



Divergent Mast Cell Responses Modulate Antiviral Immunity During Influenza Virus Infection

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Influenza A virus (IAV) is a respiratory pathogen that infects millions of people each year. Both seasonal and pandemic strains of IAV are capable of causing severe respiratory disease with a high risk of respiratory failure and opportunistic secondary infection. A strong inflammatory cytokine response is a hallmark of severe IAV infection. The widespread tissue damage and edema in the lung during severe influenza is largely attributed to an overexuberant production of inflammatory cytokines and cell killing by resident and infiltrating leukocytes. Mast cells (MCs) are a sentinel hematopoietic cell type situated at mucosal sites, including the lung. Poised to react immediately upon detecting infection, MCs produce a vast array of immune modulating molecules, including inflammatory cytokines, chemokines, and proteases. As such, MCs have been implicated as a source of the immunopathology observed in severe influenza. However, a growing body of evidence indicates that MCs play an essential role not only in inducing an inflammatory response but in suppressing inflammation as well. MC-derived immune suppressive cytokines are essential to the resolution of a number of viral infections and other immune insults. Absence of MCs prolongs infection, exacerbates tissue damage, and contributes to dissemination of the pathogen to other tissues. Production of cytokines such as IL-10 and IL-6 by MCs is essential for mitigating the inflammation and tissue damage caused by innate and adaptive immune cells alike. The two opposing functions of MCs—one pro-inflammatory and one anti-inflammatory—distinguish MCs as master regulators of immunity at the site of infection. Amongst the first cells to respond to infection or injury, MCs persist for the duration of the infection, modulating the recruitment, activation, and eventual suppression of other immune cells. In this review, we will discuss the immune modulatory roles of MCs over the course of viral infection and propose that the immune suppressive mediators produced by MCs are vital to minimizing immunopathology during influenza infection.

Keywords: mast cells, influenza virus, IL-10 (interleukin-10), innate immunity, viral infection

INTRODUCTION

Influenza A virus (IAV) infects millions of people each year, causing respiratory disease ranging from mild to life-threatening. Annually, severe influenza causes the deaths of between 250,000 and 650,000 people globally (Iuliano et al., 2018; Krammer et al., 2018). Young children (under the age of 2), adults over 65 years of age, and people who are immunocompromised or have underlying chronic health conditions such as heart disease and diabetes are most vulnerable to developing and dying of severe influenza and associated complications (Adlhoch et al., 2019). The segmented RNA genome of IAV mutates rapidly in a process called antigenic drift, necessitating the annual reformulation of the seasonal influenza vaccine (Krammer et al., 2018). In addition, genetic reassortment between strains in a host simultaneously infected with multiple influenza serotypes produces novel IAV strains with pandemic potential (Webster et al., 1992; Krammer et al., 2018). Given increasing global human, livestock, and poultry population densities, the risk of zoonotic transmission of a highly-pathogenic, antigenically-distinct strain of IAV and subsequent global pandemic remains high (Fournie et al., 2013; Vincent et al., 2014; Krammer et al., 2018). Four such pandemics have occurred in the last century, resulting from reassortment of avian or swine influenzas to which humans lacked prior exposure (Lindstrom et al., 2004; Smith et al., 2009; Krammer et al., 2018). Due to the diversity of IAV strains across species, predicting the genetic makeup of future pandemic strains and preparing a broadly-neutralizing vaccine has proven difficult, though the development of antibodies targeting cross-clade conserved epitopes shows promise (Kwong et al., 2020). Antiviral treatments for influenza infections are limited, and development of viral resistance has rendered classes of antiviral drugs, such as adamantanes, unusable (Gubareva et al., 2010; Dong et al., 2015; Krammer et al., 2018). Antivirals currently used in the clinic, such as oseltamivir and zanamivir, have been shown to have limited efficacy in cases of severe influenza and are most efficient when administered within 48 h of symptom onset (Muthuri et al., 2014; Okoli et al., 2014; Dobson et al., 2015; Venkatesan et al., 2017). In

light of the challenges to designing vaccines and therapeutics against a constantly evolving target such as IAV, development of new therapeutics effective across a broad range of influenza strains is urgently needed. One potential therapeutic alternative is boosting the host immune system to defend against the invading pathogen and minimize the tissue pathology associated with severe disease.

Extensive cytokine production in the lung is a hallmark of severe influenza infection (**Table 1**). IAV primarily infects and replicates in the pulmonary epithelial cells of the upper respiratory tract; in severe cases of IAV, the virus may reach the lower respiratory tract, replicating in alveolar epithelial cells and macrophages (Denney and Ho, 2018). Widespread epithelial cell death from both necrosis and apoptosis has been observed in the lungs of humans and mice during severe influenza infection (Short et al., 2014; Atkin-Smith et al., 2018). Recognition of the viral replication complex by the pattern recognition receptor (PRR) ZBP1/DAI triggers formation of the necrosome and cell death by necrosis, while the viral protein PB1-F2 induces the intrinsic pathway of apoptosis and the nonstructural viral protein NS1 contributes to upregulation of pro-apoptotic hallmarks of the extrinsic apoptosis pathway (Chen et al., 2001; Lam et al., 2008; Atkin-Smith et al., 2018; Fujikura and Miyazaki, 2018). Interestingly, NS1 also inhibits apoptosis through binding of pro-apoptotic proteins, suggesting the NS1 may play a role in delaying apoptosis to increase viral propagation (Obenauer et al., 2006; Liu et al., 2010; Adlhoch et al., 2019). The exact mechanisms dictating the specific fate of an infected cell are not yet fully elucidated, however, and may be strain dependent. The death of infected lung epithelial cells disrupts the integrity of the epithelial-endothelial barrier, allowing fluid accumulation in the lung and causing respiratory failure (Short et al., 2014). Secretion of inflammatory cytokines, type 1 interferons (IFNs), chemokines, and antimicrobial peptides by infected epithelial cells and macrophages recruits innate immune cells to the site of infection (**Table 1**) (Chan et al., 2005; Chan et al., 2010a; Chan et al., 2010b; Lam et al., 2010; Sanders et al., 2011; Xing et al., 2011; Denney et al., 2018). Activated innate immune cells, including macrophages, dendritic cells (DCs), neutrophils, mast cells (MCs),

TABLE 1 | Cytokine and chemokine expression by resident lung cells during influenza virus infection.

Human			
Strain	Cell type	Biological observations*	Reference
H1N1	Primary monocytes	Secretion of MCP-1 (CCL2), MIP-1 α (CCL3), and RANTES (CCL5)	Sprenger et al. (1996)
H1N1	Primary bronchial epithelial cells	Secretion of RANTES (CCL5) and IFN β	Chan et al. (2010b)
H5N1	Bronchial epithelial cell line NCI-H292	Strain-dependent differential and temporal upregulation of TNF- α , IL-6, IL-8, CCL5, and CXCL10	Lam et al. (2010)
H1N1			
H9N2	Primary nasal and bronchial epithelial cells	Secretion of RANTES (CCL5)	Matsukura et al. (1998)
H3N2	Primary tracheobronchial epithelial cells	Upregulation of IFN β , IP-10, and CCL5	Xing et al. (2011)
H9N2			
Mouse			
Virus	Cell type	Biological observations*	Reference
H1N1	Primary Balb/C alveolar epithelial cells	Upregulation of ICAM-1, VCAM-1, integrin-associated protein (IAP), CCL2, and CCL5	Herold et al. (2006)

*Relative to controls.

and natural killer (NK) cells, produce additional cytokines, contributing to the antiviral inflammatory milieu, often referred to as the “cytokine storm” (Ramos and Fernandez-Sesma, 2015; Liu et al., 2016). Adaptive immune cells, such as CD8⁺ cytotoxic T lymphocytes (CTL) and CD4⁺ T helper (Th) cells, also contribute to the highly inflammatory environment, a state which can persist even after the virus has been largely cleared from the lung. MCs, in particular, are major producers of cytokines and chemokines in the lung throughout the course of influenza infection. MC-derived cytokines and chemokines recruit and activate local and circulating innate and adaptive immune cells as well as regulate the composition, distribution, and phenotype of the structural and non-immune cells in the vicinity (Baram et al., 2001; Murray et al., 2004; Krystel-Whittemore et al., 2015; Reber et al., 2015; Oldford et al., 2018). To better understand how to minimize inflammatory immunopathology while still clearing the infection, attention has turned to better understanding how the immune system self-regulates inflammation. In this review, we will address the role of MCs in modulation of the inflammatory environment of the influenza-infected lung.

MCs are a lineage of innate immune hematopoietic sentinel cells, dispersed throughout the body but found most concentrated at the interfaces between the host and the environment, such as the skin, gut, and mucosa (Kitamura et al., 1977; Galli et al., 2008; Da Silva et al., 2014; Reber et al., 2015). The positioning of MCs at mucosal sites allows them to rapidly respond to infection and injury (Galli et al., 2008; Reber et al., 2015). Within minutes, activation of MCs can trigger the immediate release of preformed granules, which contain an array of proteases (such as tryptase and chymase), amines (such as histamine), and cytokines (Riley, 1953; Pejler et al., 2010; Caughey, 2011; Gri et al., 2012; Reber et al., 2015). Additional immune mediators, including cytokines, chemokines, and growth factors, are produced and secreted in an activation-dependent manner within hours and can continue for days (Da Silva et al., 2014; Sibilano et al., 2014; Reber et al., 2015). MCs express multiple Fc receptors on the cell surface, allowing MCs to respond to antigens previously encountered by the host (Galli et al., 2008; Krystel-Whittemore et al., 2015). The majority of Fc receptors on MCs are FcεR1, the high affinity IgE receptor. Binding of IgE to FcεR1 sensitizes the MCs, and polyvalent crosslinking of the target antigen initiates granule release and cytokine production. In addition to Fc receptors, MCs express an abundance of activating receptors on the cell surface and intracellularly, including pattern-recognition receptors (PRRs), such as Toll-like receptors (TLRs) and retinoic-acid inducible gene 1-like receptors (RLRs), complement receptors, CD48, and integrins (Sandig and Bulfone-Paus, 2012; Reber et al., 2015). PRR expression is not uniform across mast cell populations, however, and varies both with the tissue localization of the MCs and activating stimuli present (Saluja et al., 2012; Sandig and Bulfone-Paus, 2012; Agier et al., 2016; Akula et al., 2020; Plum et al., 2020). The diversity of activating receptors expressed by MCs make these cells versatile and capable of prolonged activation, able to release multiple waves of mediators, which vary with time, stimulus, and cellular environment (Gri et al., 2012).

MCs have long been associated with allergic responses and asthma; however, an important niche for MCs in host defense

against infection and injury has been established (Rathore and St John, 2020). MCs play a protective role in a number of viral, bacterial, and parasitic infections, and mitigate tissue damage caused by exposure to animal venoms and toxins (Abraham and St John, 2010; Reber et al., 2015; Marshall et al., 2019). In addition to producing an array of cytokines and chemokines, including type 1 and 3 IFNs, IL-1 α , IL-1 β , IL-4, IL-6, IL-8, IL-10, IL-17, IL-33, TNF- α , TGF- β , SCF, CCL2, CCL3, and CCL5, MCs produce proteases chymase and tryptase capable of degrading toxic peptides and venoms (Metz et al., 2006; Akaoshi et al., 2011; Gri et al., 2012). MCs have been found to phagocytose a number of gram-positive and gram-negative bacteria including *Escherichia coli*, *Klebsiella pneumoniae*, and *Mycobacterium tuberculosis*, releasing TNF- α and reactive oxygen species in response (Abraham and Malaviya, 1997; Arock et al., 1998; Munoz et al., 2009; Abraham and St John, 2010). As tissue resident immune cells, MCs are uniquely poised to respond immediately at the site of infection or injury and persist through the duration of the infection or wound healing—inducing a pro-inflammatory environment, remodeling the cellular architecture, activating tissue resident immune cells, and recruiting additional immune responders from the periphery (Abraham and St John, 2010; Reber et al., 2015; Marshall et al., 2019).

Thorough investigations of the MC pro-inflammatory cytokine profile during viral infections have been published (Graham et al., 2015; Marshall et al., 2019). However, the presence of anti-inflammatory or immune suppressive cytokines of MC origin at the site of infection also suggests that MCs play a role in the “ramp down” of the immune response as infection is cleared (Galli et al., 2008; Reber et al., 2015). Two such cytokines are IL-10 and IL-6, which have been shown to be powerful mediators of inflammation during influenza infection (Sun et al., 2009; Yu et al., 2011; Yang et al., 2017). IL-10 is the founding member of the IL-10 family of structurally similar cytokines that also includes IL-19, IL-20, IL-22, IL-24, IL-26, and the type III IFNs (Ouyang et al., 2011). IL-10 binds the cell surface receptors IL-10R1 and IL-10R2 which heterodimerize, activating the STAT3 signaling pathway and inhibiting production of pro-inflammatory cytokines (Kotenko et al., 1997; Takeda et al., 1999; Walter, 2014). IL-6 is a pleiotropic cytokine often associated with strong inflammatory responses but that can function as a powerful anti-inflammatory mediator as well (Hunter and Jones, 2015; Jones and Jenkins, 2018). All members of the IL-6 family of cytokines signal through the membrane glycoprotein gp130 (Silver and Hunter, 2010). IL-6 signaling requires binding to soluble or membrane-bound IL-6R α which, in turn, interacts with gp130 (Jones et al., 2001; Hunter and Jones, 2015). Homodimerization of IL-6:IL-6R α -bound gp130 activates the STAT3 signaling pathway (Heinrich et al., 2003). While IL-6R α expression is confined predominantly to leukocytes and hepatocytes, gp130 is universally expressed (Hunter and Jones, 2015). Interactions in *trans* between gp130 and membrane-bound or soluble IL-6:IL-6R α complexes allows IL-6 to signal to a range of cell types that are otherwise unresponsive to IL-6 and contributes to the diversity of downstream effects triggered by IL-6 signaling (Peters et al., 1996; Hunter and Jones, 2015; Reeh et al., 2019). In this review, we will address the mechanisms by which MCs suppress the immune response as infection or injury resolves and discuss a

potential role MCs in mitigating inflammatory tissue damage in influenza-infected lungs.

MAST CELL RECRUITMENT TO THE LUNG DURING INFLUENZA A VIRUS INFECTION

MCs accumulate in the lungs of mice infected with both seasonal and pandemic strains of influenza (Josset et al., 2012; Morrison et al., 2014; Zarnegar et al., 2017). Lung resident MCs are likely amongst the first cells to respond to the presence of influenza in the lungs, and MCs progenitors (MCps) in the lung proliferate during influenza infection. However, the majority of the increase in MC population in the upper airways appears to derive from MCps recruited from the blood (Zarnegar et al., 2017). Respiratory virus infection of lung epithelial cells induces expression of the vascular cell adhesion molecule-1 (VCAM-1) which is required for the recruitment and infiltration of circulating MCps into the infected lung (Wang et al., 2000; Abonia et al., 2006; Zarnegar et al., 2017). These recruited progenitors proliferate rapidly after infection and remain in lung tissue up to three weeks post-infection, a time point at which most inflammation the lung has resolved. Recruitment and proliferation of MCps has also been detected in the lung tissue of children with viral lower respiratory tract infections such as severe influenza (Andersson et al., 2018).

A number of cytokines and chemokines have been identified to play a substantial role in MCp recruitment, although none have been identified as essential. For example, administration of the TLR3-agonist PolyI:C or the cytokine IL-33 induces moderate MCp recruitment to the lungs (Zarnegar et al., 2018). However, influenza infection of *Tlr3*^{-/-} or IL-33 receptor *Il1rl1*^{-/-} mice showed no reduction in MC progenitor recruitment. Influenza-infected alveolar macrophages and pulmonary epithelial and endothelial cells produce a number of additional cytokines and chemokines that are known MCp attractants (**Table 1**) (Sprenger et al., 1996; Matsukura et al., 1998; Herold et al., 2006; Hallgren et al., 2007; Kim et al., 2008; Jones et al., 2009; Chan et al., 2010a; Chan et al., 2010b; Collington et al., 2010; Teijaro et al., 2011). Mice deficient in these cytokines or chemokines, which include IL-4, IFN- γ , CCL2, CCL3, and CCL5 (RANTES), have reduced but not complete absence of MCp recruitment to the lung (Hallgren et al., 2007; Jones et al., 2009; Collington et al., 2010). The expression of multiple, redundant molecules able to recruit MCps ensures that MCs arrive promptly at the site of infection and rapidly mount a defense against the virus, as supported by the lack of a significant phenotype in many singly-deficient mice.

PATHWAYS OF MAST CELL ACTIVATION DURING INFLUENZA A VIRUS INFECTION

MCs are activated during influenza infection through a variety of signals and stimuli present in the infected lung. Activation has

been observed to occur through Fc-mediated signaling, PRRs, and cytokine and complement signaling (Reber et al., 2015). Activation of MCs early in infection likely occurs in response to stimulation by cytokines and other distress signals produced by infected cells and other immune and non-immune resident cells of the lung while stimulation during the adaptive immune response may include Fc-mediated activation (Graham et al., 2015; Marshall et al., 2019). Teasing these responses apart is difficult as multiple stimuli are likely interacting with MCs simultaneously (Gri et al., 2012). Furthermore, activating signals need not derive solely from other cell types, but can also be the result of autocrine and paracrine signaling from the MCs themselves (Oldford et al., 2018; Marshall et al., 2019).

As described in the previous section, infection of the epithelial-endothelial barrier and of alveolar macrophages releases a flood of chemoattractant molecules as well as a variety of activating and signaling cytokines, including type I IFNs, TNF- α , IL-1 α , IL-1 β , and IL-33 (Sanders et al., 2011; Teijaro et al., 2011). Engagement of these cytokines with their respective receptors on the surface of MCs triggers degranulation of the cell within minutes and initiates antiviral signaling cascades within the cell, leading to the transcription, translation and secretion of the MCs' own repertoire of cytokines and chemokines. Cytokines such as IL-4, IL-5, IL-6, IL-8, IL-13, and TNF- α , chemokines such as CCL2 and CCL3, and the MC proteases tryptase and chymase can be detected in the supernatants of influenza infected MC cultures and in the bronchioalveolar lavage fluid (BALF) of both influenza patients and infected mice (**Table 2**) (Yu et al., 2011; Hu et al., 2012; Graham et al., 2013; Betakova et al., 2017). Multiple signals are required before MC degranulation occurs during respiratory infection. Infection of MCs in culture with rhinovirus or respiratory syncytial virus (RSV) or treatment with type I IFNs alone does not result in degranulation but does induce secretion of CCL4, CCL5, CXCL10, and additional type I and type III IFNs (Al-Afif et al., 2015; Akoto et al., 2017).

MCs rely on activating signals in combination to dictate the appropriate induction and amounts of downstream mediators. For example, while IL-33 alone induces expression of the Intercellular Adhesion Molecule-1 (ICAM-1) on MCs, concomitant binding of neuropeptide Substance P to the cell surface strongly induces production of TNF (Drube et al., 2016; Taracanova et al., 2017). Similarly, IL-1 alone induces production of IL-3, IL-5, IL-6, IL-9, and TNF- α by MCs in human cultured MCs (HCMCs) and murine bone marrow-derived MCs (BMMCs) but in combination with IL-4, TNF- α , or a synthetic double-stranded RNA TLR3 agonist, IL-1 induces much higher levels of IL-5 and IL-6 secretion (Hultner et al., 2000; Kandere-Grzybowska et al., 2003; Kandere-Grzybowska et al., 2006; Nagarkar et al., 2012).

MCs express a wide variety of PRRs, capable of detecting an array of pathogen products. Intracellular pathogen detection and innate immune pathways play a role in MC activation in response to influenza virus infection (Sandig and Bulfone-Paus, 2012). The mouse mastocytoma cell line P815 has been used extensively to probe the cytokine and chemokine expression

TABLE 2 | *In vivo* cytokine and chemokine expression during influenza virus infection.

Human				
Strain	Tissue	Biological observations*		Reference
H1N1	Serum	Increased IL-6 expression correlates with disease severity		Chiaretti et al. (2013)
H1N1 (pandemic)	Plasma	Influenza patients had higher TNF- α , IFN γ , IL-2, IL-5, IL-6, IL-10, and IL-12 Severe influenza patients had increased IL-6 and IL-10 but lower TNF- α , IFN γ , and IL-5 compared to mild disease patients		Yu et al. (2011)
H7N9	Plasma	Increased TNF- α , IFN γ , IL-4, IL-10, and IL-12 in patients with severe disease		Han et al. (2014)
Unknown	Serum	Upregulation of IL-37 in influenza A patients		Zhou et al. (2019)
Mouse				
Virus	Model	Tissue	Biological observations*	Reference
H1N1	Balb/C	Lung	Differential cytokine and chemokine expression between lethal and sublethal infections	Turianova et al. (2019)
H1N1	Balb/C	Lung	Young mice express less IL-10 and more IFN γ than adult mice, corresponding to increased immune pathology	Verhoeven and Perry (2017)
H1N1	C57BL/6	BALF	IL-10 ^{-/-} mice had increased IFN- γ but reduced IFN- α expression	Sun et al. (2010)
H1N1	C57BL/6 6.IL-10 ^{-/-}	Lung	Elevated IL-6, IL-17, and IL-22 in IL-10 ^{-/-} mice	Mckinstry et al. (2009)
H1N1 (pandemic)	C57BL/6 6.IL-10 ^{-/-}	BALF	IL-6 signaling is essential for survival of infection and for prevention of virus-induced neutrophil cell death	Dienz et al. (2012)
H1N1	C57BL/6	BALF	SIPR signaling mediates induction of type I and II IFNs, IL-1 α , IL-6, TNF- α , CCL2, CCL3, CCL5, and CXCL2	Tejaro et al. (2011)
H1N1	C57BL/6 6.IL-10 ^{-/-}	Lung	IL-6 deficiency increases morbidity, TGF- β , and epithelial cell apoptosis IL-6 is essential for macrophage recruitment	Yang et al. (2017)
H1N1 (pandemic)	Balb/C	Lung	Increased transcription of inflammatory genes with mouse adaption of virus	Josset et al. (2012)
H1N1 (pandemic)	Balb/C	Lung	IL-37 treatment inhibited increase inflammatory cytokine expression	Qi et al. (2019)
H1N1	Balb/C	Lung	Strain-dependent differential induction of type I and II IFNs, IL-6, CXCL10, and CCL4	Morrison et al. (2014)
H5N1				
H7N9				
H3N2	Balb/C	Skin	IAV antigen-IgE cutaneous anaphylaxis in IAV-recovered mice	Grunewald et al. (2002)
H3N2	C57BL/6 6.TGF β ^{-/-}	BALF	Reduced IFN β , inflammation, and neutrophil, macrophage, and monocyte infiltration in TGF β ^{-/-} mice	Denney et al. (2018)
H5N1	C57BL/6	Lung	Upregulation of TNF- α , IFN γ , IL-1 α , IL-6, IL-10, IL-12, and chemokines Downregulation of IL-1 β , IL-2, and IL-9	Jang et al. (2012)
Pig				
Virus	Tissue	Biological observations*		Reference
H1N1	Lung	Higher mortality, lower TNF- α and IFN γ , and higher IL-10 after alveolar macrophage depletion		Kim et al. (2008)

*Relative to controls.

profiles of influenza-infected MCs. Expression of IL-6, IL-18, TNF- α , IFN- γ , and CCL2 increase within 24 h of infection of P815 cells with either a H1N1, H5N1, or H7N2 strain of IAV (Hu et al., 2012; Liu et al., 2014). Infection of P815 cells also causes significant cytopathic effect (CPE) and cell death, an effect not reported in influenza-infected MCs cultured from hematopoietic stem cells of the bone marrow (mice), peripheral blood (human), or umbilical cord blood (human) (Hu et al., 2012; Liu et al., 2014). Although cultured human and mouse MCs are vulnerable to infection by a number of strains of

IAV, the infection appears to be largely abortive, producing little to no detectable progeny (Graham et al., 2013; Marcet et al., 2013; Ng et al., 2019). Nonetheless, replication of viral RNA and production of viral protein has been observed in cultured MCs (Kulka et al., 2004; Graham et al., 2013). In influenza inoculated BMMCs, signaling through double-stranded RNA-sensing PRRs RIG-I and TLR3 strongly induces IL-6 and the proinflammatory leukotriene LTB₄ (Graham et al., 2013). Infection of cells lacking RIG-I or its adaptor MAVS fail to produce IL-6 or LTB₄. The deficient cells, nonetheless, secreted equivalent levels of

histamine to wild type cells, suggesting degranulation of MCs during influenza infection is independent of RIG-I signaling. Treatment of HCMCs and murine BMMC with RSV, UV-inactivated influenza, or reovirus induces type 1 IFN secretion in a TLR3-dependent manner. BMMCs from *TLR3*^{-/-} mice degranulate upon treatment the synthetic dsRNA PolyI:C but fail to induce type 1 IFNs (Kulka et al., 2004). PRR pathogen sensing function appears to function in parallel and in combination with cytokine, chemokine, and small molecule signaling to drive the MC response to infection.

Fc receptor-mediated stimulation of MCs likely occurs as the influenza infection progresses and B cells begin producing antibodies specific to the ongoing infection. IAV-specific IgE can be detected in mice one week after influenza infection, and intradermal rechallenge with IAV antigen results in MC degranulation and cutaneous anaphylaxis (Grunewald et al., 2002). The role of antiviral antibody responses in MC activation (*via* Fc receptor binding or complement proteins) during acute influenza infection has not been studied but serves to highlight the numerous and diverse stimuli presented to MCs over the course of infection. Not only do MCs encounter multiple stimuli at any given timepoint during infection, but the profile of the stimuli also evolves as additional innate cells arrive at the site of infection and later, as the immune response transitions from innate to adaptive. The vast assortment of activating receptors expressed by MCs allows the cells to detect fluctuations in the nature and volume of incoming signals and modulate their responses accordingly.

IMMUNOMODULATORY FUNCTION OF MAST CELLS

The lungs of influenza virus infected patients contain a great number of cytokines, chemokines, and other immunomodulatory molecules (**Table 2**). Quantification of cytokine expression during human infection with various seasonal and pandemic strains of influenza shows differential expression not only across strains but between mild and severe disease as well. Patients with pandemic H1N1 2009, both mild (respiratory symptoms) and severe (pneumonia) cases, had elevated serum IL-10 and IL-6 compared to healthy controls and patients with mild or severe non-influenza illnesses (Yu et al., 2011). Severe cases had significantly higher IL-10 and IL-6 than mild cases, but no difference in IFN- γ , TNF- α , IL-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-17, or IL-23 was reported. Similar cytokine profiles have been recorded in patients infected with avian H5N1 and H7N2 strains (Betakova et al., 2017). Because severe influenza is linked to excessive inflammation in the lung, much effort has been expended in defining the role of these cytokines in mild and severe influenza.

While most studies examining the role of MCs during influenza virus infection have focused on MC-derived pro-inflammatory cytokines, a growing body of work highlights the immune suppressive or anti-inflammatory properties of MCs (Galli et al., 2008). The roles of individual pro-inflammatory

cytokines and the cell types that produce them, including MCs, have been comprehensively reviewed elsewhere (Graham et al., 2015; Ramos and Fernandez-Sesma, 2015). Although the immune suppressive functions of MCs have not yet been examined in the context of influenza infection specifically, the effects have been identified in a broad array of immune insults, suggesting that immune suppression by MCs is a conserved function that contributes to the resolution of infection and tissue damage. In the following sections, we will discuss the potential contribution of MCs to immune suppression at the resolution of influenza infection.

IL-10

Over the past decade, surprising evidence has emerged suggesting an important role of MC produced IL-10 in the regulation of inflammation during infection and tissue damage. In the skin, MCs play a vital role in reducing the pathology of allergic reactions such as to poison ivy and poison oak, as well as the sunburn caused by chronic exposure to ultraviolet B (UVB) light (Hart et al., 1998; Grimbaldston et al., 2007). Mice lacking IL-10 and those lacking MCs altogether suffered significantly more tissue damage than wild type mice after exposure to poison oak or poison ivy or after prolonged exposure to UVB. In addition to increased tissue swelling and epithelial cell death at the site of exposure, IL-10-deficient and MC-deficient mice had higher infiltration of effector T cells and macrophages in the damaged tissue. Deficiency also delayed recovery and healing at the injured site. Of note, mice lacking IL-10 healed from UVB exposure more quickly than the MC-deficient mice, indicating additional anti-inflammatory mechanisms employed by MCs. The authors also found that IL-10 expression was reduced but not absent in mice with MCs lacking the common γ -chain of the Fc receptor and therefore, lacking signaling in response to IgE or IgG. The presence of intermediate levels of IL-10 expression in the absence of Fc-mediated signaling indicates that multiple signaling pathways induce IL-10 expression in MCs. Mosquito saliva elicits IL-10 production by MCs and reduces the inflammatory response at the bite (Depinay et al., 2006). Mice lacking MCs or IL-10 have increased tissue inflammation and higher levels of pro-inflammatory cytokines such as IFN- γ in response to mosquito saliva. Tissue damage caused by other animal venoms, such as those of reptiles and insects, is mitigated both by release of MC-derived proteases capable of degrading the venom and by suppression of aggressive inflammatory responses at the site of injury (Depinay et al., 2006; Metz et al., 2006; Schneider et al., 2007; Akahoshi et al., 2011; Marichal et al., 2013; Starkl et al., 2016). Interestingly, in models of mild contact hypersensitivity (CHS), MCs behave in a largely pro-inflammatory manner and express little to no IL-10 (Biedermann et al., 2000; Bryce et al., 2004; Norman et al., 2008; Dudeck et al., 2011; Reber et al., 2017). However, in severe CHS models, MCs appear to convert to an anti-inflammatory state, expressing high levels of IL-10 (Norman et al., 2008; Reber et al., 2017; Gaudenzio et al., 2018; Galli et al., 2020). Although not directly correlative to the differential disease severity caused by different IAV strains, this work suggests that the anti-

inflammatory functions of MCs may be particularly responsive when the inflammatory state is severe.

Although IL-10 is consistently upregulated in severe influenza cases in humans, the full extent of the immune regulatory role of IL-10 during influenza infection has not been explored. A case study of a child with a deletion in the *IL10RA* gene resulted in excessive pro-inflammatory cytokine expression and fatal encephalitis as a result of influenza infection (Ishige et al., 2018). His death is attributed to the failure of IL-10 to mitigate the influenza-induced inflammatory response, suggesting that IL-10 is vital to tempering severe influenza-mediated inflammation. Studies examining the role of IL-10 in the immune response to influenza infection have produced conflicting results, however. Similar to the strong induction of IL-10 in patients with severe influenza, infection of Balb/C mice with a lethal dose (LD100) of H1N1 A/Puerto Rico/8/34 (PR8) induced strong IL-10 expression (Turianova et al., 2019). A lower, nonlethal dose (LD0) did not induce IL-10. Furthermore, *Il10*^{-/-} Balb/C mice infected with a nonlethal dose of H1N1 PR8 show identical morbidity to wild type Balb/C mice (Mckinstry et al., 2009). When challenged with a lethal dose of H1N1 PR8, the IL-10-deficient mice had reduced mortality but equivalent weight loss and only slightly elevated inflammation when compared their wild type counterparts at days 6-7 post-infection. A study by Sun, et al. likewise observed similar lung pathology and immune cell infiltration in IL-10-deficient and IL-10-sufficient C57BL/6 mice infected with nonlethal and lethal doses of H1N1 PR8 (Sun et al., 2010). In contrast, several studies have shown that absence of IL-10 signaling results in enhanced lung pathology, partially attributed to high levels of CD8+ T cells activity in mice (Zou et al., 2014). Antibody blockade of the IL-10 receptor severely reduced survival of Balb/C mice infected with H1N1 PR8 (Sun et al., 2009). *In vitro*, addition of IL-10 to cultures of splenic CD8+ T cells collected from mice 5 days post-influenza infection halted proliferation of these cells (Zou et al., 2014). Dutta, et al. proposes a biphasic effect of IL-10 during infection wherein IL-10 released early in infection inhibits viral neuraminidase enzymatic function (Dutta et al., 2015). As infection wanes and the concentration of viral particles decreases, the IL-10 is available to bind to IL-10R and activate negative immune regulation. Injection of IL-10-deficient mice with exogenous IL-10 at 4 days post-infection (p.i.) greatly reduced morbidity, and all IL-10 recipient mice survived infection. Young mice, roughly equivalent to human infants and toddlers, produce less IL-10 in the lungs and at a later time point than adult mice during influenza infection (Verhoeven and Perry, 2017). During infection, young mice also have higher levels of macrophage infiltration, immune pathology, delayed viral clearance, and delayed antibody production, suggesting the lower levels of IL-10 delay the switch from innate to adaptive responses. The reduced IL-10 response in young children may partially explain why they are among the most vulnerable to developing severe influenza. The role of IL-10 in mitigating influenza infection appears to depend on a number of factors, not only the age of the patient, but the strain and dosage of the infecting virus as well. Additional work

is needed to understand if these conflicting data are reproducible in more outbred animal models or humans, and whether the use of strains other than H1N1 PR8, a laboratory strain passaged outside of humans for more than 70 years, will yield different and perhaps more interpretable results.

IL-6

IL-6 has been implicated as a master controller of the shift from the innate to the adaptive immune response (Xing et al., 1998; Hurst et al., 2001; Jones, 2005). A human polymorphism in the promoter region of the human *IL6* gene contributes to increased IL-6 production. People with the -174G polymorphism have lower incidence of acute respiratory distress syndrome (ARDS) and mortality associated with ARDS in cases of community-acquired pneumonia (Terry et al., 2000; Martin-Loeches et al., 2012). People with an *IL6* polymorphism resulting in low IL-6 production have increased susceptibility to disease after rhinovirus or RSV exposure (Fishman et al., 1998). In agreement with these findings, commonly prescribed drugs that target IL-6 or its receptor IL-6R for treating inflammatory diseases such as rheumatoid arthritis also increase risk of both upper and lower respiratory infection (Lang et al., 2012; Van Rhee et al., 2014). Finally, in a murine acute lung injury and ARDS model, MC-derived IL-6 induces apoptosis in lung-infiltrating neutrophils, which are also known to contribute to influenza-associated inflammation and immune pathology (Ganeshan et al., 2013).

Like IL-10, IL-6 is highly upregulated during severe IAV infection of both humans and mice (Yu et al., 2011; Chiaretti et al., 2013; Betakova et al., 2017). While the high levels of IL-6 in severe influenza have been taken as an indication that IL-6 plays a role in exacerbating lung inflammation, recent work has demonstrated that IL-6 is, in fact, essential for reducing lung pathology during influenza infection. IL-6-deficient mice have increased morbidity and mortality when infected with H1N1 A/WSN/33 (Yang et al., 2017). When infected with H1N1 PR8 or pandemic H1N1 A/California/7/2009 at a dose that is sublethal in wild type mice, all IL-6-deficient mice died between 10 and 12 days p.i. (Dienz et al., 2012; Montier et al., 2012). Wild type and IL-6 deficient mice had equal numbers of inflammatory cells present in the lungs on days 9 through 11 p.i. However, both IL-6-deficient and IL-6R-deficient mice had extensive vascular leakage, emphysema-like swelling of the alveoli, and widespread cell death of the airway epithelium (Dienz et al., 2012; Yang et al., 2017). IL-6 deficient mice also had increased collagen deposition and fibroblast accumulation, indicative of developing fibrosis (Yang et al., 2017). In culture, IL-6-mediated crosstalk between human intestinal MCs and fibroblasts promotes MC survival, while also inducing fibroblast apoptosis through the production of the fibrolytic enzyme matrix metalloproteinase 1 (MMP-1) (Montier et al., 2012). IL-6-deficient mice did not develop severe lung pathologies until late in the course of infection, at a time when wild type mice are typically recovering, suggesting that the absence of IL-6 compromises recovery of the lung after infection.

An examination of the anti-inflammatory effects of IL-6 revealed increased levels of TNF- α , IFN- γ , GM-CSF, and CXCL2 in IL-6

deficient mice after inhalation or intraperitoneal injection of endotoxin (Xing et al., 1998). The survival rate of endotoxemic IL-6 deficient mice was 50% lower than wild type mice injected with endotoxin. Exogenous administration of IL-6 reduced pro-inflammatory cytokine expression to wild type level. Reciprocal regulation of IL-6 and TNF- α has been well established (Petersen and Pedersen, 2006; Tanaka et al., 2014). While TNF- α -induced NF κ B signaling induces IL-6 production, IL-6 appears to inhibit TNF- α expression, through upregulation of microRNAs that prevent TNF- α mRNA translation, downregulation of TNF- α -inducing PRRs, and induction of other anti-inflammatory cytokines such as IL-10 (Aderka et al., 1989; Schindler et al., 1990; Tanaka et al., 2014; Li et al., 2015). Administration of a TNF- α -blocking antibody rescues wild type mice from lethal endotoxin exposure (Barton and Jackson, 1993). Similarly, antibody inhibition of TNF- α reduces lung pathology, levels of IFN- γ , IL-4, and IL-5, and weight loss in mice infected with influenza or RSV (Hussell et al., 2001). The absence of TNF- α did not impair viral clearance of either infection. IL-6 and IL-13 produced by MCs stimulated with IL-33 drives polarization of anti-inflammatory alternatively activated (M2) macrophages, and in a murine model of autoimmune encephalitis, inhibited pro-inflammatory cytokine secretion by T cells (Finlay et al., 2020). In spite of the pathological role of IL-6 and TNF- α in chronic inflammatory diseases, the anti-inflammatory contribution of IL-6 to the resolution of infectious disease through mitigation of damage to the lung architecture, and reduction of proinflammatory cytokine production is clear (Tanaka et al., 2018). The role of MCs in mediating IL-6 expression during influenza infection, however, remains to be fully explored.

Additional Cytokines With Immune Suppressive Potential

The complex and rapidly changing immune landscape during infection presents a great challenge to fully mapping the signaling networks and downstream effects of MCs and the cytokines these cells produce. In addition to IL-10 and IL-6, MCs produce an array of cytokines with both pro- and anti-inflammatory functions (Mukai et al., 2018; Galli et al., 2020). MC-derived cytokines of potential interest in suppressing influenza immunopathology include: TNF α , TGF- β 1, GM-CSF, IL-2, IL-9, IL-13, and IL-33 (De Vries and Noelle, 2010; Mukai et al., 2018). However, these cytokines are also expressed by a number of other immune cell types during infection, and the cell type of origin appears to play a significant role in the downstream signaling, likely due to co-expression of other cytokines and the specific microenvironment.

For example, autocrine and paracrine signaling by MC-derived TGF- β 1 restricts the release of a variety of mediators, including IL-6, IL-13, TNF, GM-CSF, and histamine (Gordon and Galli, 1994; Bissonnette et al., 1997; Lindstedt et al., 2001; Zhao et al., 2008; Fernando et al., 2013). In contrast, membrane-bound TGF- β 1 on regulatory T cells (T_{regs}) induces IL-6 production by MCs (Ganeshan and Bryce, 2012). Like TGF- β 1, the outcome of TNF α expression appears heavily dependent on cell source, tissue localization, and TNF receptor (TNFR) expression (De Vries and Noelle, 2010). One of the earliest

sources of TNF α during infection, MCs can release pre-formed TNF α *via* degranulation immediately upon pathogen detection (Gordon and Galli, 1990). Immunopathology attributable to excessive TNF α has been observed in a number of infections as well as inflammatory disorders (Bradley, 2008). Treatment of mice with an TNF- α inhibitor at the time of lethal H1N1 influenza infection conferred a protective advantage over untreated mice (Shi et al., 2013). Interestingly, this protective effect was not observed in mice infected with an H5N1 strain of influenza (Salomon et al., 2007). TNF α -deficient mice infected with a sublethal dose, however, presented with greater lung pathology, inflammatory cell infiltration, and recovered from infection more slowly than wild type mice (Damjanovic et al., 2011). These studies suggest a biphasic role for TNF α in the immune response to influenza infection, similar to IL-6 described in the previous section.

IL-9 has similar paradoxical effects on the inflammatory environment. Produced by T helper Th9 cells as well as MCs and type 2 innate lymphoid cells (ILC2s), IL-9 is strongly upregulated in patients infected with avian H7N9 influenza and in mice infected with H1N1 or H5N1 (Hultner et al., 2000; Stassen et al., 2000; Jang et al., 2012; Hamada et al., 2013; Han et al., 2014; Artis and Spits, 2015; Kaplan et al., 2015). Autocrine IL-9 and Th9-derived IL-9 contribute not only to MC recruitment and proliferation in the lung but also to TGF- β 1 production by MCs, which can have suppressive effects on MCs as well as other immune cells as discussed above (Hultner et al., 1990; Godfraind et al., 1998; Matsuzawa et al., 2003; Kearley et al., 2011; Sehra et al., 2015). Like TGF- β 1, IL-9 expression and function appears to be regulated in a location- and temporally-specific manner.

Likewise, release of GM-CSF by MCs may play a role both in increasing inflammation and in mitigating the development of immune pathology and lung injury. Responsible for immune cell maturation, recruitment, and activation, GM-CSF in high levels is a source of inflammation in multiple sclerosis, arthritis, Kawasaki disease, chronic obstructive pulmonary disease, and lung interstitial disease (Becher et al., 2016; Hamilton, 2019). During influenza infection, however, GM-CSF appears to play an important role in reducing inflammation and inducing anti-inflammatory M2 macrophages (Huang et al., 2011; Rosler and Herold, 2016). Mice lacking GM-CSF succumbed to lethal H1N1 and H3N2 infections more quickly than wild type mice, while all GM-CSF-overexpressing transgenic mice survived infection, had lower viral titers, and reduced lung pathology (Huang et al., 2011; Subramaniam et al., 2015). Intranasal administration of recombinant GM-CSF protected GM-CSF-deficient mice from lethal infection (Huang et al., 2011). GM-CSF overexpression reduced inflammatory cytokine levels and drove macrophage polarization toward the immune suppressive M2 phenotype (Halstead et al., 2018). While the role of MC-derived GM-CSF during influenza has yet to be examined, MC-deficient mice reconstituted with GM-CSF^{-/-} MCs reject skin allografts. In contrast, GM-CSF sufficient mice tolerated engraftment through recruitment long-lived, immune-suppressing dendritic cells, suggesting that through GM-CSF, MCs direct localization and function of additional immune regulatory cell types.

The contribution of individual cytokines to the defense against influenza infection and to what degree their activity drives or impedes the inflammatory tissue damage associated with severe disease will require extensive further research. Differentiating between the positive and negative outcomes of the signaling of a single cell type or a single cytokine, however, is severely impeded by the complex networks of cell signaling in the inflammatory environment, particularly over the course of viral infection. To fully understand the impact of these cytokines in the complex immune environment of an ongoing infection, the many cell types and the mediators they produce will have to be examined both individually and as a part of the whole. While a daunting endeavor, advances in mouse genetics, live imaging, and immune phenotyping have greatly expanded the toolset for examining such complex networks (Reber et al., 2017; Galli et al., 2020).

Other Mast-Cell Derived Immune Mediators

MCs modulate the immune environment not only through the production of cytokines and chemokines but also by the expression of molecules capable of inhibiting or degrading cytokines and other signaling molecules produced by other cells. For example, MCs purified from human lungs respond to IgE-stimulation by producing the IL-1 receptor antagonist (IL-1Ra) (Hagaman et al., 2001). IL-1Ra binds the IL-1 receptor (IL-1R) with high affinity, outcompeting IL-1 α and IL-1 β and preventing the pro-inflammatory signaling of these cytokines (Dinarello, 2019). Production of the glucosaminoglycan heparin by MCs reduces inflammatory cell migration by downregulating intercellular adhesion molecule-1 (ICAM-1) on endothelial cells and blocking selectin and chemokine receptor binding of circulating leukocytes (Nelson et al., 1993; Miller et al., 1998; Kuschert et al., 1999; Wang et al., 2002). In addition to halting the migration of immune cells into the target tissue, heparin downregulates proinflammatory cytokine expression by downregulating ERK and NF- κ B signaling in lung epithelial cells (Yi et al., 2015). MC proteases also have anti-inflammatory effects, degrading proinflammatory cytokines and alarmins such as TNF and IL-33 (Piliiponsky et al., 2012; Hendrix et al., 2013; Roy et al., 2014). Theoharides, et al. has proposed a mechanism for MC-mediated control of the anti-inflammatory cytokine IL-37 through alternating expression of heparin and tryptase (Theoharides et al., 2019). IL-37 producing cells, such as macrophages, NK cells, activated B cells, and epithelial cells, secrete both the highly active IL-37 and the moderately active pro-IL-37, which requires protease cleavage to be fully active (Eisenmesser et al., 2019; Li et al., 2019). Heparin promotes formation of an inactive homodimer of IL-37 while protease cleavage converts pro-IL-37 to the fully active form, similar to the cleavage required to produce mature IL-33 (Lefrancais et al., 2014; Cavalli and Dinarello, 2018; Eisenmesser et al., 2019). Theoharides, et al. speculate that MCs may modulate the degree of inflammation at the site of infection by temporal modulation of heparin-mediated IL-37 inhibition and tryptase-mediated IL-37 activation (Theoharides et al., 2019). This hypothesis is particularly intriguing in regard to influenza infection: although IL-37 is detectable in the humans and mice throughout influenza infection, exogenous administration of

IL-37 only produced beneficial effects in infected mice late in infection, suggesting that IL-37 may be sequestered in some manner early in infection (Qi et al., 2019; Zhou et al., 2019). Influenza infection induces a variety of cytokines in the lung; how MC mediators that activate, inhibit, or degrade those cytokines control the pro- or anti-inflammatory environment in the lung remains to be fully investigated.

MAST CELLS IN OTHER VIRAL INFECTIONS

Whether MCs have a net positive or negative effect on influenza infection has yet to be determined and likely depends largely on the severity of infection. Human MC deficiency has never been identified, though as a result of being clinically inconspicuous or lethally critical for embryonic development is unknown (Rodewald and Feyerabend, 2012). Mastocytosis—excessive proliferation and accumulation of MCs—appears to rarely cause pulmonary symptoms, though rhinitis is common (Castells and Austen, 2002). Systemic mastocytosis patients participating in a clinical trial of the Kit tyrosine kinase inhibitor midostaurin, however, reported increased upper respiratory tract infections during treatment, leading a number to discontinue the trial (Kasamon et al., 2018). Midostaurin, and other tyrosine kinase inhibitors used to treat mastocytosis such as imatinib, are not Kit-specific inhibitors (Karaman et al., 2008). In addition to Kit, midostaurin binds tyrosine kinases FLT3, VEGFR, and PDGFR, inhibiting maturation and activation of a number of immune cell types, including NK cells and DCs (Huang et al., 2010; Wiernik, 2010; Valent et al., 2017; Gutierrez et al., 2018). Whether the increased risk of respiratory infection in mastocytosis-patients treated with midostaurin is the result of reduced mast cell numbers in combination with the inhibition of other immune cell types has not yet been investigated (Valent et al., 2017).

In vivo studies of MC are most commonly conducted in mice deficient in MCs as a result of mutations in *c-kit*, although these mice have non-MC hematopoietic abnormalities that have prompted the development of *Kit*-independent MC-deficient mice (Galli et al., 2020). Influenza infection of MC-deficient *Kit* mice has produced contradicting results. When infected with H1N1 A/WSN/33, MC-deficient mice exhibited reduced morbidity and mortality compared to MC-sufficient C57BL/6 mice (Graham et al., 2013). MC-deficient *Kit* mice adoptively transferred with murine BMMCs also had elevated morbidity and mortality, on par with the C57BL/6 mice. The lungs of infected C57BL/6 mice had higher levels of macrophage and neutrophil infiltration and TNF- α than the infected MC-deficient mice. In contrast, after infection with H1N1 PR8, no differences in morbidity or mortality were observed regardless of MC sufficiency. Clearly, strains of even the same influenza subtype induce disparate immune responses. Examination of the immune profiles, including cell types and cytokines, over the duration of infection with different influenza strain and subtypes, both human isolates and mouse-adapted strains, will be required to unravel the different responses induced by different viruses.

Studies of other viral infections provide insight into what immunomodulatory roles MCs may be playing during influenza infection (**Table 3**). In a murine model of vaccinia virus infection, dermal inoculation of the virus produces a large skin lesion in MC-deficient mice within 24 h that continues to expand over time (Domenico et al., 2012; Wang et al., 2012a; Wang et al., 2012b). In contrast, MC-sufficient mice and MC-reconstituted mice develop only small pinpoint lesions 3 days post-infection. MC-deficient mice had much higher viral loads at the site of infection as well as in the spleen compared to MC sufficient mice

(Wang et al., 2012a). MC numbers in MC-sufficient and MC-reconstituted mice rose significantly at the site of lesions, although whether the increase was a result of recruitment of MC progenitors or proliferation of resident MCs was not investigated. High expression of both TNF- α and IL-6 were present in the MC-deficient lesions, suggesting an anti-inflammatory role for MCs in vaccinia infection. Of particular interest was the expression of IL-6 which is not usually seen in vaccinia infection, suggesting MCs may control pro-inflammatory IL-6 expression by other cell types. In addition

TABLE 3 | *In vivo* studies of mast cells during viral infections.

Human				
Virus/strain	Tissue		Biological observations*	Reference
IAV RSV adenovirus	Lung		Recruitment of mast cell progenitors to the lungs	Andersson et al. (2018)
Mouse				
Virus/strain	Model	Tissue	Biological observations*	Reference
H1N1	Balb/C	Lung	Innate immunity-mediated recruitment and proliferation of mast cell progenitors in the lung	Zarnegar et al. (2017) Zarnegar et al. (2018)
H1N1	C57BL/6 B6.Cg- Kit ^{W-sh}	BALF	Reduced inflammation and mortality in mast cell-deficient mice infected with A/WSN/33 but not PR8	Graham et al., 2013
H1N1	C57BL/10.D2 B10.D2 IL-10 ^{-/-} B10.D2.6.5 IL-10 ^{-/-}	Lung	Proposes biphasic activity of IL-10: (1) inhibition virus-mediated activation of TGF- β early in infection; (2) suppression of inflammation late in infection	Dutta et al. (2015)
H5N1	Balb/C	Lung	Ketotifen reduces mast cell release of histamine, tryptase, and TNF- α	Hu et al. (2012)
H5N1	Balb/C	Lung Nose Trachea	Sodium cromoglycate reduce mast cell-induced inflammatory responses	Han et al. (2016)
Western reserve vaccinia	Kit ^{+/+} Kit ^{W-sh}	Skin	Mast cell deficiency results in severe ulcerated skin lesions and high levels of inflammatory cell infiltration	Domenico et al. (2012)
Western reserve vaccinia	Kit ^{+/+} Kit ^{W-sh}	Skin Spleen	TLR2-mediated degranulation of mast cells	Wang et al. (2012a) Wang et al. (2012b)
HSV-1	Kit ^{+/+} Kit ^{W-sh}	Eye	Mast cell deficiency results in elevated neutrophil infiltration, neutrophil infection and dissemination of virus	Royer et al. (2015)
HSV-2	Kit ^{+/+} Kit ^{W-v}	Skin	Mast cell derived-TNF- α and -IL-6 protect mice from HSV mortality	Aoki et al. (2013)
DENV1 DENV2 DENV3 DENV4	Kit ^{+/+} Kit ^{W-sh}	Skin Draining lymph nodes	Mast cell-mediated recruitment of recruit NK cells	St John et al. (2011)
DENV2	Kit ^{+/+} Kit ^{W-sh}	Ear Spleen Peritoneal/ mesentary tissue	Mast cells contribute to vascular permeability through chymase and leukotriene secretion	St John et al. (2013)
DENV2	Kit ^{+/+} Kit ^{W-sh}	Skin	Mast cells reduce CCL2-mediated infiltration of inflammatory macrophages	Chu et al. (2015)
DENV1 DENV2	C57BL/6 Kit ^{W-sh} Fcgr3 ^{-/-}	Peritoneal tissue Liver	Mast cells reduce CCL2-mediated infiltration of inflammatory macrophages	Syenina et al. (2015)

*Relative to controls.

to anti-inflammatory responses by MCs, the authors observed vaccinia-induced degranulation of MCs that contributed to viral clearance.

In contrast to vaccinia infection, the presence of IL-6 and TNF- α produced by MCs was found to be essential for minimizing inflammation and viral replication in a murine skin model of herpes simplex-2 (HSV-2) infection (Aoki et al., 2013). Reconstitution of MC-deficient mice with *IL-6*^{-/-} or *TNF- α* ^{-/-} MCs failed to reduce HSV-2 morbidity and mortality. In an ocular model of herpes simplex-1, MC deficiency also led to increased viral replication and inflammation as a result of increased neutrophil infiltration (Royer et al., 2015). In addition, HSV-2-infected neutrophils from the cornea facilitated dissemination of the virus to the nervous system.

As with influenza, the study of MCs during dengue virus infection has largely concentrated on the negative effects of MC activation and signaling. MCs have been implicated in the vascular leakage associated with severe dengue diseases. Activated MCs restructure the neighboring vasculature to facilitate recruitment of circulating immune cells; excessive release of chymase and tryptase, as found in the plasma of severe dengue patients, may contribute to systemic vascular permeability and hypovolemia (St John et al., 2013). As severe dengue and dengue hemorrhagic fever are most common during heterotypic secondary dengue infection, the production of heterotypic IgE may contribute to over-activation of MCs (Syenina et al., 2015). However, in the absence of MCs, dengue-infected mice exhibited increased inflammation at the site of infection and higher numbers of infiltrating inflammatory cells such as macrophages (Chu et al., 2015). MC-deficient mice also had increased viral burden and bleeding tendency, indicating failure to fully activate platelets and vascular endothelial cells in response to injury (Chen et al., 2009; Chu et al., 2015). At the site of infection, MCs in the skin produce chemokines to recruit NK and NKT cells to the skin and prevent spread of the virus to the draining lymph nodes (St John et al., 2011). Like influenza, MCs appear to play an important role activating and administering the immune response at the site of dengue infection, and again like influenza, the net positive or negative outcome of MC activation appears to be highly context dependent.

MAST CELLS AND MAST CELL MEDIATORS AS THERAPEUTIC TARGETS FOR PREVENTING IMMUNE PATHOLOGY

As has been discussed above, MCs and the mediators they produce are plastic and vary significantly over the duration of an infection. As described above, exogenous expression of IL-10, IL-37, or GM-CSF in the lungs of influenza-infected mice improved survival and recovery from infection (Huang et al., 2011; Dutta et al., 2015; Subramaniam et al., 2015; Qi et al., 2019). These studies suggest great potential in the use of MC-derived mediators as therapeutics for immune pathology and protection against an excessive and damaging inflammatory response. Therapeutically targeting MCs or their mediators will need careful consideration in order to prevent off-target effects, however. Blocking the anti-inflammatory

functions or enhancing the pro-inflammatory functions may result in excessive tissue damage resulting from infiltration and activation of cytotoxic cells. Treatment of mice with an FDA-approved TNF α inhibitor increased survival but prolonged and exacerbated lung pathology, raising concerns for the risk of severe influenza in patients prescribed TNF α -blocking drugs commonly used to treat rheumatoid arthritis, irritable bowel syndrome, and psoriasis (Shale et al., 2010; Damjanovic et al., 2011; Shi et al., 2013).

Identifying suitable MC mediators for therapeutic targeting will take careful consideration in order not to attenuate the beneficial role MCs play in both inducing and suppressing inflammation and the immune response. Use of mast cell stabilizing drugs such as sodium cromoglycate and ketotifen, which prevent mast cell degranulation and histamine release, as well as inhibitors of receptors that bind MC products such as leukotrienes have shown promise in animal models of influenza and dengue virus infection (Hu et al., 2012; St John et al., 2013; Han et al., 2016). Mast cell stabilizers, alone or in combination with the influenza antiviral oseltamivir, improved mice survival after H5N1 influenza challenge (Hu et al., 2012; Han et al., 2016). In a murine model of severe dengue, treatment mast cell stabilizers or the leukotriene receptor antagonist montelukast reduced vascular permeability and pathologic vascular leakage in infected mice (St John et al., 2013). These studies demonstrate that viability of targeting therapeutics to diminish specific inflammatory responses of mast cells, such as degranulation, without blunting the anti-inflammatory function of the MCs. To utilize the immunomodulatory effect of MCs to combat infection will require a better understanding of the various outcomes of MC mediator expression and signaling. Further, significantly more work is required to better understand the effects of over the counter or prescription pharmacological agents targeting MC functions, such as histamine release, in regulating infection and tissue damage.

CONCLUDING REMARKS

MCs play a far-reaching role in immune responses, stimulating the pro-inflammatory environment and recruitment of additional immune responders, as well as driving immune suppression and reduction of the inflammatory environment. This role for MCs in the context of infection is under-studied, but as many infections, such as influenza, cause tissue damage as a result of inflammation, a better understanding of the role of MCs in mitigating this damage may provide insight into better management of immunopathology during infection. Although no studies have yet identified an immune suppressive role for MCs in resolving influenza infection, immune mediators such as IL-10 and IL-6 are known to play an important role in mitigating influenza pathology. Many cell types produce immune suppressive cytokines, and identifying individual sources and roles for each is difficult. However, the contribution of each cell type present at the site of infection cannot be discounted, and a better understanding of the regulatory networks driving the immune responses to influenza is essential to developing new and more effective treatments.

AUTHOR CONTRIBUTIONS

AM-S and SP conceptualized the content of and wrote the article. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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