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IgE and mast cells in host defense against parasites and venoms

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Abstract

IgE-dependent mast cell activation is a major effector mechanism underlying the pathology associated with allergic disorders. The most dramatic of these IgE-associated disorders is the fatal anaphylaxis which can occur in some people who have developed IgE antibodies to otherwise innocuous antigens, such as those contained in certain foods and medicines. Why would such a highly “maladaptive” immune response develop in evolution, and be retained to the present day? Host defense against parasites has long been considered the only beneficial function that might be conferred by IgE and mast cells. However, recent studies have provided evidence that, in addition to participating in host resistance to certain parasites, mast cells and IgE are critical components of innate (mast cells) and adaptive (mast cells and IgE) immune responses that can enhance host defense against the toxicity of certain arthropod and animal venoms, including enhancing the survival of mice injected with such venoms. Yet, in some people, developing IgE antibodies to insect or snake venoms puts them at risk for having a potentially fatal anaphylactic reaction upon subsequent exposure to such venoms. Delineating the mechanisms underlying beneficial versus detrimental innate and adaptive immune responses associated with mast cell activation and IgE is likely to enhance our ability to identify potential therapeutic targets in such settings, not only for reducing the pathology associated with allergic disorders but perhaps also for enhancing immune protection against pathogens and animal venoms.

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Mast cells and their potential roles in host defense

Mast cells (MCs) are of hematopoietic origin [1, 2]. Distinct from basophils and other granulocytes, mature MCs normally do not circulate in the blood but instead are derived from circulating progenitors that enter, and then complete their differentiation/maturation in, virtually all vascularized tissues [1, 2]. MCs are particularly abundant near cutaneous and mucosal body surfaces, where immune surveillance often first takes place. This tissue distribution has positioned MCs, along with epithelial cells, macrophages, and dendritic cells (DCs), as critical sentinels in sensing microbial invasion and other environment challenges. MCs express a wide spectrum of cell surface receptors, including immunoglobulin Fc receptors (FcRs), pattern recognition receptors (e.g., TLRs), and many other innate receptors (e.g., complement receptors, T1/ST2, CD48), which enable them to respond to endogenous mediators and exogenous stimuli to release potent chemical mediators and growth factors/cytokines/chemokines [1, 3, 4]. MCs are also located in close proximity to blood vessels, lymphatics, nerves, and secretory glands. Therefore, MCs and MC-derived products can potentially influence not only innate and adaptive immune responses but also tissue remodeling and homeostasis [1, 4].

The most powerful trigger for MC activation for mediator release is the crosslinking of high affinity IgE receptors, FcεRIs, by IgE and antigen, leading to the rapid release by degranulation of preformed, granule-associated, biologically potent chemical mediators, followed by the *de novo* synthesis of lipid-derived mediators, cytokines and chemokines [3, 5-7]. IgE-mediated MC mediator release can cause many of the pathological and clinical features associated with allergic disorders, including fatal anaphylaxis [7-9]. Other adaptive stimuli (e.g., IgG immune complexes) and innate stimuli (e.g., pathogens, pathogen products, or endogenous mediators/cytokines) also can activate MCs [1, 4]. The kinetics, types and amounts of different products that can be produced by activated MCs are determined by the nature of the stimulus (or stimuli) encountered, the presence or absence of co-stimulatory or inhibitory factors, and by the location and phenotype of the MCs [1, 3, 4]. In addition to modulating local inflammation and tissue remodeling, MC granules and mediators can travel to remote sites, such as draining lymph nodes, where they can influence immune responses [10, 11]. Many MC populations have a long life span in tissues and degranulated MCs are able to replenish their granule contents, which allows them to be activated repetitively [12, 13]. Furthermore, MC populations can expand at sites of inflammation via proliferation or progenitor recruitment, and MCs numbers often return roughly to baseline levels once the inflammation has resolved [14].

Distinct from other immune cells, which can “come and go” during inflammatory processes, MCs are long-lived tissue-dwelling cells, a property which permits them to participate in the initiation, progression and resolution of immune responses. Because of the potentially catastrophic effects of extensive and systemic MC activation (as seen in fatal anaphylaxis), it

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is critical for MC activation to be tightly controlled. In allergy, MC activation can contribute to pathology and tissue dysfunction. In some infections, MC activation is regarded as beneficial, as it can enhance immunity and host defense. However, there also is evidence that excessive MC activation can lead to tissue damage. Potential protective vs. pathological roles of MCs in various bacterial [15], viral [16], and fungal [17] infections recently have been reviewed elsewhere. In this article, we focus on the roles of IgE and MCs in host defense against parasites and review evidence that MCs and IgE-associated Th2 immunity can enhance host defenses against animal venoms.

The role of IgE in parasite immunity

Host responses to intestinal nematode infections are typically characterized by Th2 immunity [18-23], with elevated levels of parasite antigen-specific and non-specific IgE, tissue and blood eosinophilia (and sometimes increased numbers of basophils), and intestinal pathology, including crypt hyperplasia, goblet cell hyperplasia, and mucosal MC (MMC) hyperplasia [18, 19, 23]. Data from epidemiological studies suggest a protective role of IgE antibodies in infections with certain parasites in humans, as the levels of parasite-specific IgE and resistance to infection correlate positively [24-26]. It is thought that IgE antibodies mediate their protective function by interacting with cells that express the high affinity IgE receptor (FcεRI) (such as MCs and basophils [in humans and mice], and possibly DCs and eosinophils [in humans]) or the low affinity IgE receptor (CD23) (including eosinophils, DCs, platelets, macrophages [in humans], and B cells [in both humans and mice]) [5, 27]. Although the features of such immune responses can vary depending on the parasite causing the infection, an increase in IgE levels occurs in many of them, with much of the IgE often not specific for defined parasite antigens [28, 29]. However, the actual contributions of antigen-specific or non-specific IgE antibodies in such settings, and their relevance for parasite clearance, or parasite-induced pathology, is still not fully understood. It is likely that binding of parasite-specific IgE and antigen to FcεRI receptors and the ensuing activation of effector cells, such as MCs and basophils, can result in the production and release of biologically active mediators that favor parasite expulsion [19, 30]. Another mechanism that is thought to contribute to parasite expulsion is antibody-dependent cellular cytotoxicity (ADCC) via IgE and/or IgG receptors [31-33]. Notably, parasite infections are initially characterized by production of large amounts of nonspecific IgE while parasite-specific IgE is detectable only at later stages of primary infections or after multiple infections. Pritchard proposed the hypothesis that the nonspecific IgE represents an advantage for the parasite, rather than the host, by competing with parasite-specific IgE for receptor binding sites, which could interfere with the ability of IgE-mediated immunity to expel the parasites [28, 29]. In support of Pritchard's hypothesis, Watanabe recently showed that administration of non-specific IgE impaired protection against *T. spiralis* infection in mice [34].

IgE−/− mice represent a valuable model system for studying the potential contribution of IgE to parasite resistance (**Table 1**). Abnormalities in host responses to *Brugia malayi*, *Heligmosomoides polygyrus*, *N. brasiliensis*, *T. spiralis* and *Schistosoma mansoni* have been observed in these mice [35-38], indicating beneficial functions for IgE in these infections. Nevertheless, findings in IgE−/− mice are not always in accord with observations from

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experiments employing other approaches to manipulate levels of IgE or IgE signaling. For example, anti-IgE treatment *decreased* worm burden and egg production in *Schistosoma mansoni*-infected mice, supporting the possibility of detrimental, rather than benificial, roles for IgE in *Schistosomiasis* [39], whereas IgE−/− mice exhibited *increased* worm burdens and reduced granulomatous inflammation following primary infection with *Schistosoma mansoni* [35]. Furthermore, deletion of FcεRI did not alter worm burden (but was associated with increased granuloma volume and liver pathology) [40] and other approaches to alter IgE levels revealed little or no impact on *Schistosomiasis* in mice (reviewed in [41]). The contribution of IgE to resistance to *Schistosomiasis* is thought to mediated at least in part via CD23, which can facilitate parasite antigen presentation and subsequent production of protective IgG_1 antibodies, whereas FcεRIs on MCs and basophils appear not to be critical for protection against *Schistosomiasis* [41], indeed, as noted above, they may contribute to granuloma volume and liver pathology [41]. Moreover, the genetic background of the host can influence the contributions of IgE in parasite immunity. For example, it has been shown that IgE-deficient SJA/9 mice were resistant to primary and secondary infections with *N. brasiliensis* or *T. spiralis* [42], whereas BALB/c IgE−/− mice were more susceptible to *T. spiralis* than control mice, exhibited prolonged clearance of the adult worms from the small intestine, and harbored higher numbers of viable *T. spiralis* larvae in the skeletal muscle after primary infection [37].

The roles of mast cells in parasite immunity

Intestinal nematodes

MCs have long been considered major sentinels in host defense against helminth infection [43, 44], and intestinal nematode infections in rodents are widely used to interrogate the contribution of MCs and other Th2 cell-associated immune response to parasite resistance [18, 23]. Depending on the type of parasite, there is evidence that expansion of MMCs can contribute importantly to host defense against certain intestinal nematodes (**Table 2**). For example, administration of exogenous IL-3 [45-47] or IL-18+IL-2 [48] which can increase numbers of MMCs (among other effects), can accelerate intestinal clearance in mice infected with *T. spiralis*, *S. ratti* or *S. venezuelensis*, whereas anti-SCF or anti-c-Kit treatments prevented MMC expansion and also delayed *T. spiralis* expulsion [49, 50]. IL-3-deficient mice, which cannot produce an intestinal MMC hyperplasia response, exhibit increased susceptibility to *S. venezuelensis* infection [51]. IL-4 deficient mice have reduced intestinal MMC hyperplasia after infection with *T. spiralis*, *S. ratti*, *H. polygyrus* or *N. brasiliensis* (reviewed in [43]). These and other studies (reviewed in [43]) highlight the association of Th2 responses and certain specific cytokines (e.g., SCF, IL-3, IL-4, IL-9, IL-10, IL-18) in the induction of intestinal MMC hyperplasia and enhanced immunity to helminthes.

Homing of MMCs to the epithelial layer of the gut mucosa is also critical for anti-parasite functions of MCs. Notch 2 signaling appears to play an important role in regulating MMC migration and distribution in gut mucosa and thus can influence anti-parasite immunity in mice infected with *S. venezuelensis* [52]. The expulsion of *T. spiralis* is slower in *Mcpt1*$^{-/-}$ mice despite their higher numbers of MMCs in the submucosa (but not the epithelial layer)

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of the infected intestines, suggesting an important role for this chymase in the tissue migration/localization of MMCs within the intestines [53].

In addition to changes in the numbers and distribution of MCs at sites of infection, degranulation of MCs can be observed in the vicinity of certain parasites, and activated MCs have the potential to contribute to anti-parasite immunity by multiple mechanisms. MC-derived proteases and other mediators can be toxic to parasites [54], stimulate intestinal smooth muscle contraction (which may hasten worm expulsion) [55-57], and/or enhance mucosal permeability [58, 59]. MC-mediated alterations in intestinal barrier function can lead to enhanced influx of fluid and blood-borne antibodies into the gut lumen, thus contributing to an unfavorable environment for the parasites. MC granule-associated glycosaminoglycans have been shown to prevent adult worm attachment and invasion of intestinal mucosa by *S. venezuelensis* [60, 61]. MCs and MC-derived cytokines/chemokines/mediators can modulate host-pathogen interactions by influencing the recruitment or function of other innate immune cells, and this could have positive or negative effects on the parasites. For example, IgE-dependent release of mMCP6 from MCs can enhance recruitment of eosinophils [62], which are thought to have effects (such as producing IL-10 at early stages of infection) that *favor* the growth and survival of parasite larvae in skeletal muscle infected with *T. spiralis* [63]. However, leukotrienes, particularly, LTB_4, can *reduce S. venezuelensis* worm burden, possibly via the recruitment of certain inflammatory cells [64]. Furthermore, MCs have the potential to shape parasite-associated adaptive immune responses via production of soluble mediators or via cell-cell interactions with DCs and other antigen-presenting cells [4, 44, 65]. Finally, IgE-*independent* MC degranulation has been shown to enhance early phases of Th2 immune responses following infections with *Heligmosomoides polygyrus* and *Trichuris muris* [44, 66].

As discussed above, MC activation is likely to contribute to intestinal worm expulsion, at least in some settings. However, because host-defense mechanisms often employ redundant or partially overlapping elements, it has been challenging to identify conclusive evidence that MCs, and particularly IgE-dependent MC activation, confer survival benefit to the host during parasite infection. In the case of infection with *N. brasiliensis*, basophils appear to play a more critical role than MCs in host resistance [38, 67, 68]. Studies in MC-deficient $WBB6F_1$-$Kit^{W/W\text{-}v}$ mice indicate that MCs make little or no contribution to the expulsion of *N. brasiliensis* during primary infections with this nematode [69], whereas a modest defect in expulsion of *N. brasiliensis* was observed in MC-deficient C57BL/6-$Kit^{W\text{-}sh/W\text{-}sh}$ mice during primary but not secondary infections [68]. Furthermore, mice deficient in the mouse MC protease mMCP1 ($Mcpt1^{-/-}$ mice) remain competent to clear *N. brasiliensis* [53]. Depending on the basophil-deficient models used to analyze the responses, basophils either have been shown to promote defense against *N. brasiliensis*, especially during the secondary infection [67, 68], or to have no role in worm clearance or tissue eosinophilia during primary or secondary infections [70].

One interpretation of these apparently discordant observations is that, under certain conditions (e.g., depending on the animals' microbiomes or other environmentally-influenced factors), mechanisms that can compensate for a lack of basophils may be engaged that preserve immune resistance to these parasites [71]. Notably, Th2 cytokine-mediated

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goblet cell hyperplasia and intestinal smooth muscle contraction [72, 73], but neither B cells nor IgE [74, 75], appear to be required for rapid expulsion of *N. brasiliensis*, and Schwartz *et al.* reported that IgE-dependent secretion of IL-4/IL-13 by basophils can contribute critically to protective immunity against this parasite [38]. Other studies employing genetically c-*kit* mutant MC-deficient mice or MC-protease-deficient mice suggest that MCs can contribute to resistance to infections with *Strongyloides ratti* [76, 77], *S. venezuelensis* [48, 51, 78], *T. spiralis* [53, 62, 79-82], *Heligmosomoides polygyrus* [44, 66] and *Trichuris muris* [66, 83] (**Table 2**). Increases in gastrointestinal MCs is a striking common feature of infection with these nematodes, except for *Trichuris muris* [83].

As in other nematode infections, infection with *T. spiralis* is associated with IgE production, expansion of intestinal MCs [84], and the release of MC-associated mMCP1 into the circulation [53]. IgE produced during *T. spiralis* infection is mainly bound to intestinal MCs and intense IgE deposition is found by immunohistochemistry around necrotic cysts. IgE−/− mice with primary *T. spiralis* infection exhibit attenuated MMC hyperplasia, enhanced numbers of adult worms in the intestine, and larger numbers of viable larvae in the muscle [37], supporting a protective function of IgE in this infection. An important contribution of the MC chymase, mMCP-1, in the clearance of *T. spiralis* was demonstrated using *Mcpt1*$^{-/-}$ mice, which exhibited significant delay in the intestinal expulsion of the parasite during primary and challenge infections [53]. The clearance of *T. spiralis* requires the destruction of larval cysts in infected muscle and the expulsion of adult worms from the intestine. While efficient expulsion of *T. spiralis* adult worms from the intestine is dependent on mMCP1, mMCP6 (a MC-specific tryptase) can significantly enhance both eosinophil recruitment and the necrosis of larvae in skeletal muscle during chronic infection with this parasite [62].

Strongyloides venezuelensis, a gastrointestinal nematode that infects rodents and is used to model human *S. stercoralis* infection [85], has a life cycle similar to *N. brasiliensis* [86]. *S. venezuelensis* infection induces a predominant Th2 response associated with the production of *S. venezuelensis*-specific IgE and IgG_1 antibodies [75]. While MCs and antibody responses are not essential for host defense against *N. brasiliensis*, there is evidence that intestinal MCs [48, 51, 78, 87] and humoral responses [75] are critical for the rapid expulsion of *S. venezuelensis* from the intestines. The importance of parasite-specific antibodies has been demonstrated using IgG/IgE-deficient AID−/− mice which exhibit delayed expulsion of *S. venezuelensis* and harbor larger numbers of adult worms in their intestines; adoptive transfer of immune sera from *S. venezuelensis*-infected WT mice restores resistance in these mice [75]. This study, and the finding that FcRγ-deficient mice exhibited delayed expulsion of *S. venezuelensis*, represent evidence that IgG and IgE antibodies can collaboratively support expulsion of *S. venezuelensis* [75]. Mice that lacked MCs (*Kit*$^{W/Wv}$ mice) or IL-3 were unable to mount an intestinal mastocytosis and also exhibited delays in *S. venezuelensis* expulsion [51], while IL-18 treatment both increased MMC numbers and accelerated parasite expulsion [48]. However, IL-18 treatment and transfer of *S.v* immune sera-derived IgE or IgG failed to promote worm expulsion in *Kit*$^{W/Wv}$ mice, suggesting that antibody-dependent MC activation is required for the rapid expulsion of *S. venezuelensis*. Taken together, the available evidence indicates that FcRγ-dependent MMC activation can importantly enhance the expulsion of *S. venezuelensis* from

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the intestines [88]. In the life cycle of *S. venezuelensis*, third stage larvae (L3) migrate to the lung, where they induce pulmonary eosinophilia and goblet cell hyperplasia, effects that may influence host defense against *S. venezuelensis*. *S. venezuelensis*-derived chitin may stimulate alveolar epithelial cells to produce IL-33, which can activate lung ILC2s to produce IL-5 & IL-13, enhancing the survival of eosinophils in the lungs [85]. MCs [89-91], as well as ILC2s, can be activated by IL-33, but it is not clear whether MCs are involved in this innate phase of the host response to *S. venezuelensis*.

Vector-borne parasitic diseases

Malaria

Malaria, a mosquito-borne pathogen, is the most deadly parasitic disease in humans [92]. Most malaria-associated mortality is caused by severe anemia and/or cerebral malaria following uncontrolled infection with *Plasmodium falciparum* [93]. While the involvement of IgE in malaria parasite transmission and pathogenesis remains unclear and is controversial [94], several studies suggest both detrimental and beneficial roles for MCs in malaria (**Table 2**). It is possible that MCs can influence multiple stages of malaria infection. As MCs are abundant in skin, their reactions to mosquito saliva during blood feeding may have a ‘gate keeper’ effect on the initial stage of malaria transmission. IgE-independent and IgE-dependent (after repeated exposures to mosquito bites) degranulation of dermal MCs triggered by mosquito saliva has been shown to *promote* aspects of the ensuing inflammatory response, including local recruitment of granulocytes and induction of hyperplasia of draining lymph nodes [94, 95]. On the other hand, dermal MCs activated by mosquito saliva can *down–regulate* antigen-specific immune responses, probably via their secretion of MIP2 and IL-10 [96]. Guermonprez *et al.* recently provided evidence, in a mouse model of lethal malaria (infection with *Plasmodium berghei* ANKA), that MCs can promote disease through the activation of tissue-damaging $CD8^+$T cells [97]. Children with malaria have increased plasma levels of Flt3 ligands, and Guermonprez *et al.* further showed that, in mice, uric acid crystals derived from *Plasmodium berghei* ANKA-infected RBCs can trigger MCs to release Flt3, which then can expand a unique class of DCs and favor subsequent activation of pathogenic $CD8^+$T cells [97].

MCs and histamine have been implicated in the severity of malaria [94] as well as in increased intestinal permeability associated with malaria infection [92]. Severe malaria is correlated with higher levels of histamine in the blood and tissues and inhibition of histamine signaling confers protection against severe malaria in mice [98]. VEGF also is increased and has been implicated in cerebral malaria. Malaria parasite antigen(s) from lysates of *P. falciparum* (FCR-3 strain)-infected human erythrocytes has been shown to induce VEGF production from a human MC line (HMC1) [99], suggesting another potential detrimental effect of MCs in cerebral malaria. Patients infected with *P. falciparum* are prone to co-infection with intestinal bacteria and are at a higher risk of developing bacteremia and invasive bacteria disease, suggesting that malaria can impair intestinal barrier function. Chau *et al.* showed that *P. yoelii*-infected mice developed L-arginine deficiency, which was associated with intestinal mastocytosis, elevated levels of histamine, enhanced epithelial permeability, and increased bacterial translocation in the gut [100]. Nevertheless, beneficial

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contributions of MCs in malaria have been suggested based on experiments in c-*kit* mutant MC-deficient mice. Furuta *et al.* showed that engraftment with TNF+/+, but not −/−, MCs reduced parasitemia and mortality in $Kit^{W/Wv}$ mice after infection with *P. berghei* ANKA, suggesting that MC-derived TNF can enhance resistance [101] (although TNF has been implicated in both malaria protection and pathogenesis [102, 103]). Furuta *et al.* further showed that MCs can produce TNF in response to the binding of FcεRI/IgE or TLR4 to malaria parasite-derived peroxiredoxin [101, 104].

These studies collectively indicate that, in malaria, MCs can be activated by multiple signals, including exogenous stimuli from disease-vectors (e.g., mosquito saliva) and parasite products (e.g., peroxiredoxin), as well as by endogenous mediators (e.g., uric acid crystal) that are generated during infection. Moreover, MC responses to those stimuli via either innate (e.g., TLR4-dependent) or adaptive (e.g., FcεRI-dependent) mechanisms can have effects which may contribute either to parasite resistance or to pathology associated with the infection. It is possible that the outcome of the infection in individual hosts may reflect the net balance between protective vs. pathological consequences of IgE-dependent and IgE-independent MC activation in this setting, which in turn might be influenced by the species of parasite, the genetic background of the hosts, and other factors that modulate MC phenotype and other aspects of the immune response in that subject.

Ixodid ticks

MCs have also been implicated in acquired immunity to the feeding of larval Ixodid ticks, which can transmit to their hosts a wide range of pathogens, including the agents of Rocky Mountain spotted fever (*Rickettsia rickettsia*), Q fever (*Coxiella burnetii*), tularemia (*Francisella tularensis*), granulocytic ehrlichiosis (*Ehrlichia ewingii*), monocytotropic ehrlichiosis (*Ehrlichia chaffeensis*), and others [105]. However, as discussed above, there can be substantial redundancy or overlap in the functions of various elements of host defense, and the relative importance of MCs vs. basophils in host resistance to the feeding of such ticks may depend importantly on the species of tick and species of host. In mice, there is evidence that basophils, more than MCs, can enhance resistance to secondary infestations with larval Ixodid *Dermacentor variabilis* ticks [106]. In guinea pigs, treatment with a rabbit anti-basophil serum (which markedly depleted basophils in the blood and tissues) essentially abrogated the ability of animals subjected to a prior primary infestation with larval Ixodid *Amblyomma americanum* ticks to exhibit resistance to the feeding of such larval ticks during a secondary infestation [107].

Studies in MC-deficient mice [108] and in mice genetically deficient in basophils [109] show that both MCs and basophils, as well as IgE, can contribute to acquired immunity to the feeding of *Haemaphysalis longicornis* ticks in mice. MC deficient $Kit^{W/Wv}$ mice exhibited a defect in resistance against *Haemaphysalis longicornis* tick infestation. Matsuta et al. showed that active immune serum, but not heat-inactivated immune serum, from tick-infested mice was able to transfer resistance to MC-engrafted $Kit^{W/Wv}$ mice, but not to MC-deficient $Kit^{W/Wv}$ mice, suggesting an essential role of IgE and MCs [108]. This study raised the possibility that, in mediating resistance to the feeding of larval Ixodid ticks, MCs provide function in mice similar to those of basophils in guinea pigs [107]. A subsequent

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study by Wada et al. using genetically engineered basophil-deficient mice [109] confirmed the inability of MC-deficient *Kit*$^{Wsh/Wsh}$ mice to exhibit acquired resistance, but also showed that basophils were required to establish acquired resistance against feeding of *Haemaphysalis longicornis* ticks. Furthermore, basophil recruitment to tick feeding sites during the secondary infestation was demonstrated by immunohistochemistry using anti-mMCP8 (basophil-specific marker) [109]. Adoptive transfer of MCs from FcRγ—deficient mice was able to restore resistance in MC-deficient mice, however basophil transfer from FcRγ deficient mice did not restore resistance in basophil-deficient mice. These findings indicate that antibodies, probably IgE antibodies, play an essential role to acquired resistance for these ticks via interacting with Fc receptors on basophils rather than MCs. However, mice deficient in either MCs or basophils are eventually able to clear the tick larvae, albeit more slowly than in WT mice.

Taken together, work in helminthic infections, vector-borne parasitic diseases, and Ixodid ticks suggests that there is redundancy in the protective mechanisms which can help to guard against the invasion or (for ticks and probably also other exoparasites) the feeding of these pathogens, the detrimental effects of the pathology they induce, or their ultimate clearance by the host. Because basophils and MCs may have overlapping or complementary functions as effectors of adaptive immune responses that interfere with tick feeding or infection with intestinal parasites, it would be interesting to evaluate these parasite infection of tick feeding models in mice that lack both cell types.

Challenges in defining the roles of MCs in intestinal helminth and *Leishmania major* infections

c-*kit* mutant MC-deficient mice have been widely used in the past three decades to investigate *in vivo* functions of MCs [110, 111], but it has been difficult to characterize definitely the MCs' roles in intestinal parasite infection using these mice. The delay in intestinal worm clearance observed in c-*kit* mutant MC-deficient mice may not be fully explained by their lack of intestinal MCs because these mice also have abnormal gut motility due to their deficiency in the interstitial cells of Cajal (ICC) network [112], as well as other abnormalities, some of them affecting elements of immune responses in addition to MCs [110, 111, 113]. It is also difficult to use "MC-knock-in" mice (i.e., genetically MC-deficient mice engrafted with WT or genetically-altered *in vitro*-derived cultured MCs [110, 111]) to confirm the contributions of MCs to mucosal immunity because *in vitro*-derived cultured MCs generated in IL-3-containing medium do not correctly engraft into the intestinal mucosa after intravenous injection into *c-kit* mutant mice [52, 77]. Engraftment of the MMC compartment can be achieved and anti-helminth immunity can be repaired by bone marrow transplantation [44, 76, 77, 114] in *c-kit* mutant mice, but this approach also replaces with donor-derived WT cells other hematopoietic cell lineages in *c-kit* mutant mice. PI3K$^{-/-}$ mice, which virtually lack gastrointestinal MMCs, exhibited increased susceptibility to *S. venezuelensis* infection. In order to engraft intestinal MMCs into these mice, Fukao *et al.* injected intravenously, on days 3, 5, 7 after *S. venezuelensis* infection, cultured MCs that had or had not been primed with IL-4+IL-10; despite achieving similar anatomical distributions in the intestines of the recipient mice, only the IL-4+IL-10-primed MCs

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restored anti-parasite resistance in the PI3k$^{-/-}$ mice [87]. Sakata-Yanagimoto *et al.* found that Notch2 signaling is required both for the normal appearance of MMCs in the small intestinal epithelium and the rapid expulsion of *S. venezuelensis* in a primary infection [52]. They also found that engraftment of either Notch2-deficient or wild type bone marrow-derived cultured MCs did not restore anti-parasite immunity in *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice after *S. venezuelensis* infection, which they speculated might reflect the abnormal anatomical distribution of the MCs in the intestines of the recipient *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice [52]. Such studies highlight the potential importance of anatomical location, as well as numbers, of intestinal MCs in resistance to infection with some intestinal nematodes.

Given the concerns about c-*kit* related but MC-independent defects in c-*kit* mutant mice (reviewed in [110, 111, 113]), it is notable that the contribution of MCs to the immune response to *S. ratti* infection has recently been confirmed using c-*kit* independent, MC-deficient mice. Blankenhaus *et al.* [115] reported that BALB/c-*Cpa3*$^{Cre/+}$ mice, in which MCs are depleted due to Cre mediated-cytotoxicity, exhibited an increased parasite burden in the small intestine at day 6 after *S. ratti* inoculation. This finding is consistent with previous observations in WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice which exhibited increased larval counts and a delay in worm expulsion during a primary infection with *S. ratti.* The impaired host response to a primary infection with *S. ratti* in WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice can be corrected by bone marrow transplantation, but not by short-term engraftment of adoptively-transferred MCs, probably because of the incomplete restoration of the MMC compartment by the adoptive transfer of *in vitro*-derived cultured mature MCs (as discussed above) [76, 77]. Blankenhaus *et al.* also provided evidence that IL-9-mediated MC activation is a key mechanism mediating *S. ratti* repulsion, a process that is suppressed by Foxp3$^+$ Treg cells in a non-redundant manner in the BALB/c, but not the C57BL/6, strain [115].

Findings in various MC-deficient models do not always yield consistent conclusions about the contributions of MCs to parasite resistance, perhaps because of differences in the other phenotypic abnormalities which occur in c-*kit* mutant vs. alternative types of MC-deficient mice and/or differences in experimental design or related to animal facilities (e.g., differences in mouse microbiomes) (reviewed in [110, 111, 113]). For example, studies in WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice suggested that MCs make no contribution [116], had effects that increased skin lesion size [117], or enhanced protection against *Leishmania major* [118]. Upon infection with *L. major*, Th1 cells in resistant mice activate macrophages, which is thought to promote destruction of the parasite whereas Th2 cells in susceptible mice inhibit macrophages and thereby favor the systemic dissemination of the pathogens. Studies in c-*kit*-independent MC-deficient mice that are either resistant (Th1 prone C57BL/6-*Cpa3*$^{Cre/+}$) or susceptible (Th2 prone BALB/c-*Cpa3*$^{Cre/+}$) to *Leishmaniasis* detected no role for MCs in the development of lesion size, parasite burden, cytokine production or immune responses in cutaneous leishmaniasis in mice [119].

Another challenge in the analysis of the roles of IgE and MCs (and basophils) in parasite immunity using experimental models in mice is the potential difficulty of extending the results directly to humans. For example, humans exhibit a broader distribution of FcεRI among hematopoietic cells types than is observed in WT mice [5, 27]. FcεRIs are primarily restricted to MCs and basophils in mice under baseline conditions, whereas FcεRIs are also

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expressed in human eosinophils and platelets, which have been reported to be able to participate in parasite killing by IgE-mediated ADCC, a mechanism of defense against parasites that has not yet been reported in rodents [31-33, 120]. Moreover, there are potentially important differences in the phenotype of MC populations in mice and humans [121].

Potential negative functions of MCs during parasite infections

While MC activation can enhance host defense in some settings, MC mediators also can potentially cause pathology. For example, $Kit^{W/Wv}$ mice are slower in *T. spiralis* parasite expulsion but also exhibit reduced Th2 responses, milder intestinal pathology/inflammation, less mucosal tissue damage, and attenuated body weight loss after infection (however, these effects are not necessarily due to their MC deficiency) [82, 114]. $Mcpt1^{-/-}$ mice have reduced immunity against *T. spiralis* infection, but also exhibit less intestinal pathology/inflammation. mMCP1 released by MCs upon *T. spiralis* infection can potentially degrade occludin and other tight junction proteins, compromising intestinal barrier function and thereby promoting intestinal inflammation and pathology [82]. Based on studies in C57BL/6J WT mice, it has been proposed that MCs may contribute to the epithelial hyper-permeability associated with reductions in tight junction proteins (occludin and zonula occludens 1) that is observed after infection with either *S. venezuelensis* or *N. brasiliensis*, and that this may enhance both systemic absorption of endotoxin through the gut and IgG flux into intestine lumen [122].

In some settings, MCs can even have effects which promote parasite-induced immunosppression. In a mouse model of chronic *Schistosomiasis* elicited by repetitive skin infection, depletion of MCs in Mcpt5iDTR mice by DT injection reduced skin IL-10 levels, but increased MHC-II+ cells, suggesting a possible role for MCs in down-regulating parasite immunity [123]. Furthermore, some effects of MCs in parasite infections might favor the parasite. As noted above, anti-SCF treatment diminished intestinal MMC hyperplasia in rats infected with *N. brasiliensis* or *T. spiralis*, but such anti-SCF treatment *decreased* parasite egg production during *N. brasiliensis* infection [124]. These findings were in accord with results from prior work reporting that, during a primary infection with *N. brasiliensis*, c-*kit* mutant MC-deficient *Ws/Ws* rats exhibited significantly *less* egg output in the feces at day 8 of infection than did the corresponding wild type rats [125]. This result raised the possibility that some effects of SCF and/or MCs (perhaps MC-dependent enhancement of local vascular permeability at sites of parasite infection), actually favored parasite fecundity in this setting. However, neither the anti-SCF treatment nor the mutations in *Ws/Ws* rats exclusively affected MCs, so neither of these studies proved that the positive effects on parasite fecundity observed in animals with reduced numbers of MCs necessarily reflected an effect of MCs on the infection.

One hypothesis that is consistent with the divergent findings from studies investigating whether MCs and IgE can influence parasite immunity is that, depending on the setting, IgE and MCs either can have net effects favoring the host or can have net effects that favor the parasite. In light of the long-term co-evolution of parasites and their hosts, with each attempting to probe weaknesses in or to co-opt the defense mechanisms of the other, it

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should not be surprising that the engagement of MCs and IgE during host/parasite interactions may not always produce results that favor the host. When viewed from the perspective that vertebrates have been co-evolving with parasites for millions of years, and that the parasites' objectives may better be served by a viable rather than dead host, it is not surprising that, depending on the parasites and the particular setting, effector mechanisms such as IgE and MCs may be exploited by the parasties to their own advantage. For example, by eliciting a Th2 response that could result in IgE-dependent MC activation and release of vasoactive mediators in response to parasite antigens at sites of parasite infection, the parasite could thereby regulate local blood flow and vascular permeability in ways that can help to enhance the parasite's ability to derive nutrition from the host.

The good and bad sides of IgE-associated Th2 immune response

IgE-associated Th2 immune responses occur both in allergic disorders and in helminth infections [126, 127]. However, because most allergens do not pose a direct threat to the non-sensitized host, Th2 immune responses resulting in the production of antigen-specific IgE antibodies to such allergens are widely regarded as "misdirected/maladaptive" immune responses [128, 129]. Although most allergens are intrinsically innocuous, certain allergenic proteins possess enzymatic activity (for instance, the papaya protein papain or the major allergen from house dust mite *Der p 1* have protease activity), and exposure to such proteins can impair the integrity of epithelial barriers in the skin, the lung, and possibly also the gastrointestinal tract [130-133]. In this regard, such allergens can be considered to be potentially harmful and therefore an appropriate target for a "protective" immune response [134]. In contrast to such potentially harmful substances, intrinsically toxic molecules, such as components of animal venoms, represent an obvious danger for the host, and IgE-associated allergic reactions against a variety of venoms have been reported [135-140]. Some of them, for instance those against components of the venoms of hymenoptera like the honeybee or the yellow jacket, have a high prevalence [141], whereas fewer cases of allergic reactions to components of snake or jellyfish venoms, have been reported [136, 142], perhaps because of lower rates of exposure to such toxins.

In 1991, Margie Profet proposed her provocative "toxin hypothesis", by postulating that acute allergic reactions, manifested as immediately occurring signs and symptoms in response to allergen exposure (such as sneezing, coughing, vomiting or diarrhea), evolved as a defense mechanism allowing the sensitized host to respond promptly to, and to expel, neutralize and/or avoid, noxious substances which might be indicative of potentially life-threatening situations [143]. She noted that most allergens are either themselves toxins (e.g., venoms) or could originate from sources that can contain toxic chemical substances (e.g. tree nuts or sea foods) and thereby might function as carriers of such toxins [143]. The immune response would then be initiated not only against the dangerous toxic compound itself (e.g., venom components), but also against associated proteins in the toxin-containing food [143]. In a mechanism termed "sensing by proxy" by Palm *et al.* in their recent update of the "toxin hypothesis" [144], a strong pre-emptive effector immune reaction would then be initiated upon subsequent sensing of proteins that are associated with or bound to toxins, even in the absence of the actually harmful (toxic) agent. This hypothesis could explain why potentially dangerous allergic immune responses can be generated against seemingly

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harmless proteins [143, 144]. A similar idea was raised by James Stebbings, Jr. 17 years before Profet's paper was published. Stebbings hypothesized that “a major function of the immediate hypersensitivity reactions has been the protection of terrestrial vertebrates from the bites of, or invasion by, arthropods” [145]. Such reactions not only could help the host to resist the pathological effects of toxins contained in arthropod saliva, but also, by inducing the bitten host to scratch or otherwise attempt to remove the arthropod, could help to reduce the transmission of arthropod-borne infections. However, until recently, Profet's “toxin hypothesis” was largely ignored by the scientific community [144]; Stebbings’ paper was mentioned even less in the literature. Evidence that supports Stebbing's and Profet's hypotheses has recently been uncovered by experimental data showing that key effector elements of allergic diseases also can contribute to defense against arthropod and animal venoms [146-148].

Evidence from animal studies

The idea that key elements of what is now sometimes called the “allergy module of immunity” (specifically, IgE and MCs) could be beneficial in host defense against components of venoms was suggested in 1965 and 1971 by the results of two studies led by R.D. Higginbotham. Higginbotham showed that subcutaneous injection of Russell's viper venom or the honeybee venom induced degranulation of skin MCs in mice [149, 150]. Mast cell granules contain large amounts of heparin, a highly anionic compound that can bind to certain cationic venom components. Higginbotham showed that the toxicity of such venoms was significantly reduced if the venom was mixed with heparin prior to its injection into mice. These findings provided evidence that MCs can be activated by venoms *in vivo* and that subsequently released heparin could contribute to host defense by neutralizing toxic venom components [149, 150]. However, since animals that genetically lack MCs were not described until many years after Higginbotham's studies [110, 111], the importance of MCs in conferring protection against venom-induced toxicity could not be tested directly.

More than 40 years after Higginbotham's discoveries, our group used genetically MC-deficient mice to provide direct experimental evidence that MCs can contribute importantly to innate resistance against the venoms of certain snakes, including the Israeli mole viper, the Western diamondback rattle snake and the Southern Copperhead snake [151], as well as the venoms of the Gila monster [152], two species of scorpions [152], and the European honeybee [146, 151]. Experiments using pharmacological inhibitors of MC-associated proteases and engraftment of MC-deficient animals with MCs treated with shRNA to knock down their levels of carboxypeptidase A3 (CPA-3) indicated that MC-mediated resistance against the venom of the Israeli mole viper and one of its important toxins, sarafotoxin 6b, was largely dependent on release of the MC-associated CPA-3 [151]. Elegant genetic and biochemical studies by Hans-Reimer Rodewald and colleagues showed that CPA-3 is indeed the critical MC-derived protease that detoxifies sarafotoxin 6b, by removing its C-terminal tryptophan [153]. Studies by our lab [151, 152] and others [153] with various mice genetically deficient in MCs or MC-specific proteases revealed that, depending on the species of venomous animal, either CPA-3 [151] or the chymase mMCP4 [152] can reduce the toxicity of either whole venoms [151, 152] or individual toxic components of such venoms [151-153]. Because these same MC-derived proteases also can degrade certain

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endogenous peptides that are structurally related to toxins in certain venoms, such as endothelin 1 (which is similar to sarafotoxin 6b) and vasoactive intestinal polypeptide (which is similar to helodermin in Gila monster venom), we have suggested that an additional function of such MC-derived proteases is to limit the pathology observed when high levels of such endogenous peptides are produced during diseases or at sites of inflammatory or immune responses (reviewed in [154]).

It seems plausible that the ability of MCs to enhance host resistance to environmental toxins by responding to them by releasing proteases which can degrade such compounds is an ancient property of MCs. Tunicates, which arose in evolution before the development of classical adaptive immunity [155], contain cells called test cells which are present in large numbers beneath surfaces exposed to the environment and which share morphological, ultrastructural and functional features of vertebrate MCs [156, 157]. Such features include containing abundant cytoplasmic granules that contain heparin, histamine and serine proteases, and being able to degranulate in response to compounds such as compound 48/80 [156, 157]. If the MC lineage (represented in tunicates by test cells) learned long ago to respond to and de-toxify certain dangerous compounds, then is there evidence that this host defense function of MCs can be enhanced by their ability to respond to such toxins via mechanisms dependent on adaptive immunity and specifically those involving IgE? Given that the aggregation of FcεRI-bound IgE by specific antigen is among the strongest of MC activation stimuli [3, 5, 6, 27], it is tempting to speculate that venom-specific IgE antibodies could increase the detoxifying potential of MCs by permitting them to be activated more rapidly and extensively than would be the case upon the host's first exposure to that venom. However, reports about the development of IgE antibodies to components of snake, honeybee, jellyfish and scorpion venoms have mainly called attention to the risk of anaphylaxis in subjects containing IgE against such venom components [135-137, 140, 141].

The possibility that anti-venom IgE antibodies might confer benefit in host responses to venoms has only recently been investigated [146-148]. Complementary studies of Ruslan Medzhitov's group [147] and our lab [146, 148] have provided experimental evidence that IgE antibodies can play a beneficial role in *acquired* host defense against whole honeybee venom (BV) [146], Russell's viper venom (RVV) [148], or an allergenic component of honeybee venom, bee venom phospholipase A_2 (bvPLA$_2$) [147]. This work recently has been reviewed in detail [153]. We will comment here on some of the important results and implications of these studies.

Palm *et al.* focused mainly on the characterization of the acquired immune response against bvPLA$_2$ [147], which constitutes ~12% of total BV protein and is one of the major BV allergens [158, 159]. They showed that repeated intraperitoneal immunization with bvPLA$_2$ could increase the resistance of wild type animals to challenge with a near lethal dose of bvPLA$_2$, as assessed by changes in body temperature. This resistance was significantly reduced when the immunized mice were deficient in B cells or in FcεRIα (the IgE-binding component of the high affinity IgE receptor FcεRI [27]), providing evidence that this protective immune response was antibody-mediated, most likely by IgE antibodies. However, bvPLA$_2$-immunized MyD88-deficient mice acquired a similar degree of resistance against bvPLA$_2$ challenge as did control mice, suggesting that additional pathways

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independent of MyD88 and IL-33 signaling (which they implicated in the initial Th2 cell-associated response to bvPLA$_2$, also can contribute to the protective type 2 antibody response against bvPLA$_2$ [147].

Our studies focused on the immune response against whole venoms [146, 148]. Consistent with the study of Palm *et al.*, we observed that wild type mice immunized subcutaneously with a sub-lethal amount of BV developed BV-specific Th2 cells and BV-specific IgG$_1$ and IgE antibodies. Mice immunized with BV were significantly more resistant to challenge with a potentially lethal dose of that venom, as assessed by body temperature and survival of the mice. Several lines of evidence support the critical contribution of IgE antibodies and FcεRI to the acquired resistance and enhanced survival of BV-immunized mice, including data from serum transfer studies. For example, IgE-depleted immune sera failed to confer enhanced resistance to BV to naïve WT mice, and immunization with BV did not enhance acquired resistance to BV in mice that can't produce IgE (*IgE*$^{-/-}$ mice) or respond to IgE via the FcεRI, (i.e., *FcεRIγ*$^{-/-}$ and *FcεRIα*$^{-/-}$ mice) [146]. By, contrast, *IgE*$^{-/-}$ mice were capable of passively acquiring enhanced resistance to BV-induced morbidity and mortality when injected with BV immune serum from wild type mice [146]. Passive immunization experiments using C57BL/6 *Kit*$^{w\text{-}sh/w\text{-}sh}$ mice (these mice lack MCs but have increased levels of basophils [160]) and C57BL/6 *Cpa3-Cre; Mcl-1*$^{fl/fl}$ mice (these animals are markedly deficient in MCs, despite having normal c-*kit*, and have reduced levels of basophils [161]) provided evidence that MCs, but not basophils, likely contribute to protective IgE-mediated immunity against BV [146].

Subsequently, we found that the acquired enhanced resistance to RVV observed in mice that had developed type 2 immune responses to that snake venom also was highly dependent on IgE (**Fig. 1**) and FcεRIα (**Fig. 2 A-F**), could be effectively transferred by immune serum into control mice (**Fig. 1 F-J**), but not into C57BL/6-*Cpa3-Cre;Mcl-1*$^{fl/fl}$ mice that are markedly deficient in MCs and have a substantial reduction in numbers of basophils (**Fig. 2 F-H**) [148]. Notably, two different types of genetically MC-deficient mice (i.e., *Kit*$^{w\text{-}sh/w\text{-}sh}$ mice and *Cpa3-Cre; Mcl-1*$^{fl/fl}$ mice) also exhibited significantly diminished *innate* resistance to the toxicity and lethality of RVV (**Fig. 3 A-C, E & F**), supporting Higginbotham's hypothesis that MCs can contribute to enhanced innate resistance to this venom [149]. Compared to the corresponding MC-sufficient mice, such naïve MC-deficient mice also exhibited many fewer attempts to scratch sites of RVV injection (**Fig. 3 D & G**). The latter finding supports the idea proposed by both Stebbings [145] and Profet [143] that elements of allergic responses, in this case, MCs, can confer benefit to hosts experiencing attacks by arthropods [145] or other sources of toxins [143] by altering the host's behavior in ways that would help to eliminate, or at least permit the host to become aware of, the threat. Finally, we found that pre-sensitization with anti-DNP IgE (but not with the same amounts of anti-DNP IgG$_1$ or IgG$_{2b}$, DNP-specific IgG isotypes with the capacity to activate effector cells *via* FcγR receptors) significantly increased the resistance of mice to challenge with a potentially lethal amount of RVV admixed with a small amount of DNP-HSA (a 1:75 ratio by weight of DNP-HSA to RVV) [148]. These findings show that local tissue responses mediated by IgE and antigen can enhance host resistance to RVV even when the antigen eliciting MC activation at such sites is not a native constituent of the venom and constitutes a

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small amount of the injected material. This result is consistent with the general idea that the host needs only to generate an IgE response against a limited number of the components of a complex venom (perhaps as few as one component) in order to manifest enhanced acquired resistance to the morbidity and mortality induce by that venom.

The extent to which Th2 cell and IgE-associated adaptive immune responses can enhance resistance to other venoms or different types of environmental toxins remains to be determined. Similarly, it is not clear why, in some species or individuals, exposure to the same venom or venom component may induce either a protective Th2 cell-associated and IgE- and FcεRI-dependent adaptive immune response (as shown in mouse studies [146-148]) or a catastrophic and potentially fatal reaction (i.e., anaphylaxis). This question is of high interest for basic and clinical research.

Potential roles of IgE in host defense against venoms in humans

Tissue injury, irrespective of the causative agent, seems to be a major trigger of Th2 immune responses in mammals, including humans [21, 127]. Such Th2 responses, which occur in many different mammalian species (including humans, mice, cats, and dogs [162]), may serve a general function in host defense, including as a protective mechanism against venom toxins and other dangerous noxious substances, as well as in the setting of acquired immunity to helminths [143, 144] and perhaps other pathogens [15-17]. Most animal venoms are complex mixtures of biologically active amines, peptides and enzymes and often have neurotoxic and/or hemotoxic activity [163]. However, many venoms also contain compounds that cause tissue damage. The tissue damage induced by venoms could therefore generate the key danger signals sensed by the immune system that initiates type 2 immunity and directs development of IgE antibodies. For instance, the intrinsic Th2 adjuvant effect of BV seems to be related, at least in part, to the cytolytic BV component melittin [158, 164, 165]. Remarkably, many venoms contain one or more isoforms of PLA_2 [163]. The key enzymatic activity of PLA_2 is the hydrolysis of membrane phospholipids and the generation of arachidonic acid and lysophospholipids [166]. Such lysophospholipids can integrate into the phospholipid bilayer membrane of mammalian cells and result in cell lysis [166], and Palm *et al.* showed that subcutaneous injection of OVA together with either $bvPLA_2$ or lysophospholipids can induce the generation of OVA-specific Th2 cells [147].

In humans, it is possible that, in most individuals, the tissue damage induced by the venom contained in a single honey bee sting can be sufficient to induce a Th2 response which may be beneficial, rather than detrimental, and which could increase tissue resistance to subsequent BV challenge. Indeed, although many humans have been stung by bees or wasps at some point in their life and many of such individuals exhibit IgE antibodies to BV or wasp venom, only a very small proportion develop clinically detrimental immune responses upon subsequent exposure to such venoms (anaphylaxis represents the most extreme form of such adverse reactions) [167]. And in two studies, of 525 [168] or 220 [169] subjects, patients with Hymenoptera venom allergy and high levels of total IgE (≥ 100 kU/l [168] or ≥250 kU/l [169]) were significantly *less* likely to develop grade III reactions to venom (i.e., those associated with full shock [168] or with bronchoconstriction, emesis, anaphylactic shock or loss of consciousness [169]) than were those with lower levels of total IgE. In one of the

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studies, serum levels of venom-specific IgE also correlated inversely to the clinical reaction grades, but this trend did not achieve statistical significance (P = 0.083) [169].

While there might be a variety of reasons for the occurrence of such associations beyond just levels of total and venom-specific IgE [168, 169], these findings support the conclusion that the connection in humans between the development of IgE responses to venom and serious IgE-induced pathology upon a subsequent exposure to venom is complex. Moreover, Th2 responses are subject to substantial immune regulation, which in turn can diminish the pathology induced by exposure to the inducing antigen. For example, beekeepers, who are frequently exposed to bee venom, can exhibit high levels of BV-specific IgG and IgE, associated, in some of these individuals, with the danger of anaphylaxis [170]. However, in many beekeepers, exposure to multiple bee stings during the beekeeping season induces the development of BV-specific, IL-10-producing, inducible type 1 T regulatory (T_R1) cells, which suppress T cell responses to BV *in vitro* and which, *in vivo*, may contribute to the observed reduction in cutaneous late phase responses to bee stings which occur as the beekeeping season progresses [171]. Mechanisms of antigen-induced, regulatory T cell-dependent immune tolerance also are thought to contribute to the success of venom specific immunotherapy in patients with hymenoptera venom allergy [172].

Given the findings of our group [146] and of Palm *et al.* [147], it is tempting to speculate that IgE-dependent enhanced resistance to the toxicity of BV or bvPLA$_2$ may represent an initial phase of a beneficial adaptive immune response to BV which, in most individuals frequently exposed to the venom, then can be supplemented or supplanted by T regulatory cell-dependent immune tolerance to BV, one important function of which is to restrain the development of overly excessive, and therefore potentially dangerous, IgE responses to BV. In this scenario, we propose that anaphylaxis (as observed in a small fraction of people with IgE antibodies to BV) represents only the most extreme and maladaptive end of a spectrum of acquired Th2 immunity to venom, and that in most individuals appropriately regulated Th2 immune responses can actually enhance resistance, rather than susceptibility, to venoms. The reasons why certain unfortunate individuals exhibit severe IgE-dependent responses to venom (including anaphylaxis) may be complex, perhaps reflecting a combination of genetic and environmental factors which inordinately enhance (and/or diminish negative regulation of) IgE-dependent effector responses [149, 173, 174]. In fact, one can speculate that the dangerous potential of allergic Th2 responses in some individuals may represent the price paid to maintain, for the species, the benefits of IgE-associated Th2 immune protection.

Conclusions

While there is no doubt that mast cells and IgE can contribute to pathology and mortality in the setting of allergic diseases, this can't be the main evolutionary driver for the development of either mast cells or IgE. As a result, there has been a long standing interest in identifying beneficial roles for mast cells and IgE as well as a suspicion that, in light of the risk incurred when mast cells are extensively activated, the beneficial roles of mast cells and IgE may be substantial. In this article, we have reviewed evidence that, in some settings, mast cells and IgE can contribute to host defense against certain parasites, particularly helminths. However,

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in other settings mast cells and/or IgE may have net effects that contribute to the pathology associated with such infections, and/or that favor the survival or fecundity of the parasite. Given the long periods of co-evolution between parasites and their vertebrate hosts, and given that it not in the parasite's interest quickly to kill its host, it is not surprising that the relationship between elements of the host's innate and immune defenses and various parasites can be quite complex.

In addition to their role in responses to parasites, mast cells and IgE also can have prominent roles in innate and adaptive immune responses to venoms. In some unfortunate people who have developed IgE to components of venom, subsequent exposure to tiny amounts of that venom can induce anaphylaxis – a dramatically maladaptive response. However, most people who have IgE antibodies to components of venom have no history of anaphylactic reactions to such venoms. In mice, it is now clear that mast cells can be critically important components of innate responses that enhance resistance to the morbidity and mortality induced by diverse reptile or arthropod venoms, and that this reflects the ability of mast cells to release proteases that can degrade and detoxify key components of the venoms. In the case of honey bee venom and Russell's viper venom, IgE, and probably mast cells, also can significantly increase the resistance of mice to the pathology and mortality associated with exposure to otherwise lethal amounts of such venom.

There are multiple other mechanisms of host defense against venoms besides mast cells and IgE, and the roles of mast cells and IgE in host responses to venoms have been evaluated for the venoms of only a small number of venomous species. However, the findings obtained to date in mice support the hypotheses of Stebbings and Profet that components of “allergic defenses”, in this case mast cells and IgE, can be critical components of defenses against both arthropods and venomous animals. Given the long period of co-evolution of vertebrates with venomous reptiles (estimated by the fossil record to be ~200M years [175]) and the much longer existence during evolution of venomous arthropods [176], we propose that enhancing innate and adaptive immune responses that increase resistance to venoms may be ancient and fundamental beneficial roles of mast cells and IgE. And while anaphylaxis is always maladaptive if it is induced by small amounts of venom that otherwise would produce little pathology, the extensive systemic IgE-dependent activation of mast cells (resulting in the systemic release of venom-destroying proteases) may be beneficial to animals envenomated with potentially lethal amounts of venom. In that context even anaphylaxis can be adaptive, assuming of course that the envenomated animal survives the episode.

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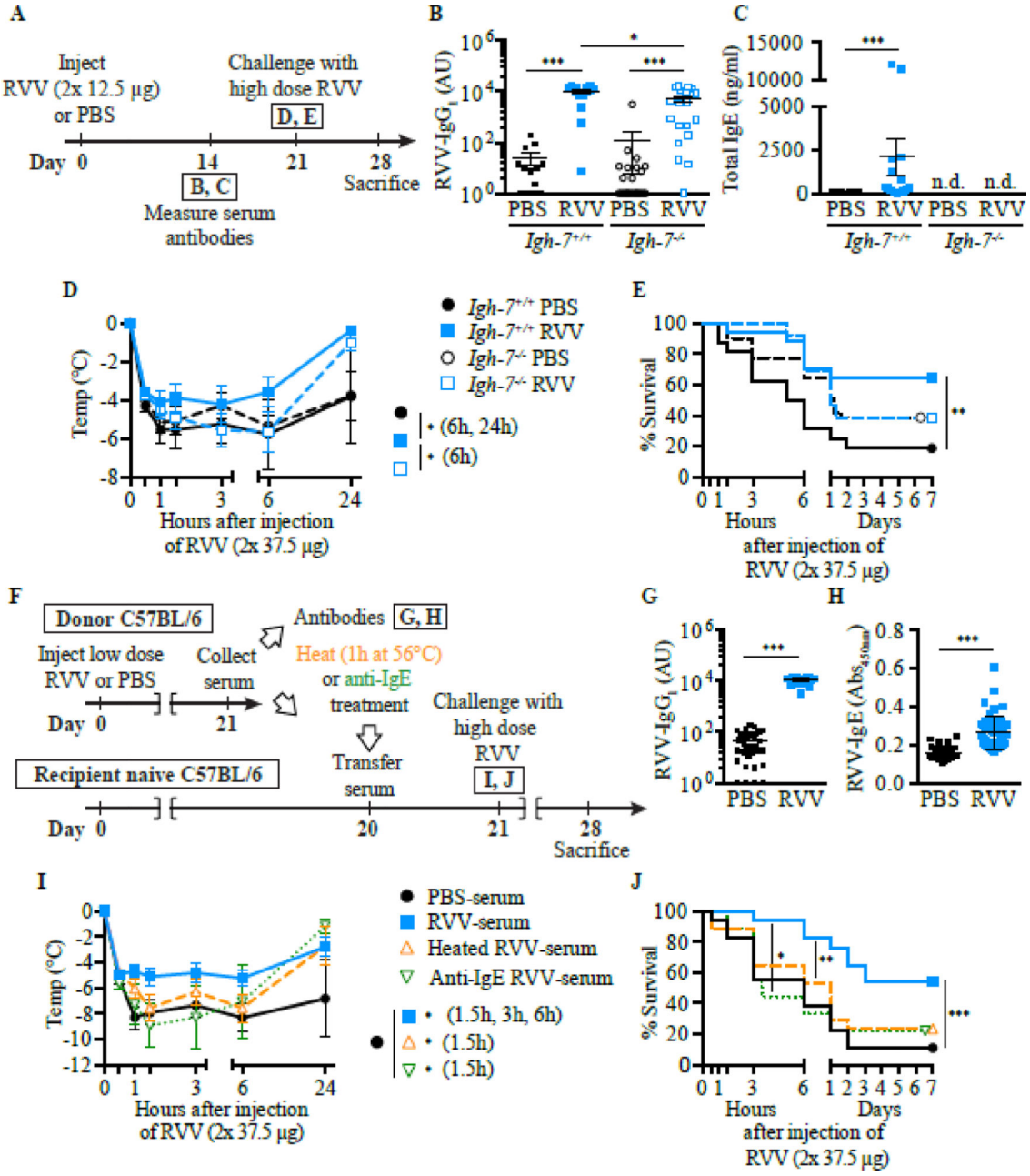

Fig 1.

IgE can contribute to acquired resistance to RVV. **A** Outline of experiments with IgE-deficient (*Igh-7*$^{-/-}$) and control (*Igh-7*$^{+/+}$) C57BL/6 mice (**B-E**). **B** and **C**, Serum RVV-specific IgG_1 (**B**) and total IgE (**C**). **D** and **E**, Body temperature (**D**) and survival (**E**). **F**, Outline of serum transfer experiments in C57BL/6 mice (**G-J**). **G** and **H**, Serum RVV-specific IgG_1 (**G**) and total IgE (**H**). **I** and **J**, Body temperature (**I**) and survival (**J**). Data were pooled from 3-4 experiments (n= 9-25/group). In **B**, **C**, **G** and **H**, data are shown as individual values and mean±SEM. *P* values were determined as follows: Mann-Whitney test (**B**, **C**, **G**, and **H**), Student *t* test (**D** and **I**) and Mantel-Cox test (**E** and **J**). *P<0.05, ** P<0.01, and *** P<0.001. n.d., Not detectable. This is a reproduction of Fig. 3 from Starkl P,

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Marichal T, Gaudenzio N, Reber LL, Sibilano R, Tsai M, Galli SJ. IgE antibodies, FcεRIα and IgE-mediated local anaphylaxis can limit snake venom toxicity. *J Allergy Clin Immunol*, 2016; 137: 246-57 (ref. [148]), reprinted with the permission of the publisher, Elsevier.

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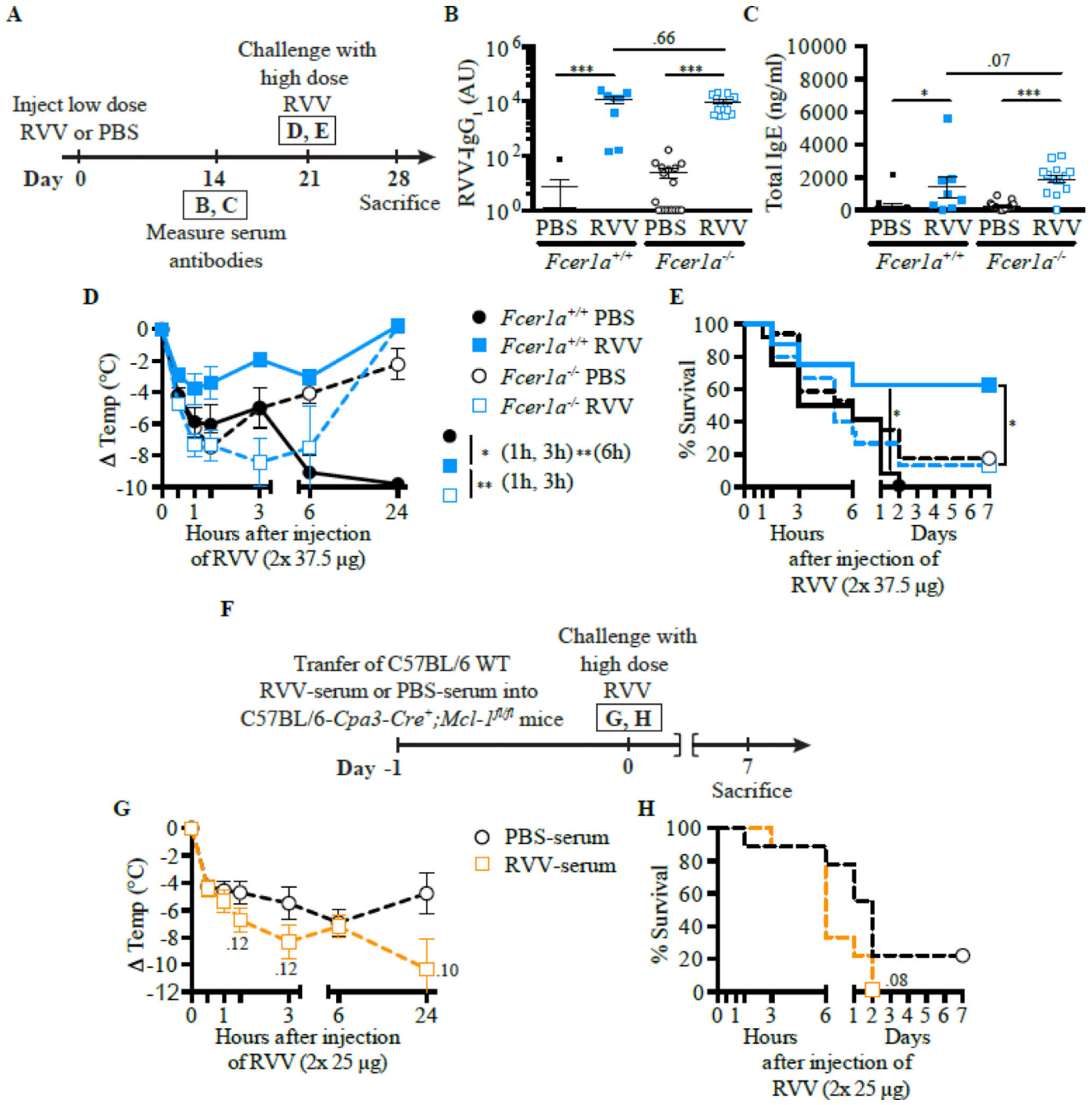

Fig 2.

FcεRIα and FcεRIα-bearing cells can contribute to acquired resistance to RVV. **A**, Outline of experiments with *Fcer1a*$^{-/-}$ and control (*Fcer1a*$^{+/+}$) C57BL/6 mice (panels **B-E**). **B** and **C**, Serum RVV-specific IgG_1 (**B**) and total IgE (**C**) levels. **D** and **E**, Body temperature (**D**) and survival (**E**). **F**, Outline of serum transfer experiments involving MC-deficient C57BL/6 mice (**G** and **H**). **G** and **H**, Body temperature (**G**) and survival (**H**). Data were pooled from 3 experiments (n=9-17/group). In **B** and **C**, data are shown as individual values and mean ±SEM. *P* values were determined as follows: Mann-Whitney test (**B** and **C**); Student *t* test (**D** and **G**); Mantel-Cox test (**E** and **H**). *P<0.05, ** P<0.01, and *** P<0.001. n.d., Not

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detectable. This is a reproduction of Fig. 4 from Starkl P, Marichal T, Gaudenzio N, Reber LL, Sibilano R, Tsai M, Galli SJ. IgE antibodies, FcεRIα and IgE-mediated local anaphylaxis can limit snake venom toxicity. *J Allergy Clin Immunol*, 2016; 137: 246-57 (ref. [148]), reprinted with the permission of the publisher, Elsevier.

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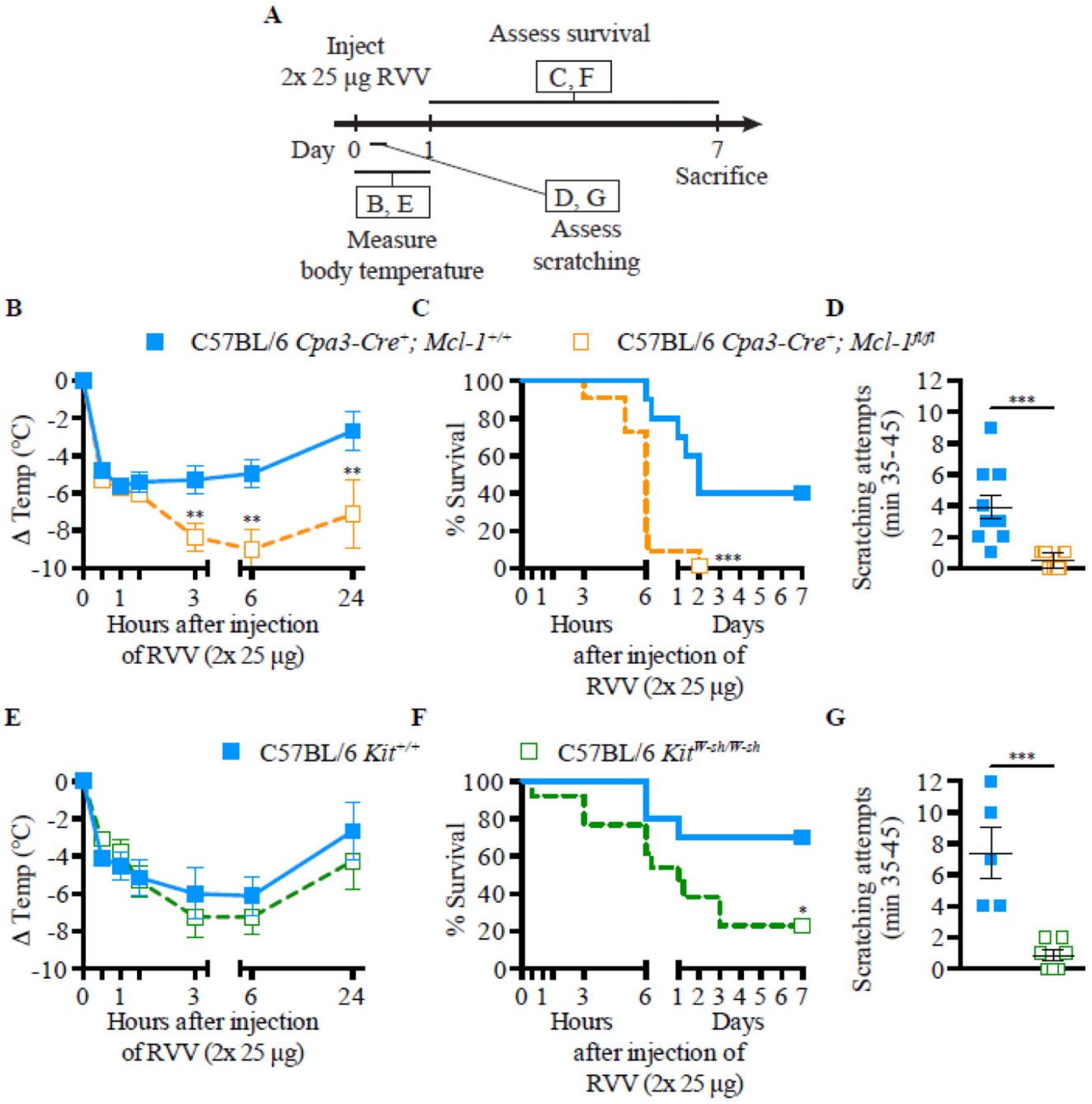

Fig 3.

MCs can contribute to innate resistance and behavioral responses to RVV. Experimental outline (**A**), body temperature (**B** and **E**), survival **(C** and **F)**, and scratching attempts (**D** and **G**) of MC-deficient *Cpa3-Cre*$^{+}$; *Mcl-1*$^{fl/fl}$ (**B-D**) and *Kit*$^{W\text{-}sh/W\text{-}sh}$ (**E-G**) mice and corresponding control mice after RVV injection. In **D** and **G**, data are shown as individual values and mean±SEM. *P* values were determined as follows: Student *t* test (**B, D, E,** and **G**) and Mantel-Cox test (**C** and **F**). Data were pooled from 2-4 experiments (n=5-21/group). **P*<0.05, ** *P*<0.01, and *** *P*<0.001. This is a reproduction of Fig. 2 from Starkl P, Marichal T, Gaudenzio N, Reber LL, Sibilano R, Tsai M, Galli SJ. IgE antibodies, FcεRIα

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Table 1

Potential contribution of IgE to parasite resistance

	Model	Results	References
Nematodes			
Trichinella spiralis	**Treatment/ Model**	**Worms**	**Muscle Larvae**	**Reference**
	Anti-IgE treatment in Wistar/Lewis rats	N.D	Increased (2-3 fold) (~week 4)	[177]
	IgE and T cell transfer in Albino Oxford rats	Decreased (by ~40%) (24 h after infection)	N.D.	[178]
	SJA/9 mice (genetically IgE-deficient mice)	N.D	No effect (week 4 or 9 in primary, week 4 in secondary)	[42]
	Transfer of IgE without parasite specificity into (BALB/c × SJL/J) F1, (C57BL/6 × DBA/2) F1, BALB/c, and SJL/J mice	N.D	Increased (~1.5 fold) except in IgE-low responder SJL/J (week 5)	[34]
	BALB/c IgE-deficient mice	Increased from days 7-28	Increased (~2 fold, day 28)	[37]

Trichinella muris	**Model**	**Worms**	
	C57BL/6 FcRγ-deficient mice	No effect throughout the experiments from days 10-35	[179]
	C57BL/6 μMT mice	Increased at day 35 (worms are expelled by day 35 in wild-type mice)	[180]

Angiostrongylus costaricensis	**Model**	**Worms**	
	SJA/9 mice	No effect on day 45	[181]

Nippostrongylus brasiliensis	**Model**	**Worms**	**Egg production**	
	BALB/c J_HD mice	No effect (day 7 in primary or day 7 in secondary)	No effect (day 7 in primary or day 7 in secondary)	[74]
	C57BL/6 AID-deficient mice	No effect (days 6 or 10)	N.D.	[75]
	SJA/9 mice	No effect (day 7 or 14 in primary, day 7 in secondary)	N.D.	[42]

Heligmosomoides polygyrus	**Model**	**Worms**	**Egg production**	
	BALB/c J_HD mice	No effect (day 14 in primary or day 14 in secondary)	No effect (day 14 in primary or day 14 in secondary)	[74]
	BALB/c IgE-deficient mice	No effect (days 14-20 in secondary infection)	N.D.	[182]
	C57BL/6 J_HD mice	Unable to mount a protective immune response (days 14-20 in secondary infection)	N.D.	
	C57BL/6 AID-deficient mice			
	C57BL/6 FcRγ-deficient mice	Partially able to mount a protective immune response (at days 14-20 in the secondary infection, there were <10% the number of worms vs. in the primary infection in wild-type mice vs. 30% in FcRγ-deficient mice)	N.D.	

Strongyloides venezuelensis	**Treatment/ Model**	**Worms**	**Egg production**	
	C57BL/6 AID-deficient mice	No effect on day 8 but 3-4 fold higher on day 10	9 day delay in clearance	[75]

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Strongyloides venezuelensis	**Treatment/ Model**	**Worms**	**Egg production**	
	BALB/c FcεRIα-deficient mice	N.D.	No effect on clearance	
	Anti-IgE antibody injection into wild-type mice	No effect	N.D.	
	Serum injection from *S.v.* infected mice (IgE, IgG, or IgE + IgG) into C57BL/6 AID-deficient mice	Lower worm burden on day 7 (~50% reduction after IgE, or IgG injections, 80-90% reduction after IgG + IgE injections)	N.D.	
	C57BL/6 FcRγ-deficient mice	No effect on day 8 but increased on day 13	Increased (days 9-13)	[61]

Brugia malayi	**Model**	**Worms**	
	BALB/c IgE-deficient mice	Increased at peak (2-3 fold, weeks 2 to 6 in primary infection); no effect in secondary infection	[36]
	C57BL/6 μMT mice	More microfilariae in blood (3-15 fold, between days 56-93)	[183]
	C57BL/6 FcRγ-deficient mice	More microfilariae in blood (8-10 fold on day 60)	

Brugia pahangi	**Model**	**Worms**	
	C57BL/6 μMT mice	Unable to mount protective immune response on secondary infection (day 14)	[184]
	BALB/c J_HD mice	Increased (weeks 3 and 12)	

Malaria

***Plasmodium berghei* (*Pb*ANKA)**	**Treatment/ Model**	**Parasitemia**	**Survival**	
	Anti-IgE treatment in C57BL/6 wild-type mice	Increased (~2 fold on days 6 and 7)	Shorter (at least 2 days)	[104]
	C57BL/6 FcεRIα-deficient mice	Lower (between days 18-22)	Higher survival rate after day 15	[185]
	C57BL/6 IgE-deficient mice	N.D.	3-4 weeks longer	

Other parasites

Schistosoma mansoni	**Treatment/ Model**	**Worms**	**Egg production**	**Granuloma size**	
	129/terSv IgE-deficient mice	Increased adult worms (by 50% at week 8)	N.D.	Smaller (by ~40% at week 8)	[35]
	BALB/c FcεRIα-deficient mice	No effect (week 8)	No effect (eggs in tissues, week 8)	Larger (by ~25% at week 8)	[40]
	Anti-IgE treatment in BALB/c wild-type mice	Decreased (by ~50% at week 8)	Decreased eggs in liver (by ~80% at week 8); Decreased egg production per worm (by ~60% at week 8)	Smaller (week 8)	[39]
	C57BL/6 μMT mice	No effect (week 8)	No effect on eggs in liver or intestine (week 8); lower egg excretion (by ~70% at week 8)	Larger (by 42% at week 8, 50% at week16)	[186]
	C57BL/6 FcRγ-deficient mice	N.D.	No effect (week 8)	Larger (by ~20% at week 8, ~50% at week 16)	
	SJA/9 mice	No effect (week 8)	No effect (week 8)	N.D	[187]

Shistosoma japonicum	**Model**	**Worms**	**Granuloma size**	
	SJA/9 mice	No effect (week 8)	Smaller (by 40-50%) on week 8	[188]

Ticks			
Haemaphyasalis longicornis	**Treatment/ Model**	**Resistance**	
	Serum transfer to WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice	IgE and mast cells were required for serum transfer of resistance to secondary infestation	[108]
	C57BL/6 FcRγ-deficient mice	No resistance to secondary infestation	[109]

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Table 2

Potential contribution of mast cells to parasite resistance

	Model	Results		References
Nematodes				
Trichinella spiralis	**Treatment/Model**	**Worms**	**Muscle Larvae**	
	Anti-c-Kit antibody treatment in NIH mice	Increased (3 fold on day 10)	N.D.	[49]
	Anti-c-Kit or anti-SCF antibody treatments in NIH mice	Increased (5-15 fold on day 10) after injections of either anti-c-Kit or anti-SCF antibodies	N.D.	[50]
	WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice	Delay in expulsion (at least 7 days)	~2 fold increase	[80]
	WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice and WCB6F$_1$-*Mgf*$^{Sl/Sl\text{-}d}$ mice	Increased (*Kit*$^{W/W\text{-}v}$ mice: 8-9 fold, *Mgf*$^{Sl/Sl\text{-}d}$ mice: 3-4 fold) on day 12	N.D.	[81]
	WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice	9-13 day delay in expulsion	N.D.	[79]
	WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice	3-4 fold increase on day 13	N.D.	[82]
	BALB/c mMCP-1-deficient mice	10-15 fold increase on days 15-16	Increased on day 30	[53]
	C57BL/6 mMCP-6-deficient mice	No effect from days 4-18	% necrotic larvae decreased (week 5)	[62]

Trichinella muris	**Treatment/ Model**	**Worms**	
	Anti-c-Kit antibody treatment in BALB/c or C57BL/6 mice	Lower (~20% on day18)	[179]
	C57BL/6-*Kit*$^{W\text{-}sh/W\text{-}sh}$ mice	Increased (~3 fold on day 21)	[66]

Nippostrongylus brasiliensis	**Treatment/ Model**	**Worms**	**Egg production**	
	MF-1 mMCP-1-deficient mice	Increased on day 8, but no effect on day 10	No effect	[189]
	SCF/anti-SCF antibody injections in Wistar rats	N.D.	SCF: increased; Anti-SCF: decreased	[124]
	WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice	No effect (days 7 or 14)	N.D.	[69]
	C57BL/6-*Kit*$^{W\text{-}sh/W\text{-}sh}$ mice	~4 day delay in expulsion in primary, but no effect in secondary	N.D.	[68]
	BALB/c mMCP-1 deficient mice	N.D.	No effect	[53]
	BN-DonryuF$_1$-*Kit*$^{W\text{-}s/W\text{-}s}$ rats	N.D.	Decreased on day 8 (~25-30%) but no effect on day 11	[125]
	BALB/c IL-3-deficient mice	N.D.	No effect	[190]
	IL-3-deficient *Kit*$^{W/W\text{-}v}$ mice (mixed background of C57BL/6 & WBB6)	N.D.	No effect	

Heligmosomoides polygyrus		**Worms**	**Egg production**	
	WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice	No effect (weeks 3 or 9)	N.D.	[191]
	WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice and C57BL/6-*Kit*$^{W\text{-}sh/W\text{-}sh}$ mice	Increased (~2 fold at week 3 in primary; ~10-20 fold in secondary)	Increased (2-3 fold on days 14-18)	[66]

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Strongyloides venezuelensis		**Worms**	**Egg production**	
	C57BL/6 and BALB/c IL-3-deficient mice	N.D.	2-3 day delay in expulsion; increased egg numbers at peak	[51]
	WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice	N.D.	12 day delay in expulsion; increased egg numbers at peak	
	IL-3-deficient *Kit*$^{W/W\text{-}v}$ mice (mixed background of C57BL/6 & WBB6)	Increased (~500 fold on days 18 and 19)	35 day delay in expulsion; increased egg numbers at peak	
	WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice	Increased (day 14)	7-10 day delay in expulsion	[78]
	129 5-lipoxygenase (5-LO)-deficient mice	Increased (2-3 fold on days 9-14)	Increased (2-3 fold on days 7-14)	[64]
	IL-2 + IL-18 injections into C57BL/6 wild-type mice	Rapid expulsion after implantation of adult worms	N.D.	[48]
	WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice	N.D.	6-7 day delay in expulsion; increased egg numbers at peak	
	BALB/c PI3K-deficient mice	Increased (~200-250 fold on day 13)	11 day delay in expulsion; increased egg numbers at peak	[87]

Strongyloides ratti		**Worms**	**Egg production**	
	IL-3 administration into Wistar rats and C57BL/6 wild type mice	Decreased (IL-3 dose-dependently)	N.D.	[46]
	WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice	Increased larvae (2-3 fold on day 2) and ≥3 day delay in expulsion assessed by counts of larvae	N.D.	[76]
	BALB/c *Cpa3*^{Cre} mice	Increased (by 3-4 fold on day 6)	N.D.	[115]

Malaria

Plasmodium yoelii		**Parasitemia**	**Survival**	
	WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice	Increased on day 3 but no effect thereafter (co-infection with *Salmonella typhimurium* on day 10)	N.D.	[92]

***Plasmodium berghei* (*Pb*ANKA)**				
	C57BL/6-*Kit*$^{W\text{-}sh/W\text{-}sh}$ mice	No effect	No effect	[185]
	WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice	Increased (~3 fold)	1-2 weeks shorter	[192]
	C57BL/6 Histidine decarboxylase (HDC)-deficient mice	Decreased (after either mosquito bites or injections of infected erythrocytes)	~13 day longer survival (after either mosquito bites or injections of infected erythrocytes)	[98]
	WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice	Increased (days 7-9)	N.D.	[101]

Other parasites

Schistosoma japonica		**Worms**	**Granuloma size**	
	WBB6F1-*Kit*$^{W/W\text{-}v}$ mice	No effect (week 7)	Smaller (by 20-40%, week 7)	[193]

Leishmania major		**Cutaneous *Leishmaniasis***	**Parasite Burden**	
	WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice	No effect on histopathological features (up to day 150)	N.D.	[116]
	WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice and WCB6F$_1$-*Mgf*$^{Sl/Sl\text{-}d}$ mice	Reduced size of cutaneous lesions in each type of mouse (throughout the experiments)	No effect	[117]

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Leishmania major		**Cutaneous *Leishmaniasis***	**Parasite Burden**	
	WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice	Larger size of lesions (weeks 2-10)	Larger number (spleen, weeks 1 & 3; ear, week 4)	[118]
	C57BL/6 and BALB/c *Cpa3*^{Cre} mice	No effect (throughout the experiments)	No effect	[119]

Ticks			
Haemaphyasalis longicornis		**Resistance**	
	WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice	No resistance on secondary or third infestation	[194]
	C57BL/6-*Kit*$^{W\text{-}sh/W\text{-}sh}$ mice	No resistance on secondary infestation	[109]

Dermacentor variabilis		**Resistance**	
	WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice	No resistance on primary or secondary infestation, but acquired resistance was observed on third and fourth infestations	[195]