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The contribution of mast cells to bacterial and fungal infection immunity

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SUMMARY

Mast cells are hematopoietic progenitor-derived, granule-containing immune cells that are widely distributed in tissues that interact with the external environment, such as the skin and mucosal tissues. It is well-known that mast cells are significantly involved in IgE-mediated allergic reactions, but because of their location, it has also been long hypothesized that mast cells can act as sentinel cells that sense pathogens and initiate protective immune responses. By using mast cell or mast cell protease deficient murine models, recent studies by our groups and others indicate that mast cells have pleiotropic regulatory roles in immunological responses against pathogens. In this review, we discuss studies that demonstrate that mast cells can either promote host resistance to infections caused by bacteria and fungi or contribute to dysregulated immune responses that can increase host morbidity and mortality. Overall, these studies indicate that mast cells can influence innate immune responses against bacterial and fungal infections via multiple mechanisms. Importantly, the contribution of mast cells to infection outcomes depends in part on the infection model, including the genetic approach used to assess the influence of mast cells on host immunity, hence highlighting the complexity of mast cell biology in the context of innate immune responses.

Keywords

mast cells; infection; fungi; bacteria; innate immunity

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DISCLOSURE OF CONFLICT OF INTEREST

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INTRODUCTION

Mast cells are particularly abundant at host-environment interfaces, such as the skin and intestinal mucosa. Because of their location, it has been hypothesized that mast cells can act as sentinel cells that sense pathogen attacks and initiate a protective immune response. Initial studies with the use of c-kit mutant mice confirmed this hypothesis and helped provide further insight into how mast cells contribute to the host's response against parasites, bacteria, fungus and viruses.

The evolution of our understanding of the role of mast cells in innate immunity is perhaps best described by what we learned from mast cells in parasitic infections. The earliest studies determined that mast cell numbers increase during certain parasitic infections and degranulate when exposed to parasite-derived antigens.(1, 2) Since then, many groups have used c-Kit mutant $Kit^{W/W\text{-}v}$ and/or $Kit^{Wsh/Wsh}$ mice as indicative of how mast cell deficiency, amongst other abnormalities in these mice, may affect host immunity against primary infections with various parasites, including *Nippostrongylus brasiliensis*,(3, 4) *Strongyloides ratti*,(5) *Strongyloides venezuelensis*,(6–8) *Trichinella spiralis*,(9, 10) and *Trichinella muris*.(11, 12) Most of these studies showed that such c-*kit* mutant mast cell-deficient mice have a delay in intestinal worm clearance during a primary infection. However, to what extent the delays in parasite clearance detected in these c-kit mast cell-deficient mice reflected their lack of mucosal mast cells vs. one or more of their other phenotypic abnormalities (including their intestinal cells of Cajal deficiency, which results in abnormal gut motility)(13) was not determined by these studies. This is because mast cell-dependency in these observations cannot not be confirmed by systemic adoptive transfer of mast cells(14–17) due to the inability to engraft intestinal mucosal mast cells in c-*kit* mutant mice. This issue was recently addressed with the generation of c-Kit independent mast cell-deficient mice. The strategy for the generation of c-Kit independent mast cell-specific conditional mice was recently reviewed by Galli SJ *et al*.(18) Mukai K *et al*. used two types of mast cell-deficient mice that have normal c-*kit* levels ("Hello *Kit*ty" and MasTRECK mice) to confirm that mast cells play an important role in *S. venezuelensis* egg clearance in primary infections.(19) The use of c-Kit-independent mice also assisted in settling conflicting results for the role of mast cells in leishmaniasis. In fact, experiments with c-Kit mutant mice led to conclusions ranging from no contribution(20) to pro-pathogenic(21) to protective(22) roles of mast cells in leishmaniasis. Paul *et al*. used *Cpa*-Cre mice to provide evidence that the involvement of mast cells in the clinical development of cutaneous leishmaniasis is unlikely.(23)

Similar discrepancies were observed when c-Kit mutant mast cell-deficient mice were used to investigate the contribution of mast cells to infection immunity against bacteria and fungi. While some of these discrepancies can be attributed to abnormalities associated with the c-Kit mutation and/or mouse background, it became clear to us and other researchers in the field that the protective role of mast cells in bacteria and fungal immunity is not as clear cut as originally thought. The relative high abundance of data generated by us and others in the field of bacterial and fungal infections allows us to challenge ourselves to draw some conclusions on the mechanisms by which mast cells influence host immunity and the environmental factors that may impact these interactions. These topics are the focus of this

review. We also speculate on potential new lines of research based on our own pressing questions that we and others expect to address in the near future.

MAST CELLS AND BACTERIAL INFECTIONS

Since the publication of two landmark studies published back-to-back in 1996 showing that mast cells were crucial for protection against enterobacteria infection in the cecal ligation and puncture (CLP) model of sepsis(24) and against i.p.-injected *Klebsiella pneumoniae* and *Escherichia coli*,(25) several additional studies have shown that mast cells protect against infections caused by a variety of bacterial pathogens.(26–32) Much of this work provided a better understanding of how mast cells detect and respond to bacteria products.

Mechanisms of mast cell activation during bacterial infections

How do mast cells recognize bacteria and/or bacteria products to undergo activation? Mast cells express a variety of pattern recognition receptors, including Toll-like receptors (TLRs) that allow mast cells to respond to TLR ligands by secreting cytokines, chemokines, and lipid mediators.(33) Moreover, it was shown that TLR4 expression on mast cells is required for mast cell protection during CLP.(34) Mast cell activation can also be modulated by factors that are bacteria unrelated. For example, the protective effects mediated by mast cells in CLP can be enhanced by growth factors, such as stem cell factor (SCF).(35)

Despite the involvement of TLRs in mast cell activation, early *in vitro* studies led to the consensus that mast cells do not degranulate in response to TLR ligands. These studies contradicted the fact that the release of mast cell pre-formed mediators, such as histamine and proteases, was detected during CLP(36–39) and that peritoneal mast cells show morphological evidence of degranulation after LPS i.p. administration.(39) One plausible explanation for this phenomenon is that mast cells release pre-formed mediators in response to endogenous peptides that are generated during CLP or after LPS administration, such as complement components, endothelin-1, and neurotensin.(37, 40, 41)

It is important to note that conventional mast cell degranulation may not be a prerequisite for pre-formed mast cell mediators to exert a protective effect during bacterial infections. For example, we recently demonstrated that mast cell protease (MCPT)4, the functional mouse homologue of chymase,(42) protects against systemic infection caused by a strain of Group B *Streptococcus* that does not induce beta hexosaminidase release.

Mast cell-mediated bactericidal and protective pro-inflammatory effects during bacterial infections

There is some evidence that mast cells can exert a direct killing effect against bacteria. It has been shown that intracellular IL-15 expression in mast cells can transcriptionally limit their MCPT2 levels, resulting in decreased mast cell-associated chymotrypsin-like activity *in vitro*, decreased mast cell antibacterial properties, and reduced survival of mice subjected to CLP.(43) Moreover, it has been shown that mast cells can produce antimicrobial peptides (AMPs), such as cathelicidins, that have direct bactericidal activity against Group A *Streptococcus* skin infection.(44, 45)

Despite this evidence, the ability for mast cells to induce the recruitment of inflammatory cells to the focus of infection has been proposed as the main mechanism by which mast cells exert their protective effects against bacteria. Moreover, for some pathogens, it has been possible to identify the mast cell mediators involved in inflammatory cell recruitment. For example, it was demonstrated that MCPT6(46) and IL-6(47) are protective against *Klebsiella pneumoniae*, and that mast cell-derived tumor necrosis factor (TNF) can amplify the inflammatory response against uropathogenic *E. coli*.(48)

CLP of moderate severity is one of the most studied models in which the contribution of mast cells to innate immunity has been investigated. CLP is a model of traumatic or iatrogenic intestinal perforation that results in a polymicrobial infection of the peritoneum. The CLP model involves ligation of the cecum immediately below the ileocecal valve (to produce a distal ischemia) followed by needle puncture.(49)

Studies conducted with c-Kit mutant mice subjected to CLP that causes a bacterial infection that results in a relatively low mortality rate in normal mice, indicate that mast cells contribute to host defense by promoting inflammation and/or the ability for myeloid cells to clear bacteria.(25, 40, 50) (Fig. 1). Despite these studies, it is still unclear how mast cells exert their pro-inflammatory effects in the CLP model.

Several groups have proposed but not demonstrated the potential role of mast cell-derived TNF in moderately severe CLP. This is because the results obtained with TNF-deficient mice(35) or TNF neutralizing antibody treated mice(51) have clearly demonstrated that TNF can have protective functions during some bacterial infections, and that such TNF-dependent effects may include the enhancement of neutrophil recruitment and/or function as well as promote bacterial clearance. However, by using knock-in mice in which only mast cells do not produce TNF, we clearly demonstrated that mast cells are not the main cell source of TNF required to trigger inflammation in response to infection induced by moderately severe CLP.(50)

IL-6 also has been proposed as a mast cell-derived cytokine that can contribute to a positive outcome after CLP. In contrast to TNF, mast cells have been shown to contribute to increased IL-6 levels at the infection site (peritoneum) at very early stages following CLP. More importantly, it has been shown that mast cell-derived IL-6 significantly contributes to mouse survival after CLP. Although it has been shown that the pro-inflammatory properties of IL-6 can enhance bacteria clearance during infection,(52, 53) mast cell-derived IL-6 seems not to protect mice from CLP by this mechanism.

It is not surprising that it has been so difficult to determine which mast cell mediators contribute to protection in CLP by enhancing the inflammatory response. CLP is a polymicrobial model of infection of high complexity in which multiple mediators may exert overlapping roles. Therefore, the effects of the deletion of a specific mediator in mast cells may be compensated by a different mediator with an overlapping function. Moreover, the effects of a deletion in mast cell mediators may be masked by c-Kit mutation-associated abnormalities, such as alterations in neutrophil numbers. Regarding the later, the use of new c-Kit independent mast cell deficient mice that lack these abnormalities has already shown

promise for a better understanding of how mast cells may contribute to inflammation during a bacterial infection. For example, by inducing ablation of connective tissue mast cells in *Mcpt5-Cre; iDTR+* mice after diphtheria toxin A injection, it was shown that mast cells and CXCL1/2 contribute to neutrophil recruitment into the peritoneal cavity after LPS-induced endotoxemia.(39) It is unknown whether mast cell-derived CXCL1/2 plays a beneficial role in CLP, but these studies are underway.

Protective effects of mast cell-restricted proteases

The defining morphological feature of mast cells is their electron-dense secretory granules, which contain large amounts of pre-formed mediators, such as biogenic amines, proteoglycans, and cytokines.(54) These granules also contain several mast cell-specific proteases, most notably, chymase, tryptase, and mast cell carboxypeptidase A3 (CPA3), whose release is induced by either IgE-dependent mast cell activation(54) or IgE-independent mechanisms.(41, 55)

The overall substrate specificities of the mast cell proteases have been conserved for over 150–200 million years of mammalian evolution.(56, 57) This suggests the presence of a strong selective pressure for maintaining mast cell protease specificity and an important role for mast cell proteases in innate immunity. Early studies on the contribution of mast cell proteases to innate immunity were focused on how these mast cell mediators can modulate the host immune response to infection as an important regulatory mechanism to prevent sepsis development. Specifically, bacterial infections can trigger a host immune response that includes the production of endogenous mediators that can induce many of the physiological symptoms observed during sepsis, such as hypotension. Using pharmacological and genetic approaches, it has been shown that mast cell proteases can contribute to “detoxification” of these endogenous peptides via proteolytic degradation and inactivation. For example, CPA3 and mast cell-associated neurolysin (a non-specific mast cell protease) promote homeostasis through the down-regulation of endothelin (ET)-1 and neurotensin levels, respectively (Fig. 1).(37, 41)

Early studies on the role of mast cell proteases in parasitic infections provided strong evidence that mast cell proteases can have an impact on host-pathogen interactions and hence infection outcomes. In these seminal studies, Knight *et al.* showed that expulsion of *T. spiralis* was significantly delayed in mice lacking MCPT1, which suggests an important contribution of intestinal mucosal mast cells and MCPT1 in the clearance of this infection.(58) Later on, it was found that MCPT1-mediated degradation of the tight junction protein, occludin, is a mechanism by which mast cells increase intestinal permeability and hence contribute to expel the parasite.(59) Despite these reports, there are a relatively small number of studies addressing similar mechanisms during bacterial infections. One of the main reasons for the scarcity of this type of study is that mice with deficiencies in mast cell restricted proteases were generated only recently.(18) This is an essential tool to identify the potential substrates for mast cell proteases during a bacterial infection. Two recent studies highlight the use of these mice to investigate the role of mast cell proteases in protection against bacterial infections by disrupting host-bacteria interactions. These studies were performed by using *Mcpt4*$^{-/-}$ mice, which do not exhibit any marked defect in the

expression of proteases with trypsin-like or CPA activity, *e.g.* MCPT6 or CPA3, respectively. (42) In the first study, Choi HW *et al.* investigated how mast cells contribute to protection against urinary tract infections (UTIs) caused by uropathogenic *E. coli*.(60) Uropathogenic *E. coli* gain access to the bladder and rapidly invade superficial bladder epithelial cells to avoid being flushed out when urine is voided. When epithelial cells become overburdened with pathogenic bacteria, they initiate self-destruction processes resulting in reduced microbial burden. Choi HW *et al.* provided evidence that mast cells recruited to the infection site via IL-1β mediate the infected bladder epithelial cell exfoliation. Cell death and exfoliation is caused by uptake of granule-associated MCPT4 by the infected cells, which triggers the disruption of lysosomal vesicles and hence lytic cell death.

The second study was performed by our own group. By using mice with c-Kit independent mast cell deficiency, we showed that mast cells are required for an effective immune response during systemic GBS infections.(61) GBS are Gram-positive bacteria that frequently colonize the lower genital tract of healthy women and can cause severe infections during pregnancy, leading to preterm birth, stillbirth, or early-onset newborn infections. In a recent study, we demonstrated that MCPT4 decreases the severity of systemic GBS infection and the preterm birth rates. We found that this can be attributed in part to the ability of MCPT4 to downregulate GBS-extracellular matrix (ECM) interactions via proteolytic degradation of fibronectin into inactive fragments (Fig. 2). (62)

Mast cells can be detrimental to the outcomes of certain bacterial infections

Studies with a CLP model of high severity, which induces more than 50% mortality in wild type mice after surgery, were the first to show that mast cells can be detrimental to the outcomes of a severe bacterial infection.(50) The high severity CLP model is widely recognized among sepsis researchers as the “gold standard for polymicrobial sepsis” (63–65) because it closely mimics the cytokine-storm mediated response to severe infection and the multiple organ dysfunction syndrome (MODS) associated with severe sepsis.(66)

In the high severity CLP model, hyper-inflammation is a main indicator of a dysregulated host response to infection that can cause severe sepsis and shock irrespective of the host’s bacterial clearance efficiency. By using knock-in mice, we found that mast cell-derived TNF is one of the main drivers of hyper-inflammation and death following severe CLP. (50) We confirmed our findings with a mast cell-specific TNF deficient mouse that we generated by crossing a mouse in which Cre recombinase is expressed under the control of the CPA3 promoter (*Cpa3-Cre* mouse) (67) with a *Tnf* “floxed” mouse (Fig. 3).(68) Additional supportive evidence came from the MCPT4-deficient mice, which are impaired in their ability to down-regulate TNF levels via proteolytic degradation. Hence, these mice exhibit the phenotype of a mouse subjected to severe CLP, with increased inflammation and mortality, when they are subjected to moderate CLP.(38)

A detrimental role for mast cells during high severity CLP (< 50% of control mice survived at 4 d after surgery) was also observed with a c-Kit independent knock-in mouse model called the red mast cell and basophil (RMB) mouse. In these mice, the 3′-UTR of the *Ms4a2* gene encoding the FcεRI β chain includes a cassette composed of an internal ribosomal entry site, a sequence coding for the bright red td-Tomato (tdT) fluorescent protein, a 2A

cleavage sequence, and the human diphtheria toxin receptor (hDTR). By deleting mast cells after diphteria toxin A injection, Dahdah A *et al*. showed that mast cells and mast cell-derived IL-4 aggravate sepsis by impairing the ability for macrophages to clear bacteria. It is unclear as to why mast cells seem to play a suppressive instead of a pro-inflammatory role in the CLP model used by Dahdah A *et al*. However, we should point out that it is well-known that subtle differences in the way CLP is induced can have a great impact on the outcome of the model.(49) For example, we usually observe twenty times more neutrophils in the peritoneal cavity of wild type mice subjected to severe CLP than what was reported for wild type mice in Dahdah *et al*'s study. According to this observation, we think that it would be informative to perform CLPs of different severities in the RMB mouse to evaluate whether the contribution of mast cells to infection outcomes varies with the CLP model severity to the same extent as it was observed in other mast cell deficient mouse strains.

High severity CLP is not the only model in which mast cells were shown to play a detrimental role. Mast cells and mast cell-derived TNF can enhance bacterial growth and hasten death after intraperitoneal inoculation of *Salmonella typhimurium*.(50) Furthermore, Chan *et al*. demonstrated that mast cell-derived IL-10 contributed importantly to the suppression of *E. coli*-specific antibody production during experimental UTI in mice, which accounted for, at least in part, *E. coli* persistence in the bladder.(69)

MAST CELLS AND FUNGAL INFECTIONS

Protective and non-protective roles of mast cells against fungi

Fungi are associated with a wide spectrum of diseases in humans and animals, ranging from acute self-limiting manifestations in immunocompetent individuals to allergy and severe life-threatening infections in immunocompromised patients.(70) Considering the harmful effects of mast cells in connection with allergic reactions, mast cell degranulation by the cell wall polysaccharides of *Candida albicans*, a commensal fungus of the skin and mucosal surfaces,(71) was meant to contribute to sensitization against food antigens by affecting the mucosal barrier in mice.(72) Controversy still exists as to whether gastrointestinal colonization by *C. albicans* contributes to atopic dermatitis aggravation. By promoting food allergy, *Candida* colonization may likely contribute to a pathogenic response in atopic dermatitis.

Similarly, mast cell activation by *Aspergillus* lectins is known to activate mast cell degranulation(73) and contribute to the allergic response *in vivo*.(74) Mature *A. fumigatus* hyphae but not conidia induced mast cell degranulation in the absence of IgE. Interestingly, hyphae of less pathogenic *Aspergillus* species, such as *flavus, niger*, and *nidulans* induced much less mast cell degranulation.(75) However, this simplistic view is currently being extensively modified, and it is becoming more and more clear that mast cells have a complex array of functions in response to fungi. In addition to being detrimental, mast cells also carry out a number of beneficial functions, most notably in connection with innate antifungal resistance and promotion of immune tolerance.

Studies have suggested that mast cells participate in a number of ways to the *Candida*/host interaction at mucosal surfaces.(76, 77) Murine mast cells phagocytose *C. albicans*, produce

nitric oxide by mechanisms involving TLR2 and Dectin-1(78), and kill the fungus through secreted granular components.(79) Moreover, as protease-activated receptors are involved in the inflammatory response to fungi,(80) the participation of mast cells may also likely occur through their proteases. *In vitro*, human MCs mount a specific temporal pattern of responses towards *C. albicans* that includes an initial phase characterized by the secretion of granular proteins, neutrophil recruitment, and reduced fungal viability followed by a late stage, which includes the release of mediators with known anti-inflammatory activity, such as IL-1ra.(76) Thus, for their strategical location at vascularized mucosal surfaces combined with a unique versatility,(81) mast cells are well positioned to respond to fungi and/or fungal allergens.

We have recently found that mast cells are key players of *Candida* commensalism and pathogenicity at mucosal surfaces (Renga *et al.*, manuscript under revision) (Fig. 4A). Despite being implicated in gut immunopathology(82) and sensitization to food antigens,(72) *C. albicans* colonization protects against local(83, 84) and distant(85) immune pathologies in mice. Mast cells appear to decode the dual pathogenic vs. protective roles of the fungus by integrating multiple signals and mechanisms in the gastrointestinal tract. Both mucosal and stromal mast cells(86, 87) were expanded in the stomach of *C. albicans*-infected mice and they mediated different infection outcomes. The different mast cell types, despite being able to phagocytose unopsonized yeasts, exhibited different candidacidal activity. As suggested,(79) mucosal mast cells were unable to kill the ingested fungi and were actually killed by them with massive MCPT-1 release. In contrast, stromal mast cells killed the ingested yeasts. Importantly, while the expression of inflammatory genes was not different between the mast cell types, mast cells discriminated between the fungal morphotypes in terms of transforming growth factor (TGF)-β and IL-10 production, in which the stromal mast cells released higher levels of these cytokines than mucosal mast cells in response to fungal hyphae. Mucosal mast cells contributed to barrier function loss, fungal dissemination, and inflammation in experimental leaky gut models, while stromal mast cells, by inducing regulatory cytokines and indoleamine 2,3-dioxygenase, contributed to mucosal immune tolerance. Of great interest, mast cells also affected the local microbial composition in *Candida*-infected mice. Much like antibiotics, intestinal inflammation may perturb the resident bacterial community, creating conditions that favor both high levels of *Candida* colonization and inflammation. Firmicutes and Proteobacteria were particularly expanded in the gut of infected-$Kit^{W/W\text{-}v}$ mice, suggesting a unique ability of mast cells to affect the microbial composition via inflammation-driven dysbiosis. These results suggest that the activity of mast cells upon *C.albicans* exposure may go beyond host immunity to include regulation of the microbiota in the gut.

Pathogenic role of mast cells in respiratory fungal allergy

Mast cells and their activation contribute to lung health via innate and adaptive immune responses to respiratory pathogens. However, there is evidence for activation of mast cells contributing to the pathophysiology of lung diseases and cancer.(88) Mast cell-deficient mice demonstrate significantly attenuated fibrosis and inflammation after environmental injury.(89) Tryptase-positive and chymase-positive mast cells are expanded in the lungs of asthmatic (90) and cystic fibrosis patients.(91) We have recently found that chymase-positive and tryptase-positive mast cells were expanded in the lungs of mice with transmembrane

conductance regulator (CFTR) deficiency (*Cftr*$^{-/-}$ mice), a murine model of cystic fibrosis in which defective fungal clearance is associated with an overzealous inflammatory response.(92) Both acute inflammation and airway remodeling were reduced in *Kit*$^{W/W\text{-}v}$ mice as well as in *Cftr*$^{-/-}$ mice upon treatment with the tyrosine kinase inhibitor, imatinib, a finding pointing to the pathogenic role of mast cells in airway fungal allergy. Consistent with the finding that mast cells express a functional CFTR that may impact mediator release,(93) lung mast cells from these mice poorly responded to IgE but released IL-2 and TGF-β in response to IL-9, which was autocrinally produced. IL-2 production by mast cells expanded CD25^{+} innate lymphoid type 2 cells, which activated CD4^{+}Th9 cells. By producing IL-9, Th9 cells in turn amplified allergic inflammation, in which the pro-fibrotic cytokine, TGF-β, plausibly contributed.(92) This study suggests that clinical targeting of the IL-9-mast cell axis could alleviate respiratory allergy and inflammation (Fig. 4B). However, *Aspergillus* growth and inflammation were apparently increased early in infection in *Kit*$^{W/W\text{-}v}$ mice or after imatinib treatment, a finding suggesting that c-Kit+ cells may contribute to antifungal resistance through regulation of fungal burden and inflammation. This may explain the immunosuppressive activity of fungal metabolites that block mast cell activation and contribute to the establishment of infections.(94)

CONCLUDING REMARKS

By taking advantage of c-Kit dependent mast cell deficient mice, c-Kit independent mast cell specific conditional mice, and mice with restricted mast cell mediator deficiencies, such as proteases,(18) the non-redundant roles for mast cells in the host response against pathogens are being elucidated. These studies clearly demonstrate that mast cells can either promote host resistance to infection or contribute to a dysregulated immune response that can increase host morbidity and mortality.

The contribution of mast cells to innate immune responses against bacterial infections depends in part on the infection model. However, the complexity of this picture is accentuated when we consider that some of these studies were performed with c-Kit mutant mice that exhibit alterations in neutrophil numbers in addition to mast cell-deficiency.(50, 95, 96) Although mast cell engraftment was performed in these studies to confirm mast cell-dependency, we cannot rule out the possibility that mast cells cannot compensate for the severe neutropenia observed in the *Kit*$^{W/W\text{-}v}$ mice or add to the pathogenic role of neutrophils in the *Kit*$^{Wsh/Wsh}$ mice, which exhibit neutrophilia in their naïve condition. In fact, the alterations in neutrophil numbers was deemed as one of the main confounding factors in the contradictory results obtained with c-Kit mutant mice in inflammatory disorders, such as rheumatoid arthritis.(97–99) C-kit independent mast cell-deficient mice will be an invaluable tool to confirm and/or rectify some of the findings obtained with c-Kit mutant mice. However, it is important to consider that the discrepancies amongst the mast cell-deficient mouse strains were observed in recent studies when the features of the model used did not replicate those previously reported.(100) This may be particularly important for certain models of bacterial infection, such as CLP, because of the high variability in the severity of the model observed amongst research groups. Ideally, the same laboratory will have access to multiple strains of mast cell-deficient mice (c-Kit mutant and c-Kit independent) to perform CLP with the same degree of severities used in previous studies. By

using this approach, Reber LL *et al.* confirmed previous findings in c-Kit mutant mice that indicated that mast cells and mast cell-derived IL-10 can limit inflammation and other pathologies at sites of severe hapten-induced contact hypersensitivity reactions.(100)

What are the factors or mechanisms that determine the contribution of mast cells to immune defense? Recent transcriptional and proteomics analyses responding to our urgent need for a better and more comprehensive understanding of mast cell biology may provide critical information to answer this question.(101–103) For example, by using a proteomics analysis approach of mast cell secretomes upon IgE-dependent activation, we recently found that mast cells can produce large amounts of coagulation factor XIIIA,(102) a coagulation factor that may prevent pathogen dissemination by contributing to pathogen entrapment into clots.(104) Although useful information can be retrieved from these studies, it should be pointed out that mast cell local and systemic responses can exhibit different features depending on the nature of the stimulus.(105) Therefore, we think that it will be necessary to perform similar comprehensive analyses of mast cells in response to stimuli relevant to a particular infection or pathogen.

Are the studies summarized here translatable to what we know about mast cell biology and infections with similar pathogens in humans? *In vitro* studies with human primary mast cells may be indicative of mast cell responsiveness to a certain pathogen during infection in humans. However, discrepancies between results obtained *in vitro* vs. *in vivo* exposure of mast cells to the same pathogen have been reported(106) indicating that critical factors or mechanisms triggered by the host during an infection can influence how mast cells will respond to pathogens. There is no comparable human model to mast cell-deficient mice to study how mast cells contribute to infection outcomes in humans. However, there is a possibility that we will obtain some insight into this question with the use of therapies that target mast cells in humans. For example, blocking the effects of c-kit in mast cells by using the tyrosine kinase inhibitor, imatinib, produces a profound decrease in mast cells in patients with chronic myeloid leukemia (CML)(107) and severe asthma (108). Thus far, a small study with twenty three CML patients showed no increase in the frequency of severe bacterial or fungal infections after treatment with imatinib. However, we should point out that the degree of mast cell reduction in tissues is unknown, as only serum tryptase levels were measured as an indicator of systemic mast cell depletion.(107) Therefore, it is possible that the small number of mast cells remaining in tissues after treatment with imatinib is enough to protect the patient from potential bacterial and/or fungal infections.

Overall, we can conclude that recent findings in the field of mast cells and infection suggest that mast cells can influence infection outcomes by multiple mechanisms. Several challenging questions remain and some of them were posed in this section of the review. Although some of these questions are difficult to answer specially, such as those pertaining to mast cells and infections in humans, we think that strong collaborations between mast cell biologists and microbiologists will provide with a better understanding of how mast cells and pathogens interact to influence host innate immunity and infection outcomes.

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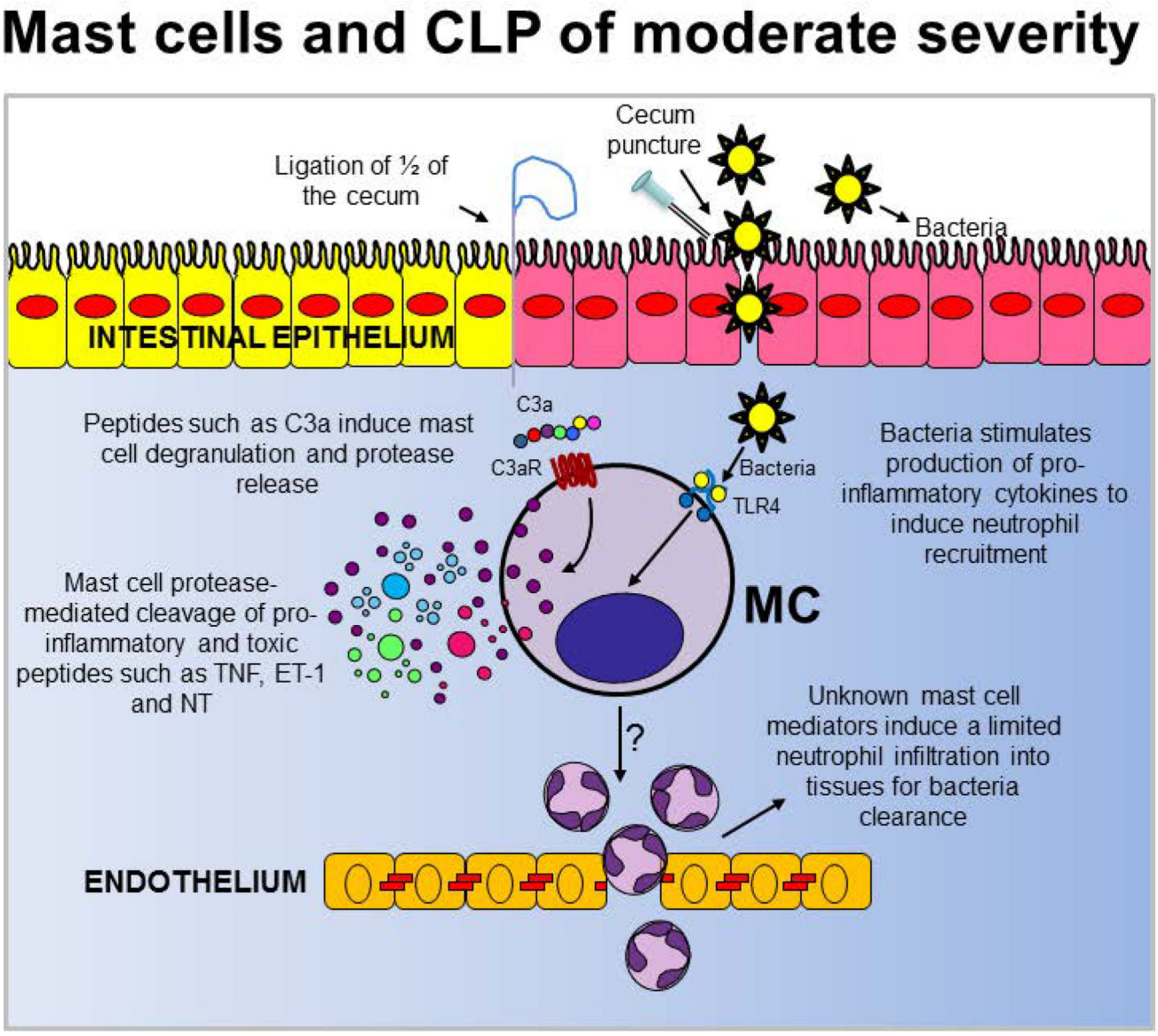

Figure 1.

The contribution of mast cells in the moderately severe cecal ligation and puncture (CLP) model (which results in less than 50% mortality rates) in wild type mice.

TNF, Tumor necrosis factor; C3a, complement component 3a; C3R, C3a receptor; TLR4, toll-like receptor 4; ET-1, endothelin-1; NT, neurotensin

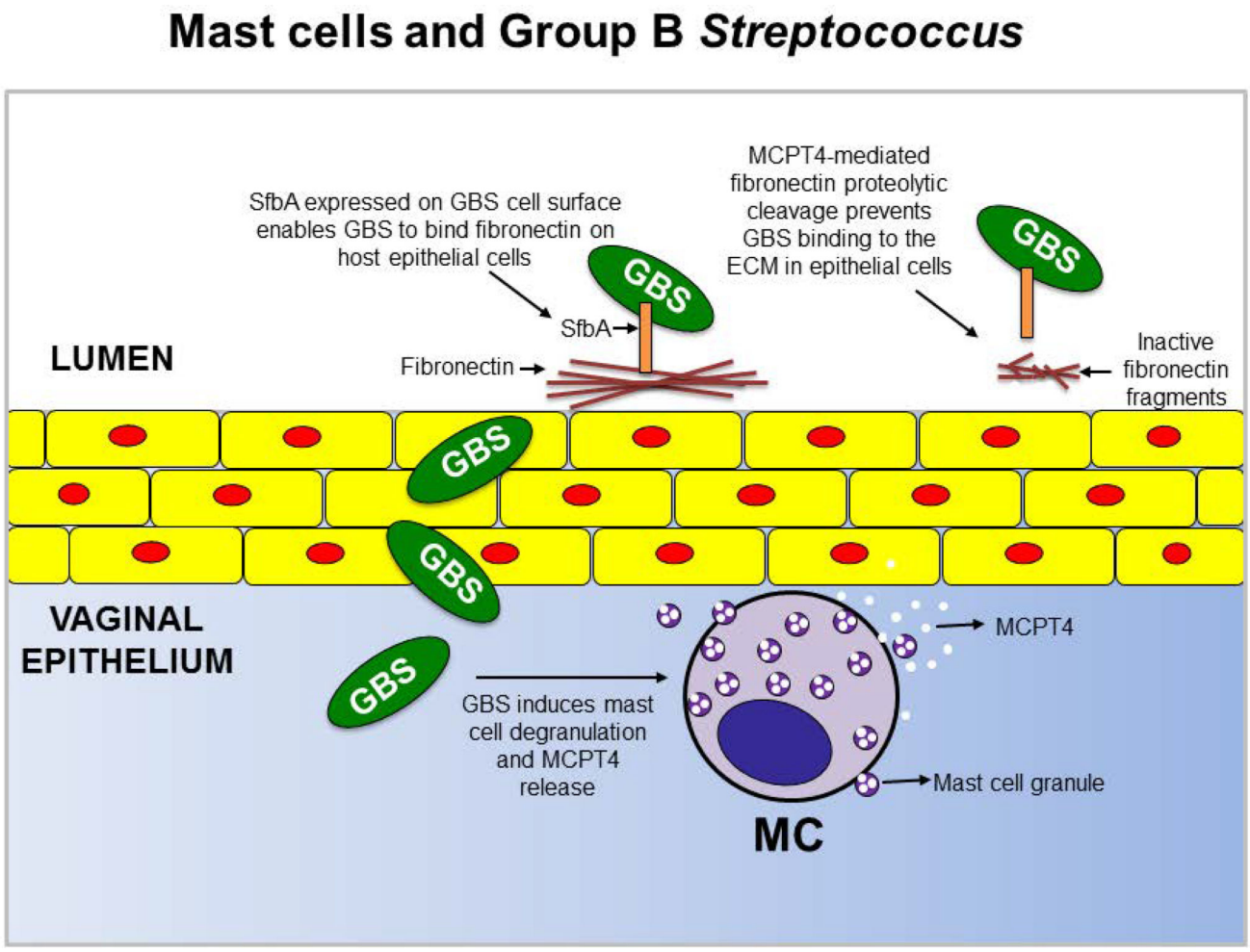

Figure 2.

Proposed mechanism for the protective effect of MCPT4 against Group B Streptococcus (GBS) dissemination and preterm birth.

MCPT4, Mast cell protease 4; MC, mast cells; SfbA, streptococcal fibronectin binding protein; ECM, extracellular matrix

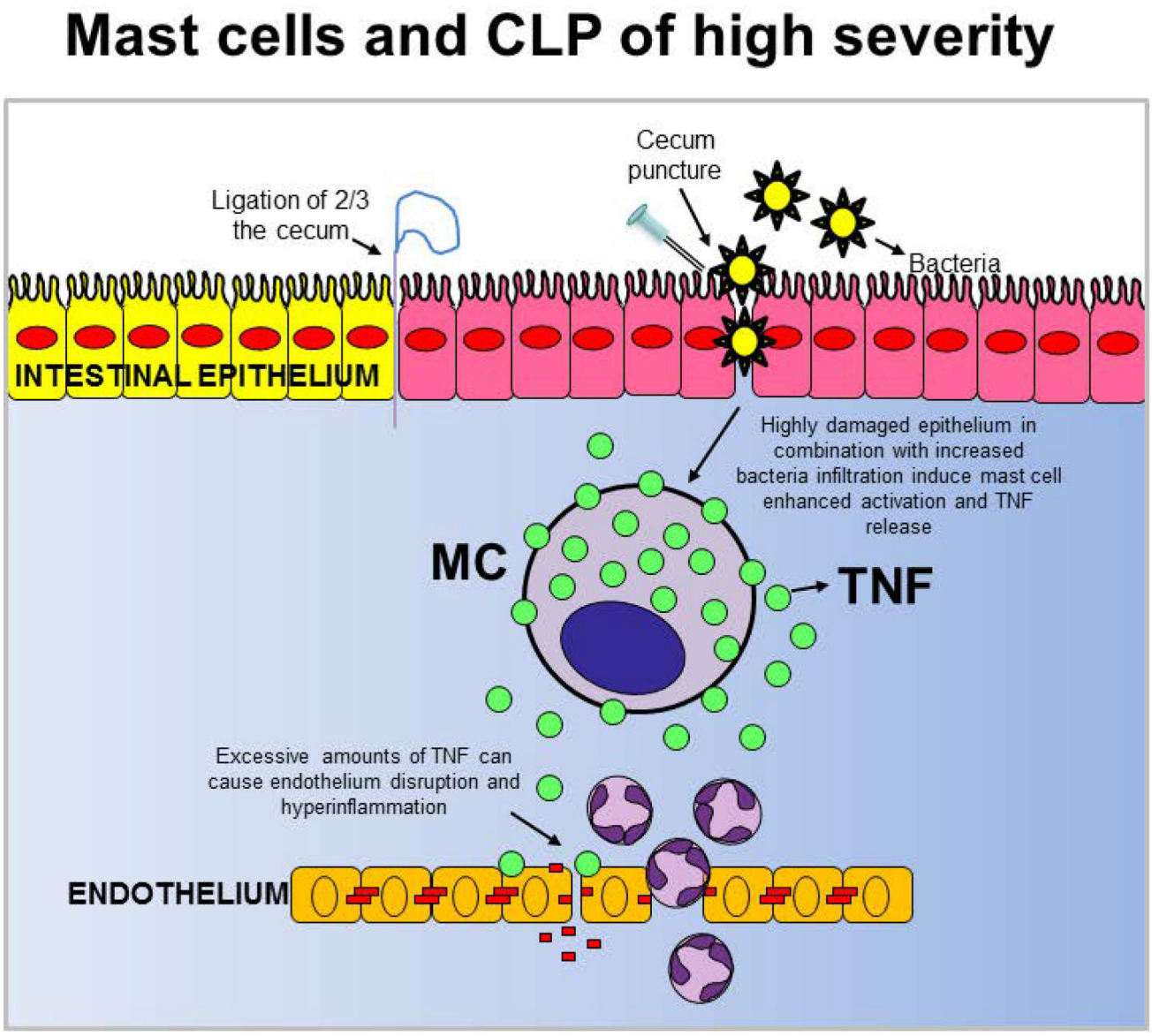

Figure 3.

The contribution of mast cells in the high severity cecal ligation and puncture (CLP) of model (which induces more than 50% mortality rates) in wild type mice after surgery. TNF, Tumor necrosis factor

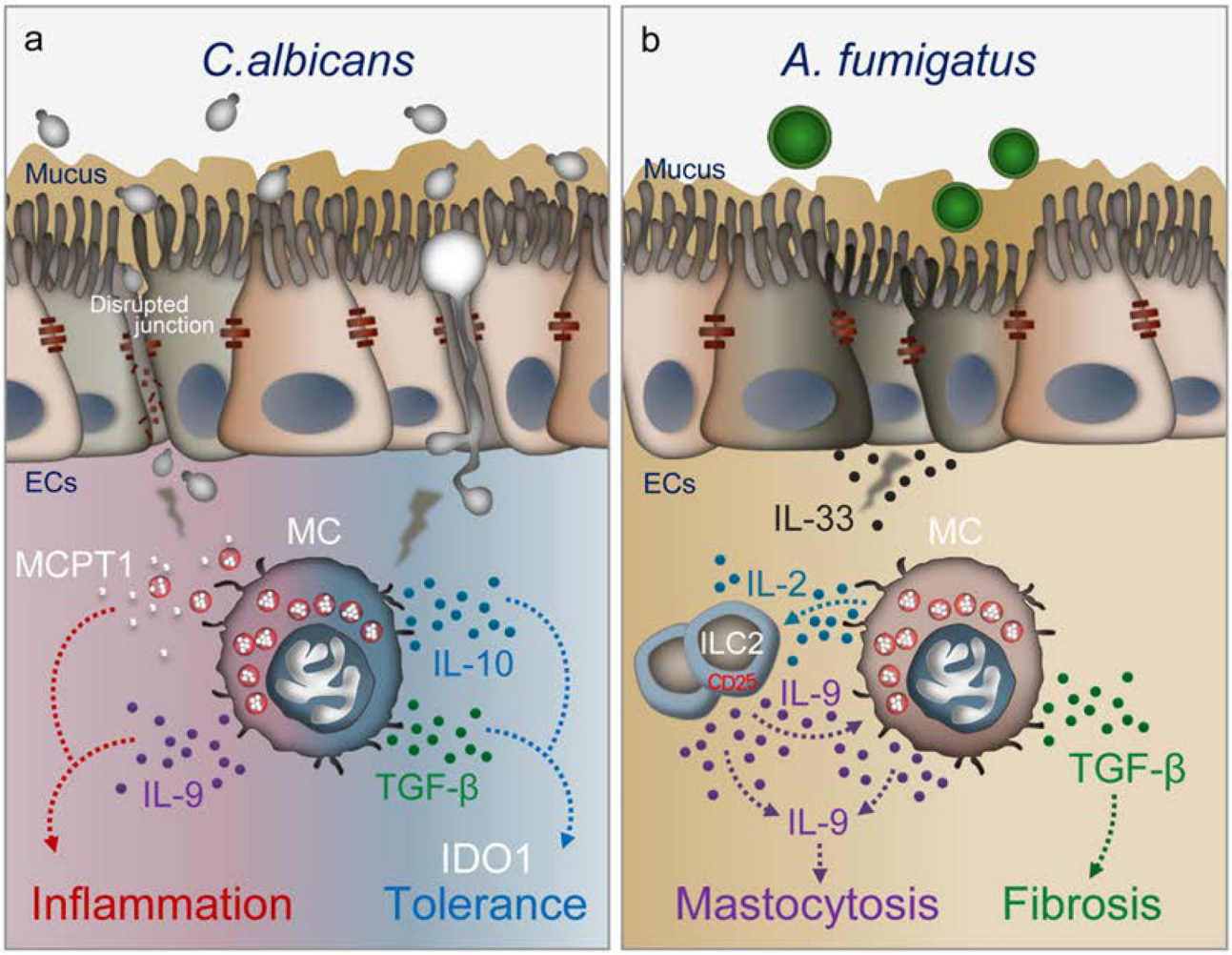

Figure 4.

Proposed model for the role of mast cells in promoting inflammation and tolerance during *Candida albicans (A)* colonization in the gut or *Aspergillus fumigatus (B)* exposure in the lung (see text for explanation).

ECs, Epithelial cells; IDO1,Indoleamine 2,3-dioxygenase 1; ILC2, Group 2 Innate lymphoid cells; MC, mast cells; MCPT1, Mast cell protease 1; TGF-b, transforming growth factor beta