

CHAPTER 10

THE MAST CELL IN INNATE AND ADAPTIVE IMMUNITY

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Abstract: Mast cells (MCs) were once considered only as effector cells in pathogenic IgE- and IgG-mediated responses such as allergy. However, developments over the last 15 years have suggested that MCs have evolved in vertebrates as beneficial effector cells that are involved in the very first inflammatory responses generated during infection. This pro-inflammatory environment has been demonstrated to be important for initiating innate responses in many different models of infection and more recently, in the development of adaptive immunity as well. Interestingly this latter finding has led to the discovery that small MC-activating compounds can behave as adjuvants in vaccine formulations. Thus, our continued understanding of the MC in the context of infectious disease is likely to not only expand our scope of the MC in the normal processes of immunity, but provide new therapeutic targets to combat disease.

INTRODUCTION

The vertebrate immune system has evolved two main response systems designed to contain and eliminate microbial predation. The first, termed innate immunity, is a rapid, relatively nonspecific response that is designed to actively clear or contain pathogens.¹ The second response, called adaptive immunity, is a slower, precisely targeted response that develops over a period of a few days to weeks, resulting in life-long immunological memory against the invading pathogen.² The initiation of both of these responses during infection is dependent upon a rapid burst of pro-inflammatory mediators at the site of infection whose function is to activate and recruit various effector cells, such as neutrophils that

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dictate innate clearance of the pathogen and dendritic cells that initiate adaptive immune responses.³ One cell type that may be integral to the development of this pro-inflammatory environment is the MC. MCs are granulated, tissue-resident leukocytes best known for their role in pathogenic inflammatory sequelae such as allergy.⁴⁻⁷ However, numerous studies over the last 15 years have reshaped our perception of the MC to that of a beneficial first responder in the innate defense against bacterial infections.^{8,9} Recently, this protective function has been extended to their role in the induction of adaptive immune responses during infection. This suggests that MCs have evolved to provide pro-inflammatory signals critical to the induction of both innate and adaptive immune responses during infection. In this chapter, we will evaluate the literature supporting three arguments that suggest vertebrate MCs are a beneficial first responder during infection in the absence of adaptive immunity. These arguments include their conserved localization in tissues throughout evolution, their diverse expression of pattern recognition receptors and their unique ability to rapidly create a pro-inflammatory environment in tissues. We will also evaluate the numerous studies demonstrating a role for the MC in the formation of both protective innate and adaptive immune responses.

THE STRATEGIC LOCALIZATION OF THE MAST CELL

One of the most attractive properties of MCs that support their role as a first responder to infection is their positioning not only within the tissue parenchyma, but their localization within the host organism. While MCs are present in most vascularized tissues, they are generally noted to be particularly abundant in tissues that are exposed to the environment.¹⁰⁻¹³ This selective increase in MC density would presumably aid in the detection of microbes that use these sites as portals of entry into the host. While this concept has not been empirically evaluated, many studies have now demonstrated that mice containing reduced numbers of MCs or that are devoid of MCs are highly susceptible to infection.^{8,9,14} Another means to assess the importance of MC placement in animals is to compare their location in different vertebrate species. In mammals, MCs are readily detected in the lung, intestines, skin and urogenital tract¹⁰⁻¹³ and, in humans, have been described to reach densities of up to 500 to 4,000 per mm³ in the lungs, 7,000 to 12,000 per mm³ in skin and 20,000 per mm³ in the gastrointestinal tract.¹⁵ These densities have been noted to increase in the skin of humans that is not covered by clothing, suggesting that regions that experience continual environmental exposure respond by either recruiting more MCs or inducing their local proliferation.¹⁶ Similarly, in lower order vertebrates, including amphibians, reptiles and birds, MC analogues that share structural and functional characteristics with their mammalian counterparts are found in the mucosa of the skin and intestines.¹⁷⁻¹⁹ In different species of fish families, including salmonids, cyprinids and erythrinids, MCs have been found in the skin, intestines and in the gills, a site that is continually exposed to pathogenic and environmental insult.²⁰⁻²⁵

Another common feature of MC placement in the tissues of different vertebrate species is that they are typically found deep beneath the epithelium in the mucosa, in close proximity to the blood vasculature. This selective placement of MCs near the vasculature may ensure that the release of MC derived pro-inflammatory products, including histamine and TNF, has near instantaneous effects on the local endothelium. In rodents, changes that MC-derived products may exert on local endothelium include increased leakiness between cells to promote edema and the induction of proteins that signal innate

effector cells, such as neutrophils or dendritic cells, to enter the tissue site to promote their antimicrobial functions. For instance, recent studies have found that MC release of tumor necrosis factor- α (TNF- α) at the local site of infection induces the expression of the adhesion molecule E-selectin on the local blood vessel endothelium.²⁶ The expression of E-selectin was required for the massive recruitment of dendritic cells into the infected tissue site and the subsequent induction of antibacterial humoral immunity.²⁶ Similarly, in fish, MCs have been noted in close proximity with capillary endothelial cells throughout the mucosa of the intestines, skin and the loose connective tissue of the gill arch.^{21,27-30} As with rodents, injection of bacterial toxins into fish results in MC degranulation that is closely associated with the recruitment of neutrophils into the inflamed tissue site. Overall, the striking commonalities in different vertebrate species concerning strategic MC density and placement within tissues, suggests that common mechanisms have been retained throughout evolution to ensure that MCs are a first responder during infection.

THE MAST CELL MICROBIAL SENSORY ARRAY

In order for MCs to behave as first line responders against microbial predation, MCs must express a diverse sensory array of receptors that facilitate the recognition of pathogens, pathogen products or host components activated in the presence of pathogens such as complement. Moreover, these sensors must translate these signals into a pro-inflammatory context. MCs have long been known to use complement products to bind both *Salmonella* and the helminth *Schistosoma mansoni*.^{31,32} MCs were also known to directly engage enterobacteria such as *E. coli* by binding FimH, the protein expressed at the tip of filamentous Type 1 fimbriae via a mannosylated receptor protein.³³ We now know that this protein is CD48 and engagement of *E. coli* through this receptor induces MCs to release pro-inflammatory cytokines such as TNF.³⁴ More recent studies have demonstrated that MCs can express a number of genetically encoded pattern recognition receptors (PAMPs) that recognize and bind conserved components of different pathogens such as lipopolysaccharide (LPS). These PAMPs include Toll-like receptors (TLRs) 1, 2, 3, 4, 5, 6, 7 and 9, whose expression appears to vary according to the MC model.³⁵⁻³⁷ For instance, analysis of TLR expression profiles in fetal skin derived MCs and bone marrow derived MCs revealed that fetal-skin derived MCs express much higher levels of TLRs 3, 7 and 9 than bone marrow derived MCs. Moreover, several studies examining the TLR expression profile in human cultured MCs have revealed differential patterns of TLR expression that collectively include TLRs 1, 2, 3, 4, 5, 6, 7 and 9. Not surprisingly, engagement of TLRs with their ligands on cultured MCs induces the secretion of copious amounts of cytokines^{35,36} that differ based on the TLRs that are activated. For instance, Kulka et al found that stimulation of human MCs with the TLR3 ligand poly I:C resulted in the production of IFN- α , but not TNF, IL-1 β , IL-5 or GM-CSF.³⁵ By contrast, treatment of human MCs with several TLR2 activators induced substantial IL-1 β and GM-CSF responses in the absence of a Type 1 IFN response.³⁸ Treatment of bone-marrow derived MCs with the TLR9 agonist CpGs resulted in the release of TNF, but not GM-CSF, IFN- γ , IL-4 or IL-12.³⁷ Recent studies have also found that stimulation of peritoneal derived MCs from mice with different TLR2 ligands can result in the production of differential cytokine responses. For instance, stimulation of peritoneal MCs with lipoteichoic acid (LTA) resulted in the production of IL-6, IL-1 and TNF- α , whereas treatment with macrophage activating lipopeptide-2 (MALP-2) resulted in the production of the anti-inflammatory cytokine

IL-10.³⁹ TLRs on MCs are also known to be functionally relevant to different primary challenges in vivo. For example, mice containing MCs deficient in TLR4 were found to be less able to survive in the cecal ligation and puncture (CLP) model of innate immunity than mice containing wild-type MCs.^{40,41} This failure was linked to the inability of these mice to recruit neutrophils into the peritoneal cavity.^{40,41} Mice containing MCs deficient in TLR3 were found to be unable to efficiently recruit T cells after injection of the TLR3 ligand polyI:C⁴² and mice containing MCs deficient in TLR7 were unable to efficiently induce dendritic cell migration to lymph nodes after injection of the TLR7 agonist imiquimod.⁴³ Cultured human MCs have also been found to express dectin-1, a PAMP involved in the recognition of fungal pathogens. In this model, exposure of human MCs to yeast zymosan induced the production of the cysteinyl leukotrienes (LT)-C₄ and LTB₄, which was inhibited in the presence of a dectin-1 inhibitor.⁴⁴ Finally, MCs have recently been found to express the NLRP3 inflammasome, an innate PAMP expressed in the cytoplasm of cells.⁴⁵ MCs expressing an allele of NLRP3 responsible for cryopyrin-associated periodic syndrome (CAPS) were found to spontaneously release IL-1 β that induced neutrophil recruitment and vascular leakage associated with the CAPS disease.⁴⁵ MCs are also activated by the adjuvant compound alum,⁴⁶ which has also been suggested to activate the NLRP3 inflammasome, however, this linkage has yet to be evaluated.

Studies have also evaluated the ability of MCs to engage humoral factors which comprise important components of the innate immune system. These include components of the complement cascade, LPS binding protein, C-reactive protein, pentraxins and collectins. Like PAMPs, such as TLRs, these circulating innate immunoproteins, which are evolutionarily conserved in both vertebrate and invertebrate species, are involved in both sensing of microbes and triggering of mechanisms to facilitate clearance of the infection. MCs in rodents and humans are now known to express several complement receptors including the C3aR,⁴⁷ C5aR,⁴⁸ CR2, CR4⁴⁹ as well as the $\alpha\beta 1$ integrin which is a receptor for C1q.⁵⁰ In vitro, engagement of C3a was found to induce MC activation and chemokine production from human MCs.^{51,52} In a murine model of septic peritonitis, C3-deficient mice were unable to induce MC-dependent neutrophil recruitment required for bacterial clearance.⁵³ Repletion of these mice with C3 restored MC-dependent effector functions.⁵³ Subsequent studies found that C3 likely engages the CR2 receptor on MCs, as mice containing MCs deficient in CR2 were unable to protect mice from septic peritonitis.⁴⁹ MCs are also able to bind several collectins, including mannose-binding lectin (MBL), surfactant protein A (Sp-A) and C1q complement protein through the $\alpha\beta 1$ integrin. This interaction is required for MC-dependent responses against *Listeria monocytogenes* and the yeast cell wall component zymosan.⁵⁰

MCs from multiple sources have also been shown to respond to the presence of peptides released from epithelial, endothelial or neural sources during infection or insult to the host. These include bradykinin,^{54,55} substance P,^{55,56} somatostatin,^{55,57} adrenocorticotrophic hormone (ACTH),^{54,55} calcitonin gene-related peptide (CGRP),^{55,58} corticotrophin-releasing hormone (CRH),⁵⁹ vasoactive intestinal peptide (VIP),^{55,60} neurotensin,^{61,62} neuromedin U⁶³ and peptide antibiotics such as β -defensins⁶⁴ and LL-37.⁶⁵⁻⁶⁷ Many of these peptides evoke release of MC mediators including histamine,^{59,64,66-68} cytokines and chemokines.^{65-67,69,70} Functionally, neuromedin U has been implicated in mediating the MC-dependent inflammatory activities of complete freund's adjuvant in a footpad model of inflammation.⁶³ Responsiveness of MCs to these peptides is dependent upon their tissue localization, as MCs derived from the skin or serosal sources are generally more responsive to these peptides than those derived from the intestines.⁵⁵ Interestingly, MCs

do not always appear to express canonical receptors for each of these peptides. With the exception of the neurotensin and neuromedin U receptors, which have been identified on MCs, many of these peptide agonists of MCs have been suggested to stimulate MCs by crossing the cell membrane to directly activate pertussis toxin sensitive G ($G_i\alpha 2$ and $G_i\alpha 3$) proteins.⁷¹ Alternatively, these peptides may act through Mas related gene (MRG)-X1 and X2 receptors on human cultured MCs or their rat analogues MRGB3 or MRGB8 on rat peritoneal MCs. MRG receptors are low affinity, nonspecific G-protein coupled receptors that can bind multiple cationic compounds and have been suggested to mediate the MC-activating properties of several host-derived peptides, including substance P, somatostatin and vasoactive intestinal peptide.⁷¹ Overall, these many observations clearly indicate that MCs from rodent or human sources have the capacity to directly respond to the presence of diverse pathogens, their products, or indirectly through host components activated by the presence of pathogens or pathogen products. A comprehensive summary of bacteria, viruses, protozoan parasites, their products or host-derived compounds demonstrated to activate MCs in vitro, as well as known receptors expressed by MCs for some of these ligands are listed in Tables 1 and 2.

Table 1. Ligands that induce MC activation in vitro

Stimulus	Preformed	Cytokines/ Chemokines	References
Bacteria			
<i>E. coli</i>	+	+	148-151
<i>K. pneumoniae</i>	+	+	148-149,151
<i>K. oxytoca</i>	+	-	149
<i>S. aureus</i>	+	+	149-150,152-153
<i>S. epidermidis</i>	+	?	149-150
<i>S. cohnii</i>	+	?	150
<i>P. vulgaris</i>	?	+	149
<i>H. pylori</i>	+/-	+	154-157
<i>M. tuberculosis</i>	+	+	158
<i>H. influenza</i>	+	?	152-153
<i>S. pneumonia</i>	+	-	82,159
<i>S. viridians</i>	+	-	152
<i>S. agalactiae</i>	+	?	150
<i>B. catarrhalis</i>	+	-	152-153
<i>B. pertussis</i>	?	+	160
<i>S. typhimurium</i>	+	?	31
<i>B. burgdorferi</i>	+	+	161-162
<i>M. hominis</i>	+	?	150
<i>U. urealyticum</i>	+	?	150
<i>B. capillosus</i>	+	?	150
<i>A. naeslundii</i>	+	?	150
<i>L. fermentum</i>	+	?	150
<i>E. cloacae</i>	+	?	149-150
<i>P. aeruginosa</i>	+/-	+	163-165

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Table 1. Continued

Stimulus	Preformed	Cytokines/ Chemokines	References
Viruses			
Sendai virus	+	?	166
Dengue virus	-	+	167-168
Reovirus	-	+	169
HIV	-	+	170-171
Influenza Virus	+	?	172
Parasites			
<i>S. mansoni</i>	+	?	173
<i>L. major</i>	+	+	174
<i>L. infantans</i>	+	+	174
<i>L. brasiliensis</i>	+	+	175
<i>T. spiralis</i> TSL-1 antigen	+	+	176
Toxins			
Toxin A (<i>C. difficile</i>)	-	+	177
Cholera toxin (<i>Vibrio cholera</i>)	-	+	178-179
VacA (Cytotoxin from <i>H. Pylori</i>)	-	+	180
Hemolysin (<i>E. coli</i>)	+	+	181
Hemolysin (<i>S. marcescens</i>)	+	+	181-182
Hemolysin (<i>A. hydrophilia</i>)	+	+	181
Hemolysin (<i>L. monocytogenes</i>)	+	+	181
Pertussis Toxin (<i>B. pertussis</i>)	-	+	160
Listeriolysin O	+	+	183
Streptococcal pyrogenic exotoxin B	+	?	184
Streptolysin O	+	?	185
Staphylococcal enterotoxin B	+	?	186
TLR agonists			
PGN	+/-	+	40
PGN	-	+	38,90,92,187-188
Lipotechoic Acid	-	+	39
MALP-2	-	+	39
Lipophosphoglycan	-	+	189
Lipoarabinomannan	-	+	188
dsRNA, poly I:C	-	+	35,90,169
LPS	-	+	40,90,92,187
Flagellin	-	+	35
ssRNA, imiquimod, R848	-	+	90
CpG DNA	-	+	37,90,170
Zymosan	?	+	44
Host derived Products			
C3a	+	+	32,51-52,190-193
C5a	+	+	51,191,193-197
C1q	+	+	50,198
Collectins	+	+	50,199
Substance P	+	+	55,64,69-70,200-206

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Table 1. Continued

Stimulus	Preformed	Cytokines/ Chemokines	References
Somatostatin	+	?	55,203-204,206
Vasoactive intestinal peptide	+	+	55,70,203-204,206
Neurotensin	+	?	55,61,200,205-209
β -defensins	+	+	64-66
LL-37	+	+	65-67
Endothelin-1	+	+	113,210-211
Bradykinin	+	-	55,205
Corticotropin releasing hormone	+	?	59,212

Pre-formed indicate MC mediators that are released from the MC granule such as histamine or β -hexosaminidase. Secondary mediators indicate mediators that are released after de-granulation, such as cytokines, chemokines or eicosanoids.

+ indicates a positive response. - indicates no response was detected. +/- indicates that both positive and negative responses have been reported. ? indicates that no such response was evaluated.

Table 2. The microbial sensory array of MCs

Receptor	Ligand	References
CD48	FimH	158,213
TLR1	Lipopeptide	38
TLR2	Peptidoglycan	38,40,90,92,187-188
	Lipotechoic acid	39
	MALP-2	39
	Lipophosphoglycan	189
	Lipoarabinomannan	188
TLR3	dsRNA/Poly I:C	35,90,169
TLR4	Lipopolysaccharide	40,92
TLR5	Flagellin	35
TLR6	Peptidoglycan, zymosan	38,40,92,187
TLR7	ssRNA/Imiquimod	43,90
TLR9	Bacterial DNA/CpGs	37,90,170
Dectin-1	Zymosan	44
C3aR	C3a	32,51-52,191-193
C5aR	C5a	194-196,214
CR2	C4b, C3b, iC3b, C3d	49,190
CR3	C4b, C3b, iC3b, C3d	14
$\alpha 2\beta 1$ integrin	C1q, collectins, SP-A, zymosan	50
ETA	ET-1	113,210-211
NT receptor	Neurotensin	200
NMU-R1	Neuromedin U	63
MRG-receptors	Substance P, somatostatin, VIP	71

THE PRO-INFLAMMATORY ARSENAL OF THE MAST CELL

One of the most compelling arguments for the notion that MCs have evolved as first responders during infection is that they are uniquely equipped for the rapid release and synthesis of numerous pro-inflammatory mediators that have the capacity, either individually or in concert, to set in motion powerful inflammatory reactions. The types of pro-inflammatory compounds released by MCs have been divided into two major classes based on whether they are prestored or de-novo synthesized. Pre-stored compounds are packaged into cytoplasmic MC granules, which are the dominant feature of MCs in all vertebrates. These granules are enveloped by a membrane and are organized around a highly sulfated glycosylaminoglycan such as heparin or chondroitin sulphate.^{72,73} Pre-stored components in rodent and human MC granules include soluble biogenic amines such as histamine and serotonin.^{74,75} Numerous enzymes and proteases such as chymases, tryptases and carboxypeptidase A,⁷⁶⁻⁷⁸ and cytokines such as TNF- α ,⁷⁹ are also packaged within the granule and remain associated with the glycosylaminoglycan matrix after release of the granule into the tissue.^{80,81} Other prestored compounds of note include antimicrobial peptides such as cathelicidin.⁸² De novo synthesized mediators produced by rodent and human MCs include arachidonic acid-derived metabolites generated through the cyclooxygenase pathways such as prostaglandin (PG)-D₂ or the lipoxygenase pathways that yield leukotrienes such as LT-C₄.⁷⁶ MCs also secrete an amazing array of cytokines and chemokines, including IL-1,^{40,83,84} IL-3,^{83,85,86} IL-4,^{40,83,85} IL-5,⁸⁷⁻⁸⁹ IL-6,^{40,83,87,90} IL-8,⁸⁹ IL-9,^{87,91} IL-10,⁹² IL-13,^{40,89,92} GM-CSF,⁸⁹ TGF- β ,⁹³ CCL1,⁹⁴ CCL2,⁹⁴ CCL3,^{89,90} CCL4,⁹⁴ CCL5⁹⁰ and CXCL2.⁹⁰ Many of these compounds have been well documented to mediate the effects of tissue inflammation, including fluid extravasation and the recruitment of effector cells into the tissue.

In lower order vertebrates, the components of the MC granule and the secretion of de novo synthesized products are not as well characterized. However, it is generally thought that the granule components are similar. For instance, in different species of fish, the granules of MCs have been noted to contain serotonin,⁹⁵ lysozyme,⁹⁶ carboxypeptidase A5,²⁵ alkaline and acid phosphatases, arylsulphatase, 5-nucleotidase,^{97,98} and potent antimicrobial peptides (called piscidins).²³ Notably, histamine has not generally been detected in the granules of fish or amphibian MCs, which is a characteristic thought to have started in the MCs of reptiles. However, recent studies have demonstrated that histamine is present in the MC granules of the Perciformes order, considered the most evolutionarily advanced order of fish. This suggests that the storage of this important pro-inflammatory compound in MC granules may have occurred as a separate evolutionary event. Functionally, activation of MCs in lower order vertebrates has been associated with inflammatory events in these species. Injection of inactivated bacteria into fish such as Atlantic salmon⁹⁹ or brown trout²⁸ elicit MC granule exocytosis followed by vasodilation and an inflammatory reaction.¹⁰⁰⁻¹⁰² Injection of fish with the MC secretagogue compound 48/80 elicits vasomotor responses in perfused brachial vascular beds of rainbow trout.¹⁰³ This last point is significant as mammalian MCs undergo rapid exocytic responses to compound 48/80, resulting in the induction of profound pro-inflammatory responses.^{74,104} This point suggests that, not only do mammalian MCs and lower vertebrate MCs store common inflammatory components, but that they may also be hard-wired to respond to similar secretagogues.

The release of MC granules and their associated pro-inflammatory contents during microbial challenge is one of the principal ways in which MCs are thought to provoke the characteristics of inflammation. Exocytosis of the MC granule results in the instantaneous

release of many or the prestored pro-inflammatory products such as histamine. Interestingly, the granule itself is released intact into the local tissue, suggesting that its associated mediators such as TNF- α and many enzymes are retained within its matrix. This might ensure that the pro-inflammatory mediators remain undiluted and active so as to efficiently exert their effects within the tissue site. Recent studies in mice have confirmed this hypothesis, demonstrating that the MC granule conveys MC-derived TNF- α to distal sites such as the draining lymph node ensuring that its pro-inflammatory effects remain un-impaired.¹⁰⁵ Intriguingly, MC granule exocytosis has been demonstrated to be somewhat variable depending on the stimulus. These observations may reflect that the de-granulation event is not an all or nothing process, but rather an exquisitely tuned response that releases an appropriate amount of pro-inflammatory mediators appropriate for the stimulus. The first type of granule release is best defined after IgE receptor (Fc ϵ RI)-mediated crosslinking on the MC surface. In this model, MC granules begin to swell within minutes, followed by fusion of individual granules into cytoplasmic channels. The channels then fused with the plasma membrane resulting in an explosive expulsion of the granular material.^{106,107} However, in the context of exposure to Type-I fimbriated *E. coli*, MC de-granulation occurs as a gradual exocytic event that takes an hour to complete.¹⁰⁸ Similarly, injection of *E. coli* into footpad tissues results in a gradual release of granule components from MCs over a four hour period, as opposed to the near immediate release of MC granules upon injection of the MC secretagogue compound 48/80.¹⁰⁹ The slow release of MC granules during infection is thought to reflect a form of granule release called piecemeal degranulation, which involves the slow release of granular material as the granule fuses with the cellular membrane followed by re-internalization of the MC granule. Interestingly, many bacterial products, including TLR ligands such as LPS or polyI:C, or toxins such as cholera toxin, do not induce MC degranulation.³⁵⁻³⁷ Rather, as noted, exposure of MCs to these bacterial components results in the release of copious amounts of cytokines.³⁵⁻³⁷

MAST CELL MODULATION OF INNATE RESPONSES TO INFECTION

Overall, these observations suggest that MCs are well positioned and armed to be a primary point in the initiation of inflammation required for the induction of innate and adaptive immune responses during infection. Proof of this hypothesis, however, requires the use of in vivo models that facilitate the direct analysis of MCs and their impact on these responses during infection. Fortunately, certain mutant mice virtually lacking MCs are available, making it possible to evaluate the specific contribution of MCs. These MC-deficient mutant mice include the WBB6F1-Kit^W/Kit^{Wv} (W/W^v) mouse, a heterozygous mutant that bears a deleted *kit* allele and a mutant *kit* allele with defective kinase activity.¹¹⁰ Recently, the Kit^{Wsh}/Kit^{Wsh} mice have been described as an alternative model to the W/W^v strains. These mice are preferable as they do not manifest some of the severe deficiencies of the W/W^v strain of mice, including profound anemia and sterility.¹¹¹ By quantitating differences in biological responses between MC-deficient mice and the congenic wild-type controls and then by analyzing the responses in MC-deficient mice that have been selectively reconstituted with cultured MCs, the specific in vivo contributions of MCs to many inflammatory reactions can be evaluated.¹¹⁰

Among the first studies that examined a role for MCs in the induction of innate immunity during infection in vivo were performed by Malaviya et al and Echtenacher et al in mice.^{9,112} Using an infectious model of bacterial peritonitis, Malaviya et al found

that injection of FimH-expressing enterobacteria into the peritoneal cavity of W/W^v mice resulted in a near 80% mortality rate, as opposed to a 0% mortality rate in wild-type controls.¹¹² Repletion of the peritoneal cavity of W/W^v mice with cultured MCs restored the ability of these mice to resist enterobacteria induced mortality.¹¹² These data confirmed that the differences observed in susceptibility to infection were due to the absence of MCs and not to other abnormalities that may exist in these mice.¹¹² MCs were found to protect mice from enterobacterial challenge by recruiting neutrophils into the infected site, as MC-deficient mice exhibited a 5-fold reduction in the presence of neutrophils in the peritoneal cavity compared to MC-sufficient controls.¹¹² These findings were associated with the release of large amounts of local TNF- α , which was required for the recruitment of the neutrophils. Similar data, obtained using the cecal ligation and puncture (CLP) model of acute peritonitis, also found that MC-induced recruitment of neutrophils is important for protection against bacterial infection.⁹ These data confirmed for the first time that MCs are an important component of innate defense based on their ability to recruit neutrophils into the site of infection.

Subsequent studies have expanded our understanding of how MCs affect innate defense in models not associated with neutrophil recruitment. The first is concerned with the limitation of the toxic effects of either host derived endogenous compounds, or exogenous mediators such as venom components that can have profound deleterious effects on host tissues. Original studies that examined this problem involved the endogenous peptide endothelin-1 (ET-1), which has significant adverse effects when present in high concentrations.¹¹³ MCs and MC-derived carboxypeptidase A were found to be required to limit the morbidity and mortality induced by ET-1 administration in mice, as well as the effects of ET-1 in the CLP model of peritonitis.¹¹³ Subsequently, MCs have been found to limit the toxic effects of the peptide neurotensin and the cytokine IL-6 through similar proteolytic activities.^{62,114} Finally, comparative work found that the sequence of ET-1 was very similar to the toxic component of the Israeli mole viper sarafotoxin 6b. Because MC proteolytic activity was required to limit the harmful effects of ET-1, it suggested that MC proteolytic activity might limit the pathogenicity of sarafotoxin as well. Injection of sarafotoxin 6b into MC deficient mice demonstrated that these mice were 10 times more sensitive to the deadly effects of the venom than MC sufficient mice. Similar data was obtained using the venom from the pit viper (*Crotalinae*) and the honeybee (*Apis mellifera*),¹¹⁵ suggesting that MC derived proteases can limit the toxicity of noxious substances.

An additional means by which MCs affect innate immune responses is through the release of prestored peptide antibiotics. Antimicrobial peptides are distinguished by their ability to rapidly inactivate a wide range of infectious agents.¹¹⁶⁻¹²⁰ These peptides are thought to act by disrupting the integrity of the microbial membrane,¹¹⁷ a feature thought to be mediated by two common structural characteristics shared by most antimicrobial peptides, including a net-positive charge and the propensity for folding into amphipathic secondary structures that promote their binding and insertion into microbial membranes. The presence of antimicrobial peptides in MCs was first noted in hybrid striped bass.²³ These fish-associated antimicrobial peptides, now called piscidins, were found to be largely associated with MCs in the skin, gastrointestinal tract and the gills of nine different families of fish of the Perciformes order.^{24,121} Piscidins comprise a family of 21-22 amino acid antimicrobial peptides that display a broad range of antimicrobial activity against many bacterial and protozoan pathogens.^{24,121-122} These include not only disease-causing microbes in fish, but pathogens that cause disease in mammals such as *Candida albicans*.¹²³

Subsequently, several antimicrobial peptides, including beta defensin-4, beta defensin AMP and cathelicidin were found to be expressed in both cultured human and murine MCs.⁸² Similar to piscidins, these antimicrobial peptides display a wide range of antimicrobial activity. Interestingly, murine MC-derived cathelicidin was found to be important in protecting mice against infection with Group A streptococcus (GAS). For instance, injection of GAS into the skin of Wsh mice reconstituted with cathelicidin-deficient MCs exhibited GAS induced lesions of 120mm², compared to lesions of 25mm² in the skin of Wsh mice reconstituted with cathelicidin⁺ MCs.¹²⁴ Therefore, the expression and release of antimicrobial peptides are likely an important weapon in the antimicrobial functions of the MC.

Collectively, these observations have been augmented by many *in vivo* studies that have evaluated the role of MCs, their microbial sensory array and/or MC pro-inflammatory products in models of innate host defense (Table 3). These studies have largely reaffirmed the idea that MCs and their products play a vital role in host defense against many different types of pathogens or toxins. There are however, several important exceptions to this general hypothesis. Infection of MC-repleted, MC-deficient mice with the enteric pathogen *S. typhimurium* in the peritoneal cavity did not improve the ability of these mice to resist infection. In fact, repletion of Wsh mice with MCs appeared to aggravate the severity of the disease and resulted in reduced mortality.¹²⁵ In addition, the few *in vivo* studies that have examined a role for MCs in protection from viral infection, including infection with Encephalomyocarditis Virus and Coxsackie B3 Virus, have suggested that MC deficiency results in reduced pathology of the disease.^{126,127} However, reconstitution of Wsh mice with MCs restores the pathogenic effects of the viral illness.^{126,127} In calves infected with RSV, MC activation and systemic release of their products appears to correlate with the severity of symptoms.¹²⁸⁻¹²⁹ Finally, in models where large doses of TLR ligands are administered to mice, MC deficiency appears to ameliorate the pathogenic inflammation induced by these TLR ligands. For instance, MC deficiency reduced LPS-induced uveitis or cystitis and SM360320 (a TLR7 agonist) induced hypothermia.¹³⁰⁻¹³² These models offer a startling contrast to those that suggest MCs have a protective role. However, an explanation may lie in the fact that pathogens such as *S. typhimurium* and RSV are highly evolved to cause active disease in their respective hosts. This suggests an intriguing concept, that such pathogens may have evolved strategies to overwhelm or insidiously reprogram the MC to induce changes in the local tissue site that allow it to gain access and systemically infect the host. In addition, large, systemic amounts of TLR ligands reflect a state of overwhelming sepsis, which may result in unabated stimulation of MCs leading to persistent inflammation of the tissue site and/or systemic tissue edema and shock, similar to what is observed in IgE-mediated, MC-dependent systemic anaphylaxis. Therefore, depending on the type of microbial stimulus, MCs may exhibit beneficial or pathogenic responses.

MAST CELL MODULATION OF ACQUIRED IMMUNITY DURING INFECTION

Another compelling role for the MC has recently been suggested by the realization that the inflammatory context that drives the innate response is also pertinent to the induction of the adaptive immune response. Inflammation facilitates the enhanced recruitment of naïve antigen-specific T cells and antigen-laden antigen-presenting cells (APCs), most

Table 3. In vivo models examining a role for MCs and their products in host defense

Challenge	Site of Challenge	Host	MC Dependent Response	Refs.
Bacteria				
<i>E. coli</i>	Peritoneal cavity	Mice	Bacterial Clearance	8,215
<i>E. coli</i>	Bladder	Mice	Bacterial Clearance	216
<i>K. pneumonia</i>	Lungs	Mice	Bacterial Clearance	112
<i>K. pneumonia</i>	Peritoneal cavity	Mice	Bacterial Clearance	217
<i>M. pulmonis</i>	Lungs	Mice	Bacterial Clearance	218
<i>C. rodentium</i>	Intestines	Mice	Bacterial Clearance	219
<i>S. pneumonia</i>	Skin	Mice	Lesional size	124
<i>H. pylori</i>	Stomach	Mice	Bacterial Clearance	220
<i>H. influenza</i>	Middle ear	Mice	Bacterial Clearance	221
<i>L. monocytogenes</i>	Peritoneal cavity	Mice	Bacterial Clearance	222
<i>F. novicida</i>	Lungs	Mice	Bacterial Clearance	223
<i>S. aureus</i>	Peritoneal cavity	Mice	Bacterial Clearance	214
<i>M. tuberculosis</i>	Lungs	Mice	Bacterial Control	224
<i>P. aeruginosa</i>	Skin	Mice	Bacterial Clearance	225
CLP	Peritoneal cavity	Mice	Survival/Bacterial Clearance	226
CLP	Peritoneal cavity	Mice	Survival/Bacterial Clearance	40
CLP	Peritoneal cavity	Mice	Survival/Bacterial Clearance	49,227
TLR Ligands				
PGN	Ear	Mice	Lymph node hypertrophy	142
PGN	Skin	Mice	Vasodilation	40
Poly I:C	Peritoneal Cavity	Mice	T-cell recruitment	42
Imiquimod	Skin	Mice	Adjuvant activity	43
Viruses				
Newcastle Disease Virus	Peritoneal Cavity	Mice	T-cell recruitment	42
Parasites				
<i>L. major</i>	Skin	Mice	Parasite Clearance	228
<i>L. major</i>	Skin	Mice	No role	229
<i>L. amazonensis</i>	Skin	Mice	No role	230
<i>T. spiralis</i>	Intestines	Mice	Parasite Clearance	231
<i>T. spiralis</i>	Intestines	Mice	Parasite Clearance	232-233
<i>N. brasiliensis</i>	Intestines	Mice	No role	234-235
<i>P. burghei</i>	Spleen	Mice	Parasite Clearance	236
<i>S. ratti</i>	Intestines	Rat	Parasite Clearance	237
<i>H. longicornis</i>	Skin	Mice	Parasite Clearance	238
Endogenous/ Exogenous Peptides				
Substance P	Skin	Mice	Inflammation	239
Endothelin-1	Peritoneal Cavity	Mice	Reduced toxicity	113
Neurotensin	Peritoneal Cavity	Mice	Reduced toxicity	62
Neuromedin U	Footpad	Mice	Inflammation	63
Sarafatoxin 6a	Peritoneal Cavity	Mice	Reduced toxicity	115

likely dendritic cells, into local draining lymph nodes. This massive recruitment of both cell types into lymph nodes ensures the maximal engagement of antigen-specific T-cell receptors on naive T cells with peptide/MHC Class II complexes on dendritic cells. In addition, inflammation induces the expression of costimulatory molecules (CD40, CD80, CD86) on dendritic cells, allowing them to efficiently stimulate antigen specific naive T cells.^{3,133} Both of these signals provided by dendritic cells to antigen specific T cells are required for the efficient induction of antigen-specific immunity, the clearance of the pathogen and the formation of immunological memory. Therefore, the pro-inflammatory environment created by MCs during innate responses, may well have an important role in the induction of adaptive immunity.

Historically, most reports have not supported a role for MCs in the development of primary adaptive immunity.^{5,134-138} These data are largely derived from contact sensitization models that did not find a role for MCs, largely in the challenge phase which automatically ruled out a role for the mast cell in the sensitization, or antigen presentation phase of the response.¹³⁹ Similarly, several studies employing prime boost regimens for the study of humoral response in MC-deficient mice found that these mice were capable of producing antibody responses, suggesting that MCs had no impact on the development of adaptive immunity.^{5,134-138} However, a growing body of evidence has been convincingly derived from several lines of investigation employing *in vivo* mouse models implying that MCs do have an effect on the adaptive immune response. For example, MC-deficient mice were observed to exhibit impaired T-cell activation in a T-cell-dependent contact sensitization model.¹⁴⁰ The relevant experiment in this study demonstrated that transfer of splenocytes from MC-deficient mice primed with the contact sensitizer FITC failed to allow the development of a contact sensitization response after subsequent challenge of the ear with FITC compared to controls. These data suggested that, in the absence of MCs, inefficient sensitization priming of the FITC specific T-cell response occurred and that this was correlated with reduced dendritic cell migration from the epidermis. MCs were also found to be required for the full expression of the multiple sclerosis (MS) phenotype in the experimental autoimmune encephalitis (EAE) model of MS in mice. In these studies, the induction of EAE was found to be severely impaired in both the time-course and intensity in MC-deficient mice. It was subsequently found that T cells in this model exhibited a poorly activated phenotype after the administration of CFA and the MOG peptide.¹⁴¹ In addition, several studies have demonstrated that MCs can elicit dendritic cell mobilization and accumulation in lymph nodes by crosslinking FcεRI or the injection of the TLR2 agonist PGN^{138 142} or after mosquito bite.¹⁴³

Initially, the search for a role for MCs in the development of adaptive immunity during infection began with linking MC activation to the enhanced sequestration of lymphocytes in draining lymph nodes. Lymph node swelling is a common occurrence in response to infection and is the result of the recruitment and entrapment of massive numbers of lymphocytes within a 24-48 hour time period.^{3,133} This process is thought to increase the likelihood that rare antigen-specific lymphocytes will be appropriately stimulated by specialized antigen presenting cells (APCs) that have acquired fragments of the invading pathogen.^{3,133} The first studies to examine this response used a modestly pathogenic strain of *E. coli* in a footpad model of infection in mice. Injection of *E. coli* rapidly elicited MC de-granulation, followed by lymph node swelling that peaked at 24 hours. This suggested that MC activation and release of their mediators, preceded lymph node swelling, raising the possibility that MC products could directly impact lymph node hypertrophy. To evaluate this, *E. coli* was injected into the footpads of MC

deficient mice; and it was found that *E. coli* failed to elicit comparable levels of lymph node swelling. Lymph node swelling could be repaired by reconstitution of MC-deficient footpads with cultured MCs. Importantly, it was found that MCs affected the sequestration of lymphocytes in the distal lymph node by the release of TNF- α that flowed into the lymph node and provoked the increased expression of adhesion molecules known to affect lymphocytes trapping such as V-CAM-1. This “remote control” of lymph node hypertrophy by MC-released TNF- α established that MCs could affect the entrapment of lymphocytes through communication with distal organs.¹⁰⁹ Subsequent to this study, several groups have found that the stimulation of MCs with different MC secretagogues can induce lymph node hypertrophy, although the MC mediators required are different.^{138,142,143}

As noted, a second important arm of the primary immune response is the recruitment of antigen-laden DCs into lymph nodes during infection. During infection, DCs acquire pathogen-derived fragments in peripheral tissues and translocate to lymph nodes, where they find and activate rare antigen-specific lymphocytes.¹⁴⁴ Therefore, cues that affect DC homing to lymph nodes are very important to the development of primary immune responses. Interestingly, host-derived factors such as TNF- α are known to affect DC migration.¹⁴⁵ Because MCs produce copious amounts of TNF- α , we examined the idea that MCs might affect the migration of DCs to lymph nodes during infection. In these studies, injection of *E. coli* into the footpad of MC-deficient mice resulted in markedly impaired DC accumulation in lymph nodes compared to wild-type controls. Reconstitution of the footpad site of MC-deficient mice with MCs repaired DC trafficking to lymph nodes. MC control over DC trafficking during infection was dependent upon MC-derived TNF- α , which was found to affect DC migration at two levels. The first was through the recruitment of DCs into the infected tissue site by increasing the expression of the adhesion marker CD62E on local blood vessel endothelium. The second was in the induction of DC chemo-attractants such as CCL21 in the lymph node. Therefore, MCs activated not only the local tissue site, but also the distal lymph node in order to increase the expression of proteins that were required for the recruitment of DCs into the tissue site followed by their egress to lymph nodes. A final point of this study was to establish that MCs were actually involved in the induction of primary immune responses during infection. Injection of *E. coli* into MC-deficient mice resulted in impaired antigen-specific immune responses compared to wild-type mice or MC-repleted, MC-deficient mice. Therefore, MCs are in fact required for the development of optimal antigen-specific immune responses through their ability to provoke the increased recruitment of DCs and lymphocytes into lymph nodes during an infection.²⁶

The combination of these findings suggested that MCs might act at the pinnacle of the adaptive immune response by directing the mobilization of two of the important effector cells in the induction of adaptive immunity into draining lymph nodes. This led to the question, if one activated MCs in the context of a vaccine antigen, could you elicit an immune response? Subsequently, injection of the small molecule MC-activating molecule compound 48/80 (c48/80) with the vaccine antigen, protective antigen (PA) from *Bacillus anthracis*, in the footpad was found to generate rapid and profound anti-PA humoral responses. Injection of c48/80 plus PA failed to elicit robust responses in MC-deficient mice, implying that MCs were required for the adjuvant effects of c48/80. Not surprisingly, repletion of MC-deficient mice with MCs was able to repair the defect. An additional finding was that nasal instillation of MC activating compounds evoked antigen-specific secretory IgA along various mucosal surfaces, suggesting that MC activators could behave as potent mucosal adjuvants. This is significant because there are

very few safe adjuvants that can induce robust mucosal immunity along mucosal surfaces. These immune responses were not only robust, but functional, in that they provided neutralization in several lethal challenge models, including an in vitro anthrax lethal toxin assay and protected mice against a lethal vaccinia virus infection in vivo.¹⁴⁶ Subsequent studies found that c48/80 also acted as an effective adjuvant when administered through an intradermal route.¹⁴⁷ Therefore, MC-activating compounds are an effective and novel class of vaccine adjuvant.

CONCLUSION

Collectively, these numerous studies provide compelling evidence that MCs have evolved as a first line of defense to protect vertebrates against microbial predation. This hypothesis contrasts the notion that MCs are a vestigial remnant of evolution that is only capable of causing disease such as allergy. In support of these ideas are their consistent positioning in tissues of vertebrates, extensive microbial sensory array and ability to rapidly convert these signals into a pro-inflammatory context that in vivo studies have found to be important for innate and adaptive immunity during infection. However, it remains important to note that MCs may also play a negative role in the pathology of some infectious diseases and it will be important to determine how this occurs. Nevertheless, the clear beneficial context of the MC suggests that these cells might be manipulated for clinical benefit. As noted, MC-activating compounds have proven to be highly effective mucosal vaccine adjuvants and certainly, continued evolution of our understanding of the MC may result in tailored vaccine adjuvants that can provide the appropriate, protective immune stimulus for different pathogens. We can also envisage manipulating the MC to stimulate innate immune responses to therapeutically manage many different types of infection. Therefore, our continued study and understanding of this fascinating cell in the context of infection will likely provide insights leading to improved therapies for not only infectious disease, but many other pathological conditions where MCs have been suggested to play a role.

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