Indeed, there is now a solid documentation supporting that MCs are protective against a wide array of bacterial pathogens. However, there are also conflicting findings suggesting that MCs, in fact, can worsen the outcome of a bacterial infection and, moreover, there are reports indicating that MCs, under certain circumstances, can be dispensable for the protective response toward bacterial pathogens. Finally, there is evidence suggesting that bacteria can exert immunosuppressive functions through effects on MCs. In this review, we discuss the role of MCs in bacterial infection.

MCs in the Protection against Bacterial Infection

There is a widespread notion that MCs are protective against bacterial insults (Table 1 and Figure 1). This was introduced through two hallmark studies published back-to-back in 1996 in which it was shown that MCs were crucial for protection toward enterobacteria in the cecal ligation and puncture (CLP) model of sepsis and against i.p.-injected Klebsiella pneumoniae and Escherichia coli. Both of these studies used MC-deficient KitW/W-v mice, in which MC deficiency is the effect of defective signaling through c-kit [caused by a mutation in the c-kit gene (KIT)], ie, the cell surface receptor for stem cell factor]. Stem cell factor is the currently available in vivo evidence for a role of MCs in bacterial infection has been generated through studies on KitW/W-v mice (Table 1).

In many cases, the exact mechanisms underlying the antibacterial activities of MCs have not been fully elucidated. However, as further elaborated below, MCs can hypothetically combat bacteria either directly by antimicrobial mechanisms or indirectly by recruiting or modulating the function of other immune cells.

Immune Cell Recruitment and Immunomodulation by MCs

Considering the impressive repertoire of inflammatory mediators that MCs are able to secrete on appropriate stimulation, MCs have the capacity to interact with and thereby have a functional impact on virtually all other immune cells. Such interactions of MCs with other immune cells can be subdivided into the recruitment of cells to directly control infection, modulation of the function of inflammatory cells, or interactions with cells involved in the adaptive immunity. In support of the first scenario, it was early on established that one of the major functions of MCs during bacterial infection was to promote neutrophil recruitment. It was demonstrated that MC-derived TNF was of major importance for recruiting neutrophils into the peritoneum, although it should be recognized that...
### Table 1  Protective Functions of MCs in Bacterial Infection

<table>
<thead>
<tr>
<th>Bacteria/bacterial component</th>
<th>Model*</th>
<th>Mechanism</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cecal microbiota (CLP)</td>
<td>KitW/W-v</td>
<td>TNF-dependent recruitment of neutrophils</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MC TLR4-mediated recruitment of neutrophils and cytokine production</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Protection conferred by MC-derived IL-12</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SCF-induced expansion of peritoneal MC populations increases survival</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>KitW-sh/W-sh</td>
<td>Protective effect independent of TNF</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>mMCP4-deficient (Mcpt4/−)</td>
<td>Degradation of TNF by MC chymase (prevents toxic effects of elevated TNF levels)</td>
<td>20</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>KitW/W-v</td>
<td>IL-15-mediated suppression of chymase expression</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>KitW/W-v</td>
<td>TNF-dependent recruitment of neutrophils</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>KitW/W-sh/W-sh</td>
<td>Protection by MC-derived IL-6 by promoting neutrophil killing of bacteria</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>mMCP6-deficient (Mcpt6/−)</td>
<td>Promotion of early neutrophil recruitment and cytokine production by tryptase</td>
<td>24</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>KitW/W-v</td>
<td>Promotion of E-selectin expression on vascular endothelium by MC TNF facilitates DC recruitment into infected tissues; promotion of DC accumulation in DLNs by MC-derived TNF</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Participation of TNF in CD4+ T-cell recruitment into DLN</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leukotriene-driven recruitment of neutrophils in response to E. coli expressing FimH</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>In vitro BMMCs</td>
<td>Phagocytosis of FimH-expressing enterobacteria and killing via acidic vacuoles</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>In vitro BMMCs</td>
<td>Phagocytosis of bacteria and presentation of antigen through class I molecules</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>KitW/W-v</td>
<td>Activation of MCs by FimH-expressing E. coli; promotion of bacterial clearance during urinary tract infection by MCs</td>
<td>30</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>Tlr2/−</td>
<td>Restoration of myeloid cell recruitment and granuloma formation in Tlr2/− mice by Tlr2+/+ MCs; recruitment of CD8+ T cells in response to infection by MCs</td>
<td>31</td>
</tr>
<tr>
<td>Francisella tularensis</td>
<td>KitW/W-v</td>
<td>Inhibition of bacterial replication inside macrophages in an IL-4− and contact-dependent manner in vitro by MCs; MC-deficient mice show decreased survival in vivo</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>In vitro BMMCs</td>
<td>Decreased survival and increased bacterial spread caused by MC deficiency, despite unimpaired neutrophil recruitment and lymphocyte activation</td>
<td>33</td>
</tr>
<tr>
<td>Citrobacter rodentium</td>
<td>KitW/W-v</td>
<td>Direct antimicrobial activity</td>
<td>34</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>KitW/W-v</td>
<td>MC-mediated recruitment of neutrophils</td>
<td>35</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>MC depletion (anti-c-kit)</td>
<td>MC-mediated recruitment of neutrophils</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>KitW/W-v</td>
<td>MC-mediated recruitment of neutrophils; dependent on MC-expressed α4β2 integrins</td>
<td>37</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>KitW/W-v</td>
<td>Protection against tissue necrosis by MCs</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>In vitro BMMCs; HMC-1 (human)</td>
<td>Direct antimicrobial activity: release of extracellular DNA traps (MCETs)</td>
<td>39</td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td>KitW/W-v</td>
<td>Mediation of vaccine-induced bacterial clearance by MCs</td>
<td>40</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae Group A streptococci</td>
<td>KitW-sh/W-sh</td>
<td>Defective innate responses</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>KitW-sh/W-sh Camp−/−</td>
<td>Direct antimicrobial activity of MC-derived cathelicidin</td>
<td>42</td>
</tr>
<tr>
<td>Peptidoglycan (Staphylococcus aureus)</td>
<td>KitW/W-v</td>
<td>Mediation of death of plasmacytoid and CD8+ DC subsets into DLN by MCs</td>
<td>43</td>
</tr>
<tr>
<td>S. aureus</td>
<td>In vitro BMMCs and HMC-1</td>
<td>Direct antimicrobial activity: release of extracellular DNA traps (MCETs)</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>KitW/W-v</td>
<td>Protection from S. aureus α-toxin—induced pathology by MCs</td>
<td>45</td>
</tr>
<tr>
<td>LPS (Salmonella minnesota)</td>
<td>Mcpt5-Cre (iDT/R-DTA)</td>
<td>Mediation of neutrophil recruitment during LPS-induced peritonitis by MC-derived CXCL1 and CXCL2</td>
<td>46</td>
</tr>
</tbody>
</table>

*Findings are derived from in vivo studies unless otherwise specified.

BMMC, bone marrow—derived mast cell; CLP, cecum ligation and puncture; DC, dendritic cell; DLN, draining lymph node; LPS, lipopolysaccharide; MC, mast cell; MCET, MC extracellular trap; SCF, stem cell factor; TLR, Toll-like receptor; TNF, tumor necrosis factor.
the role of TNF in neutrophil recruitment during sepsis has been the subject of some controversy. Other studies have, in addition, implicated MC-derived leukotrienes, chemokines CXCL1 and CXCL2, or tryptase in this process, suggesting that MCs can promote neutrophil recruitment through various alternative routes. Intriguingly, in addition to promoting actual recruitment of neutrophils, there is evidence that MCs can also enhance their antimicrobial activity. This was indicated by a study on the role of MCs in Klebsiella infection, in which it was shown that IL-6 was the major MC-derived factor to account for this effect.

In addition to promoting the recruitment of neutrophils, there is evidence suggesting that MCs can play a role in attracting other immune cell types. For example, there is evidence that CD8+ T cells can be recruited to sites of bacterial insult through a mechanism involving MC-derived Toll-like receptor 2. Additionally, cells that are recruited during the course of a bacterial infection include natural killer cells, which are important for the control of intracellular bacteria, such as Listeria monocytogenes. Intriguingly, it has been demonstrated that MCs can have a role in the recruitment of natural killer cells during viral infections, but it is not yet known whether MCs have a corresponding function in the context of bacterial disease.

The Role of MCs in Adaptive Immunity to Bacterial Infection

Although the major lines of evidence available to date suggest a role for MCs in mediating the recruitment of effector cells that directly control bacterial infection, there is also limited support for a role of MCs in orchestrating the adaptive immunity to bacterial pathogens. In a study where E. coli was administered intradermally, it was demonstrated that MC-derived TNF participated in CD4+ T-cell recruitment into the draining lymph nodes (DLNs). Along the same line, intradermal injection of Staphylococcus aureus peptidoglycan initiated MC-dependent migration of certain dendritic cell (DC) subsets into DLNs in mice. Furthermore, it was shown that the recruitment of DCs into infected tissues and their subsequent homing to DLNs was dependent on MC-derived TNF in an E. coli urinary tract infection model and in s.c. infection. Mechanistically,
MC-derived TNF was shown to up-regulate E-selectin on proximal blood vessels, which, in turn, promoted DC migration. Collectively, these findings suggest that MCs, at least partially, may be responsible for increasing the likelihood of effective T-cell/DC interaction in DLNs, which, in turn, may enhance the adaptive immunity against bacterial pathogens. It has also been demonstrated that MCs can present bacterial antigens to T-cell hybridomas via class I major histocompatibility complex molecules. Hence, the latter findings provide further support for a role of MCs in regulating adaptive immune responses against bacteria. Consistent with this, Shelburne et al. showed that MCs promoted the antibody response to E. coli, and it has been demonstrated that MCs play a critical role in anti-Helicobacter vaccination.

**Direct Killing of Bacteria by MCs**

Several studies have indicated that MCs can act directly on bacteria, although it should be recognized that there is only limited in vivo evidence to support this notion. In an early report, it was shown that MCs can phagocytose FimH-expressing enterobacteria (E. coli, K. pneumoniae, and Enterobacter cloacae) in vitro and kill them via acidic vacuoles. Consistent with this, antigen-activated MCs are capable of generating antimicrobial reactive oxygen species, and there are indications of a role for MC-derived reactive oxygen species production in the killing of bacteria.

There is also some evidence that MCs can express and secrete various antimicrobial peptides. In one study, it was shown that MCs deficient in the antimicrobial peptide cathelicidin show a 50% reduction in the killing of group A Streptococcus compared with WT MCs. Moreover, it has been shown that MC-deficient mice exhibit defective killing of group A Streptococcus and that MC-deficient mice reconstituted with cathelicidin-deficient MCs developed significantly larger lesions compared with mice reconstituted with WT MCs after cutaneous group A Streptococcus infection. Hence, this study provides in vivo support for a direct antibacterial activity of MCs. It has also been shown that MCs, similar to neutrophils, can exert antibacterial activities through the formation of extracellular traps. This has been observed as a response to Streptococcus pyogenes and S. aureus. Finally, it has been demonstrated that MCs confer antibacterial activity by inhibiting intramacrophage...
replication of *Francisella tularensis* by an IL-4—and cell-cell contact-dependent mechanism.32

**Role of MC Proteases in Bacterial Infection**

Various MC-restricted proteases are major components of MC granules, and are thus released in high quantities when MCs degranulate.3,55 As reviewed recently, MC proteases can have a major impact on various pathological settings, and a large number of potential substrates for the various MC-restricted proteases have been identified.3,47 There is now considerable evidence supporting the notion that MC proteases can contribute significantly to the body’s antibacterial defense. In one study, mice lacking the tryptase mouse mast cell protease 6 (mMCP6; encoded by *Mcpt6*) showed decreased survival in response to i.p. *Klebsiella* infection, and it was suggested that mMCP6 conferred protection by activating the release of neutrophil chemoattractants from cells present at the site of infection.24 In agreement with this, it has been demonstrated that administration of various recombinant tryptases in vivo leads to the recruitment of immune cell populations, including neutrophils56—59 and eosinophils.60,61 It has also been shown that tryptase is a component of MC extracellular traps produced in response to *Streptococcus pyogenes*.38 However, the functional significance of MC extracellular trap—associated tryptase remains to be determined, although it may be speculated that MC-derived tryptase can have similar direct antibacterial activities as those expressed by neutrophil proteases.62

There is also evidence for a protective role of the MC chymases in settings of bacterial infection. Orinska et al21 showed that the ablation of IL-15 in mice resulted in increased survival in the CLP model, and it was suggested that this was because of increased expression of the chymase mMCP2 that could activate the chemokine neutrophil-activating peptide (NAP)-2/CXCL7 by limited proteolysis. The latter notion is thus in agreement with another study in which human chymase was shown to proteolytically activate NAP-2/CXCL7,63 and it has also been reported that chymase can activate a range of additional chemokines.64 Together, these findings suggest a proinflammatory role of chymase, and there are several studies supporting this notion by demonstrating that the administration of recombinant or purified chymases in vivo causes an inflammatory reaction.65—67 According to published data, the proinflammatory activities of chymases may thus be because of activation of chemokines, but there are also reports suggesting that chymases can contribute to inflammation by cleaving cell-cell or cell-matrix contacts.68—70 A protective role of chymase is also supported by a study showing that mice deficient in mMCP4 (ie, the main chymase expressed by MCs of connective tissue subtype; encoded by *Mcpt4*) were considerably more vulnerable to CLP than were corresponding WT controls.20 Intriguingly, it was shown that mMCP4 had a role in reducing the levels of TNF, thereby preventing excessive and potentially harmful accumulation of this cytokine. These findings are thus in good agreement with previous studies indicating that MC-derived TNF is a major pathogenic factor during severe CLP.19 There are, to date, no reports in which *Cpa3*−/− mice have been assessed in models of bacterial disease. However, it is notable that CPA3 has a major role in degrading endothelin, a toxic peptide that may be released during ...
sepsis.71 Hence, CPA3 may have a protective role by reducing the levels of endothelin and, potentially, other toxic peptides released from either bacteria or endogenous sources during bacterial infection. It has also been demonstrated that MC-derived neurolysin has a prominent role in degrading neurotensin, thereby limiting the toxic effects of this peptide during severe CLP.72

**Detrimental Effects of MCs**

Although most published studies point to a protective function of MCs in the context of bacterial disease, there are studies suggesting that MCs, in fact, can worsen the outcome of a bacterial insult (Table 2 and Figure 2). In a hallmark study, Piliponsky et al19 showed, by using the Kit\(^{W-sh/W-sh}\) mice, that the type of impact of MCs on CLP was critically dependent on the extent of disease severity, where MCs were protective during moderately severe CLP, whereas they were detrimental in severe CLP. Moreover, the data suggested that MC-derived TNF was the major pathogenic factor behind the detrimental impact of MCs during severe CLP.19 In another study, further proof for a detrimental function of MCs during severe CLP was obtained.73 In this study, the authors developed a model in which MC deficiency was independent of c-kit, by engineering mice to express the diphtheria toxin receptor under control of the FcεRI β-chain promoter.73 By assessing these mice in severe CLP, they demonstrated that MC deficiency resulted in improved survival in comparison with MC-sufficient animals. Moreover, it was demonstrated that the detrimental effect of MCs was because of suppression of the phagocytic activity of macrophages, and that this suppression was because of secretion of IL-4 by MCs.73 However, the mice were not assessed in milder CLP, and it thus remains to be confirmed, by using these new-generation, MC-deficient mice, whether MCs have a protective role in less severe bacterial disease. A detrimental impact of MCs on bacterial disease is also supported by a study in which toxic doses of lipopolysaccharide were administered to WT and MC-deficient mice.75 It has also been reported that MC-derived IL-10 can cause immunosuppression in the context of chronic bacterial infection, leading to bacterial persistence.77 Moreover, cathepsin C, expressed by MCs, has been shown to adversely affect survival in CLP.74

**MCs in Immune Evasion**

Many immune cells are exploited by pathogens as a means of immune evasion. MCs are no exception. As a strategy to evade host immunity, *Mycobacterium tuberculosis* has been observed to enter MCs and to replicate intracellularly *in vitro*.72 Furthermore, *S. aureus* can invade MCs, and persists intracellularly by increasing the thickness of its cell wall.73 Furthermore, pulmonary MC-derived IL-1, IL-6, and TNF promote granuloma formation in tuberculosis.31 Notably, although granulomas are associated with decreased mortality, they also prevent bacterial clearance and thus promote chronic infection.83

**MC Suppression**

Immunosuppression is an important strategy by which pathogenic bacteria can avoid the host immune response, and there is now substantial evidence from *in vitro*, *in vivo*, and *ex vivo* studies that MCs can be targets for such immunosuppression.

**MC Suppression by Commensal Bacteria**

It has been shown that high densities of unfimbriated and nonpathogenic *E. coli* strains inhibit degranulation of peritoneal MCs *in vitro* and *ex vivo*.84 Considering the high density of *E. coli* found in the intestine, it is thus likely that intestinal MCs may be the subject to immunosuppression through this mechanism. Similarly, it has been demonstrated that another commensal bacterium, *Enterococcus faecalis*, can interfere with IgE receptor–mediated MC degranulation.85 Furthermore, an *in vitro* study using four probiotic bacterial strains (*Lactobacillus rhamnosus*, *Propionibacterium freudenreichii* species, *Shermanii*, and *Bifidobacterium animalis* species *Lactis*) revealed a bacteria-dependent down-regulation of proinflammatory genes (TNF and IL8) and up-regulation of anti-inflammatory genes (IL10) in MCs. This effect was most pronounced when all four strains were combined,86 raising the possibility that similar synergistic effects on MCs may be prevalent *in vivo*, considering the highly heterogeneous microbiota of the intestine.

**MC Suppression as a Mechanism of Pathogenesis**

In a recent study, striking evidence for a role of MC suppression in enhancing the virulence of pathogenic bacteria was obtained.87 The authors showed that *Salmonella typhimurium* suppressed the neutrophil-recruiting activity of MCs by delivering a tyrosine phosphatase (SptP) to MCs, and it was demonstrated that SptP acted by inducing the dephosphorylation of Syk and N-ethylmaleimide–sensitive factor. It was shown that this mechanism allowed rapid dissemination of *S. typhimurium* and, in support for this, an SptP-deficient *S. typhimurium* mutant was markedly less virulent than the WT strain.

**MCs and Bacterial Toxins**

Toxins are abundantly expressed by many bacteria88 and, in many cases, there is evidence that the impact of MCs on bacterial disease may be associated with effects related to these toxins. In some cases, bacterial toxins promote MC responses that could be beneficial to the host. For example, *Clostridium difficile* toxin A induces MC-dependent neutrophil recruitment,89 and MCs are responsible for the transient inflammation caused by *Streptococcus pyogenes*–derived streptolysin O. Moreover, MCs have been shown to...
limit the detrimental effects of S. aureus α-toxin.44 In other cases, toxins may promote harmful MC activation. For example, it has been suggested that MCs are responsible for the diarrhea induced by S. aureus peptidoglycan.79 On a different angle, it has been shown that IgE specific to S. aureus enterotoxins can be induced independent of sensitization to other allergens and that elevations of these IgE antibodies show a positive correlation with the incidence of asthma.90 A direct link between staphylococcal toxins and inflammatory skin disease was recently described. Skin colonization by a δ-toxin—producing S. aureus strain induced inflammation in WT mice, whereas δ-toxin—deficient S. aureus did not.11 Moreover, it was shown that the induction of skin inflammation by δ-toxin was diminished in MC-deficient KitW-sh/W-sh mice, suggesting a detrimental role of MCs. In another study, perorally administered staphylococcal enterotoxin A was found to bind to submucosal MCs in the gastrointestinal tract of the house musk shrew (Suncus murinus), and was demonstrated to induce MC degranulation associated with the release of serotonin. Because staphylococcal enterotoxin A is associated with food poisoning, the authors suggested a link between MC-derived serotonin and the vomiting reflex typically seen in staphylococcal food poisoning.80

There are also indications that MCs may have a detrimental impact on cystic fibrosis. This disease is typically associated with pulmonary P. aeruginosa infection, and it has been shown that one of the toxins produced by P. aeruginosa, exotoxin A, has the capacity to induce MC apoptosis.76 It has also been shown that the E. coli toxin z-hemolysin induces lysis of human intestinal MCs in vitro,78 potentially leading to the release of inflammatory compounds, such as alarmins, and various granule-contained mediators that could worsen the pathology.

Settings Where MCs May Be Redundant in Antibacterial Responses

In a recent study, the impact of MCs on bacterial infection was assessed by using a newly developed mouse model where MC deficiency is independent of the effects on c-kit.13 In contrast to many other studies on this subject, the authors did not see any difference in inflammation, bacterial clearance, or cytokine production when comparing the response of WT versus MC-deficient mice to mild bacterial infection induced by i.p. administration of S. aureus.13 Hence, in this setting, MCs were dispensable for combating bacterial infection, and there are also indications from other studies that MCs under certain conditions may be dispensable in antibacterial responses.19

Can Knowledge of MC-Mediated Actions on Bacterial Disease Be Exploited for Therapeutic Intervention?

An important question is how we can use the knowledge of the role of MCs in bacterial infection for therapeutic purposes? As reviewed herein, it appears that MCs can be detrimental under certain settings of bacterial disease, and it is therefore plausible that agents that interfere with MCs can have beneficial effects under such circumstances. Potential regimens for this purpose include agents that have global inhibitory actions on MCs, such as MC stabilizers that prevent MC degranulation or agents that induce selective MC apoptosis.92 Alternatively, if the exact detrimental mechanism of MCs can be identified at the molecular level, it may be possible to specifically target this mechanism. However, given that MCs in many settings have been shown to be beneficial to the host, it is critical to fine-tune any anti-MC regimens such that beneficial MC activities are not compromised. As an alternative, it may be possible to take advantage of identified protective functions of MCs. For example, given the demonstration that MC proteases can be protective against bacterial infection, it may be possible to treat bacterial disease by administering these compounds. However, MC proteases are known to have detrimental activities in certain settings,2 thus limiting their use in antibacterial therapy. As another approach to exploit MCs for host protection toward bacterial insult, it has been suggested that MC-activating compounds can be used as adjuvants to enhance effectiveness of vaccination strategies.93

Concluding Remarks and Future Directions

As reviewed herein, past efforts have revealed a bewildering array of functions for MCs in various contexts of bacterial infection. It is also apparent that, according to published findings, MCs can have fundamentally different impact on bacterial infection in different settings (ie, protective, detrimental, or dispensable). One plausible explanation for these apparent discrepancies may lie within the use of different mouse models of MC deficiency. This is most likely a critical issue, especially considering that the relevance of c-kit—dependent models of MC deficiency (KitW/W-v and KitW-sh/W-sh) has recently been questioned.91,94 A careful assessment of new-generation (c-kit— independent) MC-deficient mice in various models for bacterial infection will therefore be an important direction for future research. Another potential explanation for the complexity of published studies on this subject is that MCs might have differential impact on different bacterial species, and perhaps that the effect of MCs on a given bacterial species can differ markedly depending on the virulence of the respective bacterial strain used in the experiments. Moreover, it appears that MCs may affect bacterial infection differently depending on the bacterial load used for infection and also depending on the route of administration. Clearly, all of these issues will warrant a careful and systematic evaluation to get more comprehensive insight into the role of MCs in bacterial disease. It is also striking that so few studies have addressed the in vivo impact of MCs on bacterial infection in humans. For example, the possibility that human sepsis is associated with systemic release of MC-derived compounds or the possibility that human antibacterial responses are accompanied by MC
activation (eg, degranulation) has not been extensively investigated. To obtain a full understanding of how MCs contribute during bacterial disease, further studies are needed.

References

Mast Cells and Bacteria


51. McDermott JR, Bartram RE, Knight PA,Miller HR, Garrod DR, Gresics RK: Mast cells disrupt epithelial barrier function during enteric nematode infection. Proc Natl Acad Sci U S A 2003, 100: 7761–7766


55. Jenkins CE, Swiatonowski A, Issekutz AC, Lin TJ: Pseudomonas aeruginosa exotoxin A induces human mast cell apoptosis by a...

77. Chan CY, St John AL, Abraham SN: Mast cell interleukin-10 drives localized tolerance in chronic bladder infection. Immunity 2013, 38: 349–359


