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## Mast cells: Versatile regulators of inflammation, tissue remodeling, host defense and homeostasis

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### Summary

The possible roles of mast cells in health and disease have been a topic of interest for over one hundred and twenty five years. Many adaptive or pathological processes affecting the skin or other anatomical sites have been associated with morphological evidence of mast cell activation, and/or with changes in mast cell numbers or phenotype. Such observations, taken together with the known functions of the diverse mediators, cytokines and growth factors which can be secreted by mast cells, have suggested many potential functions for mast cells in health and disease. Definitively identifying the importance of mast cells in biological responses in humans is difficult. However, mutant mice which are profoundly mast cell-deficient, especially those which can undergo engraftment with wild type or genetically-altered mast cells, provide an opportunity to investigate the importance of mast cells, and specific mast cell functions or products, in various adaptive or pathological responses in mice. Such work has shown that mast cells can significantly influence multiple features of inflammatory or immune responses, through diverse effects that can either promote or, surprisingly, suppress, aspects of these responses. Through such functions, mast cells can significantly influence inflammation, tissue remodeling, host defense and homeostasis.

### Keywords

Allergy; asthma; immunosuppression; IL-10; innate immunity

### 1. Introduction

Von Recklinghausen may have been the first to observe what later came to be called mast cells [1]. However, Paul Ehrlich provided the first description of some of the distinctive histochemical features of the cells that he shortly thereafter named “Mastzellen” (or “well fed cells”) [2]. Ehrlich also reported that human tissues affected by chronic inflammation exhibited striking increases in mast cell numbers [2].

The application of morphological approaches to the analysis of human and experimental animal tissues has resulted in the description of a long list of conditions in which mast cell numbers are increased, mast cell anatomical distribution or phenotype is altered, and/or mast cell

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activation is evident [3–8]. Moreover, the list of agents that can stimulate immunological or non-immunological activation of mast cells continues to grow [3,4,7–10] (Table 1), as does our understanding both of the diversity of actions that can be mediated by the secreted products of mast cells and of mast cell functions that can be expressed independently of the secretion of stored or newly synthesized products [3,5,8,9,11–13].

Such findings invite speculation about a extremely broad spectrum of potential mechanisms by which mast cells might influence the development, extent or duration of inflammatory and other biological responses [3,4,8–10,13]. However, it can be quite challenging to prove that mast cells can perform such proposed functions *in vivo*, and even more difficult to assess the biological importance of such mast cell-dependent contributions.

In this article, we review some basic principles of mast cell biology and then describe one approach for investigating mast cell function *in vivo*: analyzing models of adaptive or pathological responses in *c-kit* mutant mast cell-deficient mice, the corresponding wild type mice, and *c-kit* mutant mice that have been selectively engrafted with wild type or genetically-altered mast cells. We then describe how this approach has been used to study the roles, and importance, of mast cells in some biological responses which are associated with inflammation and tissue remodeling, or that contribute to host defense or homeostasis.

## 2. Mast cell biology

### 2.1. Mast cell development, anatomical distribution and phenotype

Mast cells occur in virtually all vascularized tissues where they ordinarily reside in close proximity to blood vessels, nerves, smooth muscle cells, epithelial cells, mucus-producing glands and hair follicles; they can be especially numerous in anatomical sites that are directly exposed to the environment, including the skin, airways and gastrointestinal tract [3–5,8,14].

Mast cells arise from hematopoietic progenitor cells and mature mast cells ordinarily do not circulate in the blood; instead, mast cells acquire their mature phenotype locally in the tissues where they ultimately reside [14]. Moreover, several lines of evidence indicate that changes in mast cell numbers, tissue distribution and/or phenotypic characteristics can be regulated by growth factors such as the c-Kit ligand, stem cell factor (SCF), the main survival and developmental factor for mast cells, interleukin-3 (IL-3), and the T helper type 2 (Th2) cell-associated cytokines IL-4 and IL-9, and probably many other factors [3–5,8,14].

Variation in the phenotype of mast cells at different anatomical sites, or during the course of individual biological responses, has been called “mast cell heterogeneity” [8,14–17]. The ability of the mast cell lineage to generate individual populations that differ in functional properties, mediator content and/or other aspects of phenotype probably confers on mast cells a potentially complex functional repertoire, in which both the ways the cell can be activated and the specific functions it can express can vary according to the requirements of the individual physiological, immunological, inflammatory, or other biological responses in which this cell participates.

### 2.2. Mast cell activation and secreted products

As a group, mast cells have the potential to secrete a wide variety of biologically active products upon exposure to many different immunological or non-immunological stimuli. Depending on the particular mechanism of mast cell activation and the strength of the stimulus, mast cells may release either distinct subsets of mediators and/or a large array of products [4,5,9,18].

The best studied mechanism of mast cell activation is that induced by the crosslinking of FcεRI, the high affinity receptor for IgE, e.g. with IgE and specific bi- or multi-valent antigen

(Table 1). IgE can also bind to the IgG receptors FcγRII and FcγRIII, and to galectin-3, which are expressed on some mast cell populations, but IgE is thought to influence mast cell function mainly through its interaction with FcεRI [4,5,18,19]. In mice, mast cells can also be activated to degranulate and release mediators in response to antigen- and IgG<sub>1</sub>-dependent signaling through FcγRIII [5,20–22].

However, activation through Fc receptors is only one of many potential mechanisms of mast cell activation (Table 1). For example, mast cells can be activated directly by pathogens, including bacteria, viruses and parasites, as well as by many soluble products derived from these pathogens. Microbial products can activate mast cells directly via toll-like receptors or receptors for bacterial toxins, or indirectly, e.g., by activating the complement system that then can generate products that interact with appropriate receptors expressed by mast cells [9,23, 24]. Furthermore, mast cells can be activated by a variety of endogenous and exogenous peptides, cytokines and other inflammatory mediators [4,5,10,25,26].

Upon appropriate activation, mast cells can release a diverse array of potent biologically active products (which sometimes are called “mediators”). These mediators can be classified as: 1) preformed mediators, that are stored in the cells’ prominent cytoplasmic granules; including histamine (and in rodents, serotonin), proteoglycans, and proteases such as chymase, tryptase and carboxypeptidase A; 2) *de novo* synthesized lipid mediators, e.g., metabolites of arachidonic acid via either the cyclooxygenase (e.g., PGD<sub>2</sub>) or lipoxygenase (e.g., LTC<sub>4</sub>) pathways; and 3) a large number of cytokines, chemokines and growth factors [3,4,8,11,12].

Many of these products are regarded as “pro-inflammatory” in that, individually or in concert, they can elicit features of inflammation that are observed in settings of acute and/or chronic inflammation, e.g., vasodilatation, plasma extravasation and the recruitment and activation of granulocytes (i.e., neutrophils, eosinophils and basophils), T cells, B cells, dendritic cells and monocytes [4,8,9,27,28]. Mast cell products also can promote changes in the tissues that are affected by such inflammatory responses, including the local degradation or remodelling of structural elements of the tissues, which can be associated with significant changes in the function of the affected organs [29–31].

However, some of the products which might be released by mast cells during individual biological responses can suppress features of these responses. IL-10 and TGF-β, for example, each of which is known to have anti-inflammatory or immunosuppressive properties, are expressed by mast cells and can be released upon their appropriate activation [4,32–34]. It therefore can be difficult to predict, in a particular biological response, whether the net effect of mast cell participation will be to promote or to suppress the response (or perhaps to have both effects, but at different stages of the response).

### 3. *C-kit* mutant mast cell-deficient and ‘mast cell knock-in’ mice

Although *in vitro* studies of mast cells can be very useful for investigating mechanisms by which mast cells might influence adaptive immunity or other biological responses, it is important to attempt to assess the *in vivo* relevance and biological importance of such *in vitro* observations. *c-kit* mutant mice that virtually lack mast cell populations can be employed to assess the importance of mast cells in regulating the expression of biological responses *in vivo*.

The most commonly used model for such studies has been the (WB/ReJ × C57BL/6J)F<sub>1</sub>-*Kit*<sup>W/W<sup>-v</sup></sup>, or WBB6F<sub>1</sub>-*Kit*<sup>W/W<sup>-v</sup></sup>, mouse [35–37] (Fig. 1). However, C57BL/6-*Kit*<sup>W<sup>-sh</sup>/W<sup>-sh</sup></sup> mice are now gaining popularity as an alternative model [38–40]. Although each of these *c-kit* mutant mice is profoundly mast cell-deficient and also virtually lacks melanocytes and interstitial cells of Cajal, the double dose of *W<sup>-sh</sup>* mutations in C57BL6-*Kit*<sup>W<sup>-sh</sup>/W<sup>-sh</sup></sup> mice results in fewer, or

less severe, phenotypic abnormalities than are observed in *Kit*<sup>W/W<sup>-v</sup></sup> mice; for example, unlike WBB6F<sub>1</sub>-*Kit*<sup>W/W<sup>-v</sup></sup> mice, C57BL/6-*Kit*<sup>W-sh/W-sh</sup> mast cell-deficient mice are not anemic and are fertile, and therefore can easily be crossed with mice carrying other defined genetic abnormalities of interest [5,38–40].

The mast cell deficiency of C57BL/6-*Kit*<sup>W-sh/W-sh</sup> mice, like that of WBB6F<sub>1</sub>-*Kit*<sup>W/W<sup>-v</sup></sup> mice, can be selectively “repaired” by the adoptive transfer of genetically compatible, *in vitro*-derived mast cells [39,40] (Fig. 1). Such mast cells can be derived from bone marrow cells (i.e., bone marrow-derived, cultured mast cells) of the congenic wild-type mice or various transgenic or mutant mice [36], from BMCs that are transduced with shRNA in order to reduce expression of proteins of interest [26], from other sources of hematopoietic cells (such as fetal liver), or directly from embryonic stem cells (embryonic stem cell-derived cultured mast cells [ESCMCs])[37]. These *in vitro*-derived mast cells can be administered by intravenous, intraperitoneal, or intradermal injection [14,36,39] or by direct injection into the anterior wall of the stomach [41] to create so-called “mast cell knock-in mice” (Fig. 1).

Mast cell knock-in mice can be used to assess the extent to which differences in the expression of biological responses observed in *c-kit* mutant mast cell-deficient mice and the corresponding wild-type mice reflect the absence of mast cells (or the reduction or absence of specific proteins expressed by mast cells), as opposed to consequences of the *c-kit* mutations that are independent of their effects on mast cells. However, in conducting studies of this type, it is important to recognize that the phenotypic characteristics, and the anatomical distribution and numbers, of adoptively-transferred mast cells change in the interval after the injection of the mast cell populations into the recipient *c-kit* mutant mice. Therefore, decisions about how to design and interpret the results of experiments employing such mice should take these facts into consideration, as described in detail elsewhere [5,28].

## 4. Functions of mast cells in specific biological responses

We will now provide a few examples of how mast cell knock-in mice can be used to identify and to assess the importance of mast cell functions during adaptive or pathological host responses, particularly those involving the skin, and to define the mechanisms by which mast cells express such functions in these settings.

### 4.1. Mast cells, and mast cell-derived TNF, can promote elongation of cutaneous nerves during contact hypersensitivity in mice

Several groups have investigated the role of mast cells in contact hypersensitivity (CHS) in mice. As reviewed in detail elsewhere [42], studies in genetically mast cell-deficient *c-kit* mutant mice and the congenic wild type mice have shown that mast cells can enhance tissue swelling, and leukocyte infiltration, in some models of CHS in mice but not in others. Indeed, we found that, in some experiments assessing the magnitude of CHS responses in mice, reactions measured 24 h after challenge in sensitized mice were slightly but significantly greater in mast cell-deficient mice than in the corresponding wild type mice [43].

In a different model of CHS, mast cells, and antigen-independent effects of IgE, were required for optimal sensitization for CHS, presumably reflecting effects of mast cells on the phenotype, function and/or migration of cutaneous dendritic cells (DCs) in this setting [42]. Mast cells also can promote DC migration from the skin to local lymph nodes in other settings: after activation with IgE and antigen (by a mechanism involving histamine) [44] or, in a model of CHS, during the first 24 h after initial epicutaneous application of fluorescein isothiocyanate (by a mechanism involving mast cell-derived TNF) [45].

Thus, the potential roles of mast cells in CHS are complex, and may vary depending on the details of the CHS protocol tested, such as the type and concentrations of hapten used for sensitization and challenge, and the composition of the vehicle used in that model. However, most studies of the roles of mast cells in such reactions have focused on the increases in vascular permeability, the tissue swelling, and/or the leukocyte infiltration elicited at sites of hapten challenge. We were interested in observations that lesions of contact eczema [46] or atopic dermatitis [47] in humans can exhibit increases in epidermal nerves, and attempted to assess in a mouse model whether mast cells might influence cutaneous nerves at sites of CHS.

We found that CHS reactions to oxazolone (OX) in mice were associated with significant increases in the length of nerves in the epidermis and dermis [48] (Fig. 2). Using the mast cell knock-in approach, in which genetically mast cell-deficient *c-kit* mutant mice were engrafted intradermally with either wild type or TNF-deficient mast cells, we found that mast cells, and mast cell-derived TNF, significantly contributed to the elongation of epidermal and dermal PGP 9.5<sup>+</sup> nerves and dermal CGRP<sup>+</sup> nerves (Fig. 3), as well as to the inflammation, at sites of CHS to OX [48].

We do not yet know whether TNF, or other mast cell products, influenced nerve elongation in this reaction directly, indirectly (e.g., via the promotion of local inflammation) or by both direct and indirect mechanisms. However, these observations show that mast cells, and mast cell-derived TNF, can promote the elongation of cutaneous nerve fibers during this model of CHS in the mouse.

#### 4.2. Mast cell-dependent tissue remodeling in a mouse model of chronic asthma

Mast cells also can regulate tissue remodeling in the lungs. For example, we demonstrated that mast cells contribute significantly to increases in both the number of mucus-producing goblet cells in the airways and in lung collagen content in a mouse model of chronic allergic inflammation [49]. Although the mast cell-derived products that are responsible for these “tissue remodeling” effects remain to be defined, we showed that mast cell-dependent enhancement of goblet cell numbers can occur even in mice whose mast cells lack the ability to signal either via the high affinity IgE receptor (FcεRI) or via FcγRIII (which can bind immune complexes of IgG1 and specific antigen). By contrast, other features of this chronic asthma model are markedly diminished in mice in which only mast cells lack the signaling FcR γ chain common to FcεRI and FcγRIII. Thus, in this mouse model of chronic asthma, it appears that mast cells markedly enhance the development of multiple features of the response, but they do so in response to factors which activate the cells via either antibody/FcR γ-dependent or alternative mechanisms.

Our studies of the roles of mast cells in various cutaneous or pulmonary responses, and work by others with mast cell knock-in mice showing that mast cells can contribute to the development of pathology in models of EAE [27] or antibody-dependent arthritis [50], strongly suggest that mast cells can contribute to tissue damage and tissue remodeling in various anatomical sites via multiple direct or indirect mechanisms, and can be activated to express such functions by different potential stimuli in different settings.

#### 4.3. Mast cells, and mast cell-derived IL-10, can limit the magnitude and duration of CHS responses to urushiol or DNFB in mice

CHS can develop in response to exposure to plants in the Toxicodendron genus (Anacardiaceae), including poison oak, poison ivy and poison sumac, and the cashew, mango and Japanese lacquer trees [51]. CHS to poison oak (*Toxicodendron diversilobum*) or poison ivy (*T. radicans*) is mediated by T lymphocytes specific for catechols (e.g., heptadecylcatechol or pentadecylcatechol) present in urushiol, the allergen-containing sap of such plants [52]. As

reviewed in [34], antigen-specific CD8<sup>+</sup> T cells are thought to be effectors of urushiol-induced CHS in humans and in mice; CHS to 2,4-dinitrofluorobenzene (DNFB) in mice is also mediated by DNFB-specific CD8<sup>+</sup> T cells.

CHS to urushiol in humans can include the development, 8 – 48 h after exposure, of intensely pruritic vesicular skin lesions that can remain for up to 3 weeks [51]. In severe cases, lesions can develop frank necrosis, with ulceration of the epidermis and the development of striking epidermal hyperplasia [51,53].

As noted above, while the importance of mast cells in the elicitation of CHS was once controversial, it is now clear that mast cells can enhance the magnitude of the tissue swelling and leukocyte infiltration associated with some but not all models of CHS in mice. However, the prior studies of the role of mast cells in CHS examined the reactions for only 24, 48 or, in one study, 72 h [43] after a single challenge with hapten. Because we wished to evaluate whether mast cells might influence the long-term consequences of CHS responses, including their resolution, we examined CHS reactions to urushiol or DNFB for up to 15 d after a single epicutaneous challenge with hapten.

Beginning 3 d after challenge with urushiol or DNFB, mast cell-deficient WBB6F1-*Kit*<sup>W/W-v</sup> (Fig. 4) or C57BL/6 (B6)-*Kit*<sup>W-sh/W-sh</sup> mice exhibited significantly stronger CHS responses than did the corresponding wild-type mice [34]. In mast cell-deficient mice, tissue swelling increased progressively and peaked ~ 5 – 7 d after hapten challenge [34]. The tissue swelling and histological evidence of inflammation associated with CHS responses to urushiol or DNFB (Fig. 4) in WT BMCMCs→*Kit*<sup>W/W-v</sup> mice resembled that in wild-type mice [34]. Comparison of responses in *Kit*<sup>W/W-v</sup> mice engrafted with WT *versus Il10*<sup>-/-</sup> BMCMCs showed that the ability of mast cells to produce IL-10 contributed significantly to their ability to limit and hasten the resolution of the ear swelling associated with CHS responses to either urushiol or DNFB [34]. At 5 d after hapten challenge, reactions in mast cell-deficient *Kit*<sup>W/W-v</sup> mice or *Il10*<sup>-/-</sup> BMCMCs→*Kit*<sup>W/W-v</sup> mice, compared to those in wild-type mice or in WT BMCMCs→*Kit*<sup>W/W-v</sup> mice, were associated with substantial dermal leukocyte infiltration, hyperplasia and focal ulceration of the epidermis, and expansion/edema of the dermis.

Very similar findings were obtained when the experiments were repeated in mast cell-deficient *Kit*<sup>W-sh/W-sh</sup> mice, the corresponding wild-type B6 mice, and B6 (WT) or *Il10*<sup>-/-</sup> BMCMCs→*Kit*<sup>W-sh/W-sh</sup> mice, using either urushiol or DNFB [34].

Thus, work with two different types of genetically mast cell-deficient mice indicates that mast cells, and mast cell-derived IL-10, can markedly limit the magnitude of CHS responses to urushiol or DNFB, including the numbers of activated granulocytes and macrophages, and CD8<sup>+</sup> and CD4<sup>+</sup> T cells in the reactions sites, and can markedly reduce focal necrosis (Table 2) and ulceration of the epidermis at such sites [34]. Our *in vitro* and *in vivo* data indicate that, in the models of CHS tested, the mast cells' ability to limit the responses reflects, at least in part, the cells' activation *via* IgG1 antibodies and FcR3 [34]. Taken together, our findings suggest that, in mice which have been sensitized epicutaneously to certain haptens, the development of an antigen-specific IgG1 response can result in enhanced Fcγ-dependent mast cell IL-10 production, and that this represents one mast cell-dependent mechanism for limiting the extent and duration of such CHS reactions. However, our finding that several aspects of the pathology associated with DNFB-induced CHS in *FcγR3*<sup>-/-</sup> BMCMC-engrafted mast cell-deficient mice (in which mast cell signaling *via* FcγR3/Fcγ could not occur) were intermediate in magnitude between those of WT BMCMC-engrafted mast cell-deficient mice and mast cell-deficient mice indicates that mast cells may be activated to express anti-

inflammatory and/or immunosuppressive functions in this setting by at least one additional mechanism, that is not mediated *via* FcR $\gamma$ .

#### 4.4. Mast cells can limit responses to chronic UVB irradiation

To assess whether mast cells and mast cell-derived IL-10 might have anti-inflammatory functions in a setting other than CHS, we investigated an example of an innate tissue response to a ubiquitous environmental stimulus: UVB irradiation. As reviewed in [34], excessive exposure to solar UV radiation (particularly UVB and UVA radiation with wavelengths between 280–320 nm and 320–400 nm, respectively) causes a variety of acute and chronic photocutaneous reactions with several deleterious effects, including sunburn and photoaging (accelerated aging of the skin caused by environmental UV exposure).

To test whether mast cells contribute to the pathology observed in chronically UVB-irradiated skin, we exposed the ears of wild-type mice, mast cell-deficient *Kit*<sup>W/W<sup>-v</sup> mice and WT or *Il10*<sup>-/-</sup> BMCMCs→*Kit*<sup>W/W<sup>-v</sup> mice to 1 minimal erythema dose (MED) of UVB every 2 d for a total of 15 exposures (total cumulative dose = 30 kJ/m<sup>2</sup>). *Kit*<sup>W/W<sup>-v</sup> mice and *Il10*<sup>-/-</sup> BMCMCs→*Kit*<sup>W/W<sup>-v</sup> mice developed more striking ear erythema and tissue damage, and significantly greater ear thickness, after such UVB irradiation than did the corresponding wild-type mice or WT BMCMCs→*Kit*<sup>W/W<sup>-v</sup> mice (Fig. 5), even though both groups of BMCMC-engrafted *Kit*<sup>W/W<sup>-v</sup> mice had similar numbers of mast cells in the ear pinnae [34]. As expected, the smallest responses to UVB irradiation occurred in wild-type mice, the only group of mice with extensive skin pigmentation (they are black, unlike any of the other groups, each of which virtually lacks skin melanocytes because of their *c-kit* mutation [39]).</sup></sup></sup></sup></sup></sup>

In contrast to our findings in the CHS models, we detected no significant requirement for FcR $\gamma$ -dependent mast cell activation in the mast cell's ability to limit the magnitude or duration of cutaneous responses to chronic irradiation with UVB [34]. Moreover, even though the ear swelling responses in *Il10*<sup>-/-</sup> BMCMCs→*Kit*<sup>W/W<sup>-v</sup> mice were very similar to those of *Kit*<sup>W/W<sup>-v</sup> mice during the 30 d period of UVB treatment, the reactions in the *Il10*<sup>-/-</sup> BMCMCs→*Kit*<sup>W/W<sup>-v</sup> mice resolved more rapidly than those in *Kit*<sup>W/W<sup>-v</sup> mice after UVB treatment was stopped (Fig. 5). This finding indicates that mast cells can contribute to the resolution of the UVB-induced responses at least in part by mechanisms that are independent of the ability of mast cells to produce IL-10.</sup></sup></sup></sup>

#### 4.5. Mast cells can limit the pathology associated with snake or honeybee venoms

We found that mast cells can limit the toxicity of the endogenous peptide ET-1 *in vivo*, and that this represents one of the mechanisms by which mast cells can contribute to survival in the cecal ligation and puncture model of sepsis [25]. The amino acid sequence of ET-1 exhibits striking similarity to that of sarafotoxin 6b [54], the most toxic component of the venom of the Israeli mole viper (*Atractaspis engaddensis*). This raised the possibility that mast cells might be able to enhance resistance in mice to envenomation with *Atractaspis engaddensis* venom.

Indeed, we found that mast cell deficient mice were ~ 10 times more susceptible than wild-type mice to the deadly effects of *A. engaddensis* venom, and both pharmacological and shRNA knock down experiments implicated mouse mast cell carboxypeptidase A (mMC-CPA) as an important contributor the mast cell's ability to “detoxify” either sarafotoxin 6b or the whole venom [26]. Mast cells also enhanced resistance in mice to the venom of two species of pit vipers (Crotalinae) and the honeybee (*Apis mellifera*) (Fig. 6); in these settings, the ability of mast cells to enhance resistance appeared to reflect, at least in part, the ability of mast cells to release proteases [26].

Animal venoms can contain toxins which act by a variety of mechanisms, and most venoms represent complex mixtures of toxins (reviewed in [26]). Accordingly, we think it very unlikely that mast cells can enhance resistance to all venoms. On the other hand, we think that it will be of great interest to investigate the extent to which mast cells might be able to modulate host responses to the diverse toxins found in nature, including those from microbes and plants, as well as animals. Indeed, enhancing innate host defense against environmental toxins may represent one of the most ancient functions of mast cells.

## 6. Conclusions

Mast cells have been proposed to have important roles in host defense against pathogens, as well as in many diseases characterized by inflammation and tissue remodeling, including those associated with IgE antibodies (such as asthma, atopic dermatitis and other allergic disorders) and those in which IgE antibodies are not thought to have a significant role. Many of these conditions are associated with changes in the numbers or the phenotype of mast cell populations at the affected organ or anatomical site, and, in many of these settings, there is clear morphological evidence of various forms of “mast cell activation”. Moreover, many mast cell-derived products have effects that can significantly influence the survival, proliferation, phenotype or function of many other cell types that participate in inflammation, immunity and tissue remodeling.

We have proposed that genetic approaches that permit the roles of mast cells to be investigated in wild type mice, *c-kit* mutant mast cell-deficient mice, and mast cell-engrafted *c-kit* mutant mice (i.e., mast cell knock-in mice) can provide useful direct evidence for or against significant roles of mast cells, and some of their specific products, in experimental models of adaptive host responses or diseases.

In humans, it is much more difficult to be sure of the roles of mast cells in pathological or adaptive biological responses. Not only do mouse and human mast cells differ in some aspects of phenotype and function, but, so far, no “experiment of nature” that has resulted in a selective defect in human mast cells has been reported.

Therefore, in attempting to decide on the potential importance of mast cells in biological responses in humans, one must use a combination of several lines of indirect evidence, including: inference from mouse and other animal models of disease; observational studies in humans (e.g., employing biopsies of affected sites, measurements of mast cell-associated mediators in sites of disease or in the blood or urine); and the clinical results of interventions that “target” particular mast cell-associated mediators (many of which can be produced by other cell types as well) or that attempt to influence mast cell activation.

Eventually, it may be possible to evaluate the results of clinical trials of agents that have been designed to interfere specifically with mast cell activation, or that perhaps can ablate this cell selectively. If these agents actually are specific in suppressing mast cell function or eliminating mast cells in humans, then it may be possible to know in which disorders this cell is a friend or a foe, or, in more complex situations, at what stages of the particular biological response mast cells work for us or against us.

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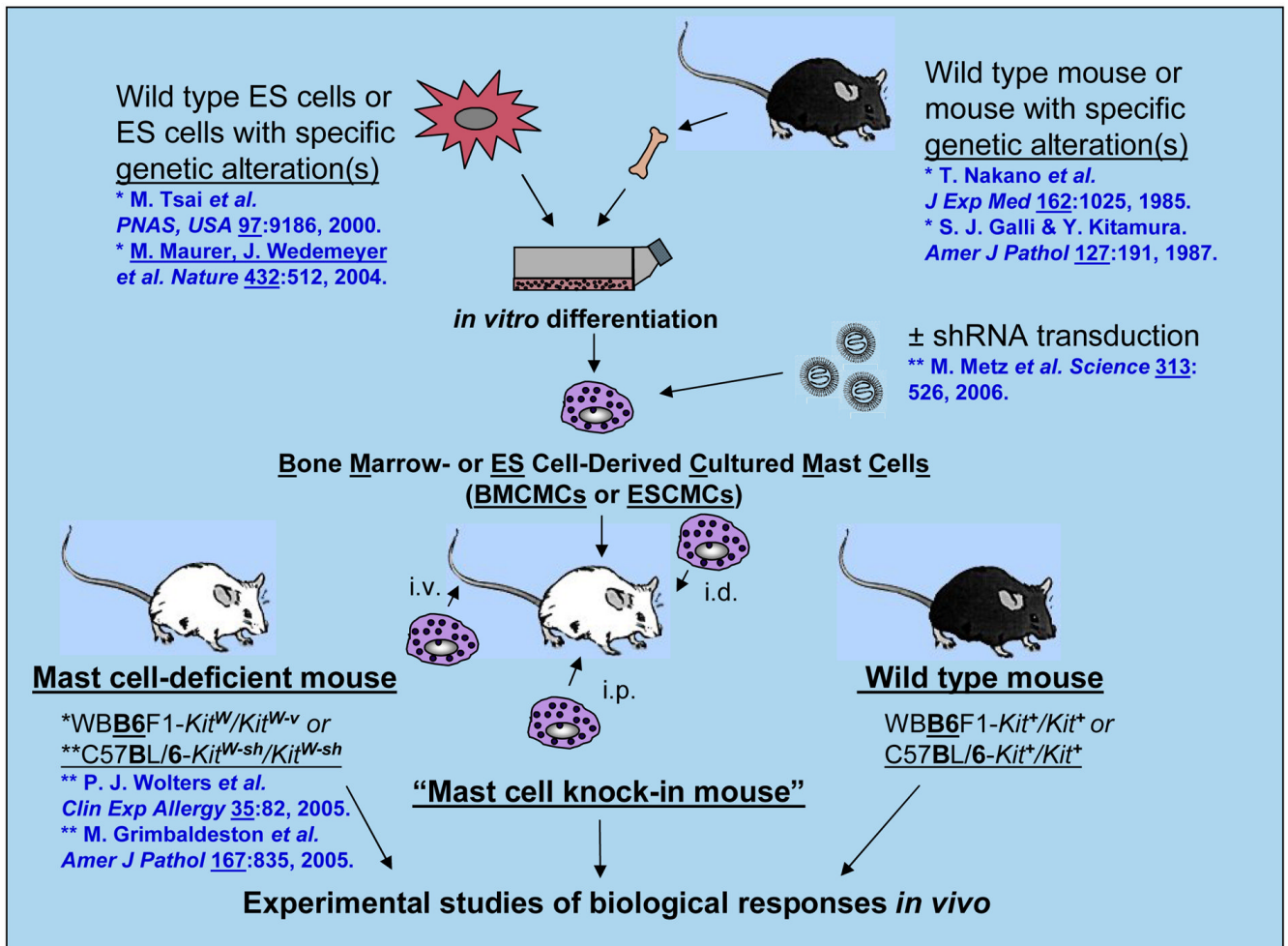
## Biography



Stephen J. Galli, M.D.

Stephen Galli received his BA and MD from Harvard, in 1968 and 1973, respectively, and completed a residency in Anatomic Pathology at Massachusetts General Hospital in 1977. He served on the faculty at Harvard until 1999, when he moved to Stanford as chair of the Department of Pathology and the Mary Hewitt Loveless, MD, Professor. Dr. Galli's research focuses on the development and function of mast cells and basophils, and on developing new animal models to study the diverse roles of mast cells in health and disease. Dr. Galli received a MERIT Award from the National Institutes of Health and the 1997 Scientific Achievement

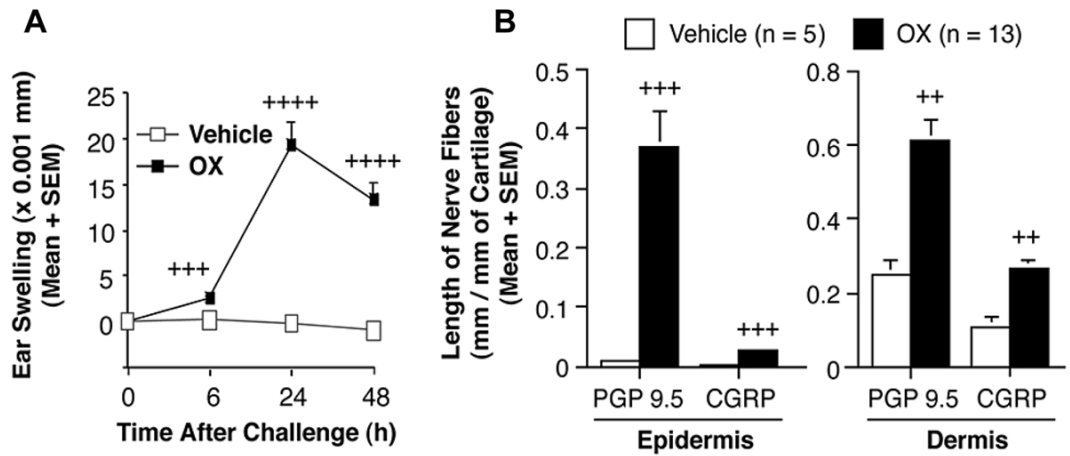
Award from the International Association of Allergy & Clinical Immunology. He was President of the American Society for Investigative Pathology (2005–2006) and has been elected to the Pluto Club (Association of University Pathologists), the *Collegium Internationale Allergologicum* (in which he is the Vice President), the American Society for Clinical Investigation, the Association of American Physicians, and the *Accademia Nazionale dei Lincei* in Rome.



**Fig. 1.**

How to make mast cell knock-in mice, *c-kit* mutant genetically mast cell-deficient mice which have been selectively engrafted with genetically-compatible *in vitro*-derived mast cells. Mast cells are generated from bone marrow cells (or other hematopoietic cells, e.g., those in the fetal liver) from wild-type mice or from mice with specific genetic alterations. Alternatively, embryonic stem (ES) cell-derived cultured mast cells (ESCMCs) can be generated from wild-type or genetically-altered ES cells or mast cells can be transduced *in vitro* with shRNA to silence specific genes of interest. Those cultured mast cells can then be transplanted intravenously (i.v.), intra-peritoneally (i.p.) or intra-dermally (i.d.) into mast cell-deficient *c-kit* mutant mice, such as WBB6F1-Kit<sup>W</sup>/Kit<sup>W-v</sup> or C57BL/6-Kit<sup>W-sh</sup>/Kit<sup>W-sh</sup> mice, to produce “mast cell knock-in mice”. A suitable interval is then allowed for the engraftment and phenotypic maturation of the adoptively transferred mast cells (the length of this interval can vary based on the route of mast cell transfer, the anatomical site of interest, etc.). The importance of mast cell function(s) in biological responses can be analyzed by comparing the responses in wild-type, *c-kit* mutant mast cell-deficient and selectively mast cell-engrafted *c-kit* mutant mice (mast cell knock-in mice). The contributions of specific mast cell products (surface structures, signaling molecules, secreted products, etc.) to such biological responses are analyzed by comparison of the features of the responses of interest in mast cell knock-in mice engrafted with wild-type mast cells versus mast cells derived from mice or ES cells that lack or express genetically-altered forms of such products or that have been transduced with

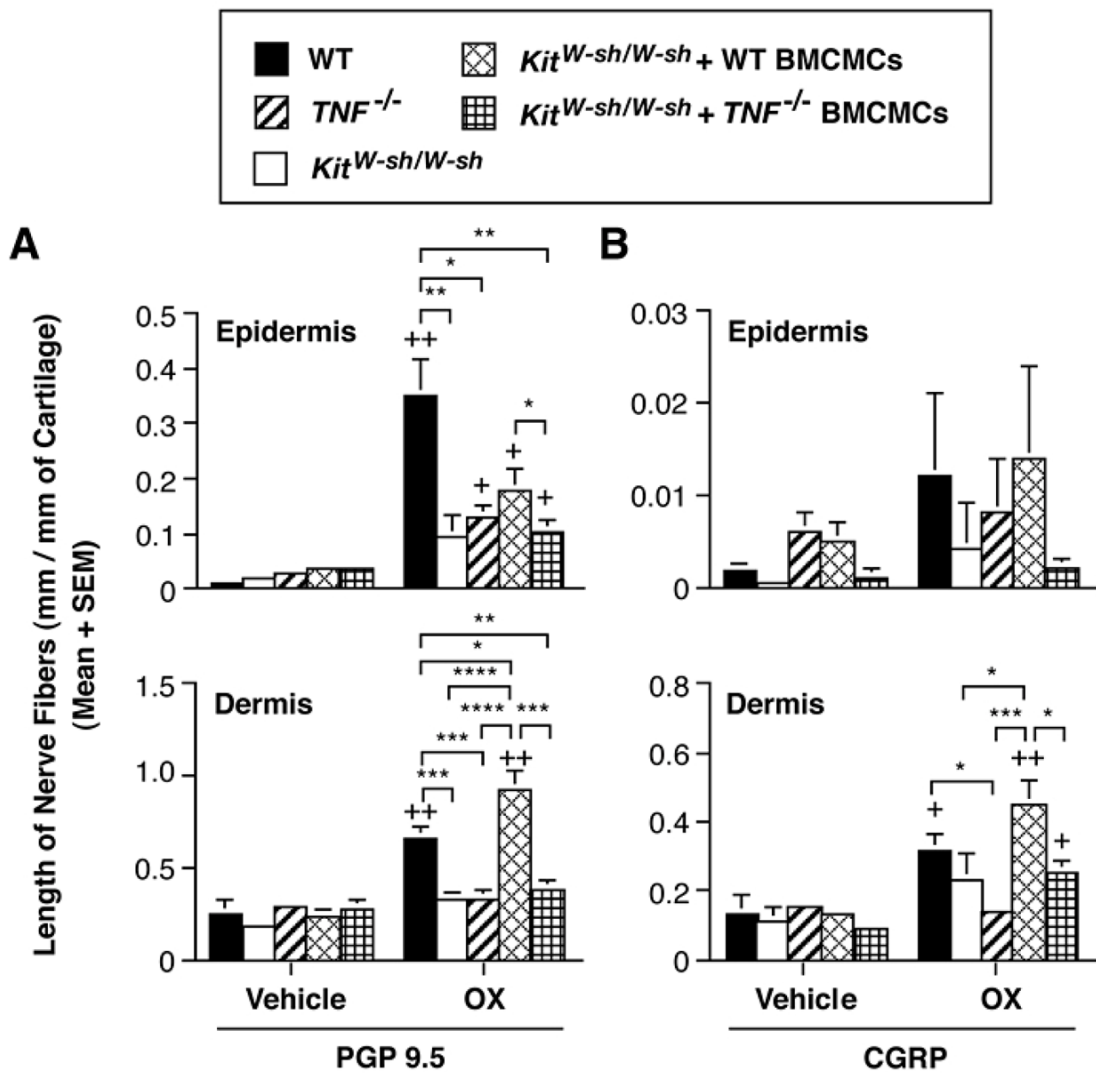
shRNA to silence the specific genes that encode these products. Reproduced, with the permission of the publisher, from reference [4].



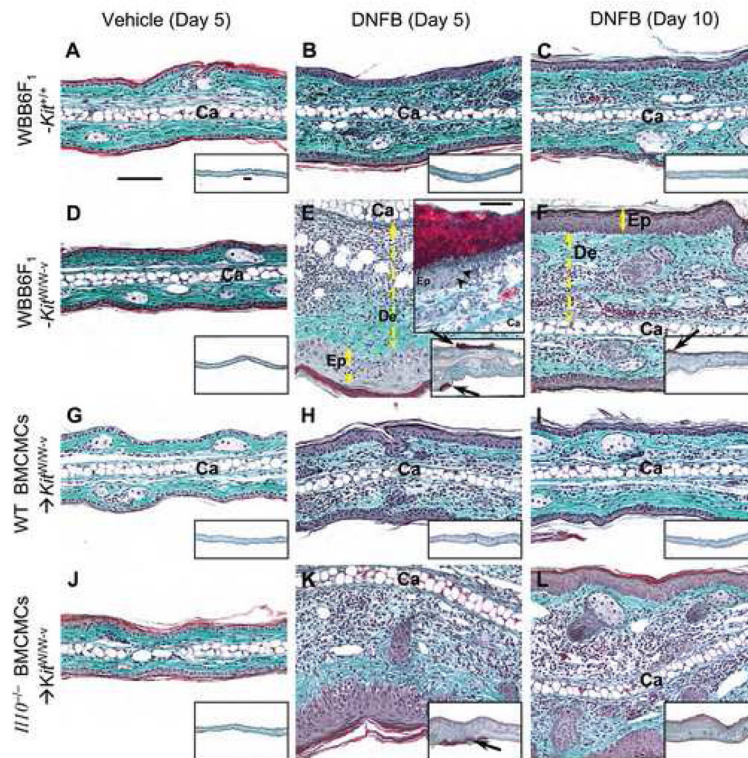
**Fig. 2.**

Elongation of cutaneous nerves during CHS responses to oxazolone (OX) in C57BL/6 mice. **(A)** Tissue swelling responses to vehicle (open squares) or OX (closed squares) in C57BL/6 wild-type mice, which had been sensitized with 100  $\mu$ l 2.0% OX in ethanol to shaved abdomen and challenged 5 days later with a total of 20  $\mu$ l of ethanol to right (control) ear (10  $\mu$ l to each side) and a total of 20  $\mu$ l 1.0% OX in ethanol to left ear (10  $\mu$ l to each side). Ear swelling was measured up to 48 h after challenge. **(B)** The length of PGP 9.5-positive or CGRP-positive nerve fibers in epidermis or dermis, respectively, in vehicle-treated ears (open columns) or OX-challenged ears (closed columns) of OX-sensitized mice 48 h after challenge. Data are the pooled results from three independent experiments, which gave similar results (vehicle: n = 5, OX; n = 13). In **A**, <sup>+++</sup>, <sup>++++</sup> =  $p < 0.001$ ,  $< 0.0001$  vs. corresponding values for vehicle-treated ears; In **B**, <sup>++</sup>, <sup>+++</sup> =  $p < 0.01$ ,  $< 0.001$  vs. corresponding values for vehicle-treated ears (Student's  $t$  test, 2-tailed). Reproduced, with the permission of the publisher, from reference [48].

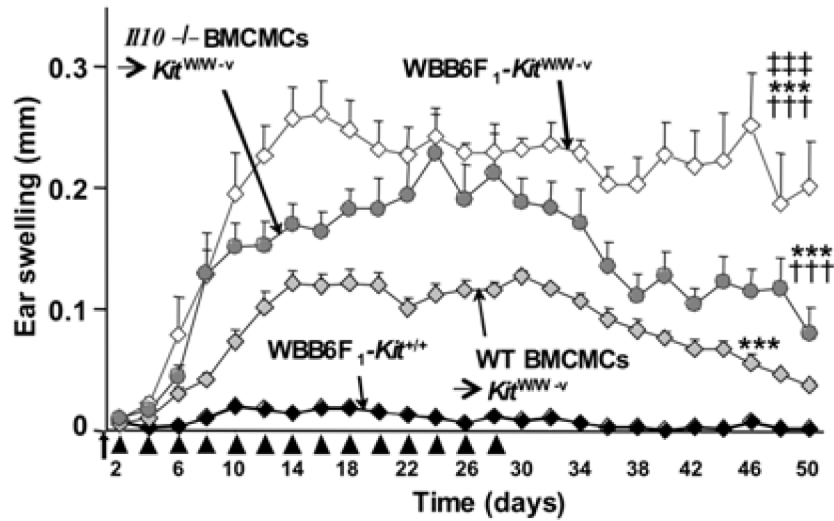


**Fig. 3.**

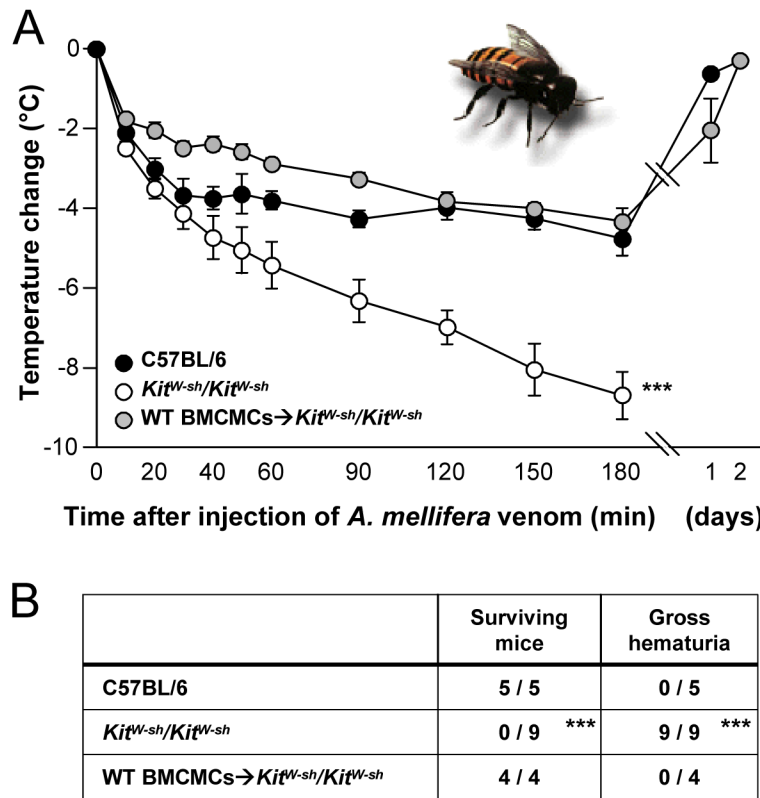
Mast cell-derived TNF contributes to elongation of cutaneous nerves during CHS to OX in C57BL/6 mice. The length of (A) PGP 9.5-positive or (B) CGRP-positive nerve fibers in ears examined 48 h after hapten challenge in OX-sensitized C57BL/6 wild-type (vehicle; n=5, OX; n = 10),  $TNF^{-/-}$  mice (vehicle; n=5, OX; n = 10), mast cell-deficient  $Kit^{W-sh/W-sh}$  mice (vehicle; n=5, OX; n = 10), and  $Kit^{W-sh/W-sh}$  mice that had been selectively repaired of their mast cell deficiency by the intra-dermal injection of wild type or  $TNF^{-/-}$  BMCMCs (vehicle; n=5, OX; n = 9 in each group). Data show the length of nerve fibers at 48 h after OX or vehicle challenge in OX-sensitized mice. +, ++ =  $p < 0.05$ ,  $< 0.01$  vs. corresponding values for vehicle-treated ears; \*, \*\*, \*\*\*, \*\*\*\* =  $p < 0.05$ ,  $< 0.01$ ,  $< 0.001$ ,  $< 0.0001$  for the comparisons indicated by brackets (Student's  $t$  test, 2-tailed). Reproduced, with the permission of the publisher, from reference [48].



**Fig. 4.** Mast cells and mast cell-derived IL-10 can limit the skin pathology associated with CHS to DNFB. Cross-sections of ears (stained with Masson's Trichrome) from (A–C) WBB6F<sub>1</sub>-*Kit*<sup>+/+</sup> (wild-type) mice, (D–F) mast cell-deficient *Kit*<sup>W/W-v</sup> mice or *Kit*<sup>W/W-v</sup> mice engrafted with wild-type (WT) BMCMCs (WT BMCMCs→*Kit*<sup>W/W-v</sup> mice) (G–I) or *Il10*<sup>-/-</sup> BMCMCs (*Il10*<sup>-/-</sup> BMCMCs→*Kit*<sup>W/W-v</sup> mice) (J–L) were obtained 5 d after challenge with vehicle (100% acetone) only (A, D, G and J) or 0.2% DNFB (B, E, H and K), or 10 d after challenge with 0.2% DNFB (C, F, I and L). Upper inset in E: *arrowheads* indicate border between intact epithelium (Ep) and, to the right, complete loss of epithelium at the base of an ulcer covered by an exudate. Ca\*: cartilage; double-headed arrows show thickness of dermis (De) or epidermis (Ep); arrows in insets: sites of ulcers with adherent exudate (red). Scale bars in A and in insets in A & E = 100 μm. Photomicrographs are representative of the findings observed in the 6 different experiments we performed, with *n* = 4–6 mice/group per experiment; each experiment gave similar results. Reproduced, with the permission of the publisher, from reference [34].



**Fig. 5.** Mast cells are required for optimal resolution of tissue swelling after chronic low-dose UVB irradiation. Ear swelling examined for up to 22 d after the last of 15 exposures of 2 kJ/m<sup>2</sup> UVB irradiation in WBB6F<sub>1</sub>-Kit<sup>+/+</sup> (wild-type [WT]) mice, mast cell-deficient Kit<sup>W/W-v</sup> mice, or Kit<sup>W/W-v</sup> mice engrafted with WT BMCMCs (WT BMCMCs→Kit<sup>W/W-v</sup> mice) or H10<sup>-/-</sup> BMCMCs (H10<sup>-/-</sup> BMCMCs→Kit<sup>W/W-v</sup> mice); *n* = 4–6 mice/group. The first exposure (arrow) was on day 0, immediately after we measured baseline ear thickness. Subsequent exposures are shown as arrowheads. \*\*\**P* < 0.0001 versus corresponding UVB-irradiated wild-type mice; †††*P* < 0.0001 versus corresponding UVB-irradiated WT BMCMCs→Kit<sup>W/W-v</sup> mice; ‡‡‡*P* < 0.0001 versus corresponding UVB-irradiated H10<sup>-/-</sup> BMCMCs→Kit<sup>W/W-v</sup> mice. Reproduced, with the permission of the publisher, from reference [34].



**Fig. 6.** Mast cells can limit the toxicity of honeybee venom. (A) Changes in rectal temperature and (B) 24-hour survival and occurrence of gross hematuria after subcutaneous injection of *A. mellifera* venom (A.m.v.) at five different sites (three injections distributed over the length of the back skin and two into the belly skin, each containing 100  $\mu$ g A.m.v. in 50  $\mu$ l PBS) into WT mice, mast cell-deficient *Kit<sup>W-sh</sup>/Kit<sup>W-sh</sup>* mice, or *Kit<sup>W-sh</sup>/Kit<sup>W-sh</sup>* mice that had been engrafted intra-dermally, 6 weeks earlier, with  $1.5 \times 10^6$  BMCMCs into each of the five injection areas (WT BMCMCs→*Kit<sup>W-sh</sup>/Kit<sup>W-sh</sup>*). The amount of venom per injection (100  $\mu$ g) roughly reflects the amount that can be delivered by one bee sting. All of the WT or WT BMCMCs→*Kit<sup>W-sh</sup>/Kit<sup>W-sh</sup>* mice appeared healthy, and their body temperatures returned to baseline within 2 days. \*\*\* $P < 0.005$  versus either C57BL/6 or WT BMCMCs→*Kit<sup>W-sh</sup>/Kit<sup>W-sh</sup>* mice. Reproduced, with the permission of the publisher, from reference [26].

**Table 1****Mechanisms by which mast cells can be activated<sup>a</sup>**

<b>Via immune receptors</b>	
IgE	Via FcεRI; IgE can also bind to IgG receptors (FcγRII and FcγRIII), and to galectin-3, which are expressed on some mast cell-populations
IgG <sub>1</sub>	Mouse: FcγRIII, human: FcγRI after treatment with IFN-γ
Ig-binding superantigens	Endogenous (e.g., protein Fv in HBV & HCV infections), bacterial (e.g., <i>S. aureus</i> Protein A, <i>P. magnus</i> protein L) or viral (e.g., HIV gp120)
<b>Products of complement activation</b>	
C3a, C5a, C3b, C4b	Via their respective receptors: C3aR, C5aR, CR3, CR4
<b>Ligands of toll-like receptors, e.g.</b>	
Peptidoglycan	TLR2
ds viral RNA, polyI:C	TLR3
LPS	TLR4/CD14
Flagellin	TLR5 (human mast cells)
ss viral RNA	TLR7
CpG-DNA	TLR9
<b>Bacteria and their products, e.g.</b>	
<i>E. coli</i> FimH	CD48
<i>Pseudomonas aeruginosa</i>	Human mast cells
Virulence factors/toxins	e.g., <i>C. difficile</i> toxin A, cholera toxin, VacA (cytotoxin of <i>H. pylori</i> ), streptolysin O
<b>Viruses, e.g.</b>	
Respiratory syncytial virus, influenza virus, Dengue virus, Sendai virus	Via TLR and possibly by other mechanisms
<b>Parasites, e.g.</b>	
<i>Schistosoma mansoni</i>	Activation by cercariae
<i>Leishmania major</i>	Activation by living promastigotes
<b>Cytokines and inflammatory mediators, e.g.:</b>	
Tryptase	Functional PAR2 has been shown in human skin mast cells and HMC-1
SCF	Via c-Kit
IL-1, IL-12	Secretion of selective mediators (in human mast cells)
TNF	In human mast cells
PGE <sub>2</sub>	Secretion of selective mediators (in human mast cells, via EP <sub>2</sub> ) or potentiation of IgE/Ag-induced mediator release (in mouse, via EP <sub>1</sub> /EP <sub>3</sub> )
LIGHT	Activation via LTβR in the presence of ionomycin or activated T cells
CD30	Reverse signaling via CD30L induces selective secretion of chemokines
Adenosine	Increase of IgE/Ag-induced degranulation via A <sub>3</sub> R
<b>Endogenous peptides, e.g.</b>	
Nerve growth factor, Substance P, CGRP and other neuropeptides, Endothelin-1	Via respective G protein-coupled receptors on mast cells
Neurotensin	Via ET <sub>A</sub>
Antimicrobial peptides	e.g., β-defensin 2 and LL-37
<b>Venoms or venom components, e.g.</b>	
Sarafotoxin 6b	Component of <i>Atractaspis engaddensis</i> venom, via ET <sub>A</sub>
Phospholipase A <sub>2</sub>	Component of many different animal venoms
Mast cell degranulating peptide	And other components of honeybee venom
Numerous venoms or venom components	e.g., from scorpions, the platypus, frogs, ants, sea urchins, Portuguese man-of-war, etc.
<b>Physical stimuli</b>	
UV light, cold, heat, pressure, vibration	Possibly through direct and indirect effects on mast cells

<sup>a</sup>This is not a complete list. Receptors other than the ones mentioned also may be involved in the activation of certain mast cells by some of the listed agents. In some instances, the occurrence and extent, and biological significance, of mast cell activation via the listed receptors *in vivo* is not yet clear.

<sup>b</sup>Reproduced, with the permission of the publisher, from reference [28]; please see that review for references for some of the stimuli listed in the table.

**Table 2**

Mast cell-derived IL-10 limits epidermal necrosis associated with CHS to DNFB.

Time after DNFB challenge	Mice with full thickness epidermal necrosis	
	5 days	10 days
WBB6F <sub>1</sub> - <i>Kit</i> <sup>+/+</sup>	0/19	0/5
WBB6F <sub>1</sub> - <i>Kit</i> <sup>W/W-v</sup>	8/10*	2/3*
WT BMCMCs→ <i>Kit</i> <sup>W/W-v</sup>	0/16	0/3
<i>Il10</i> <sup>-/-</sup> BMCMCs→ <i>Kit</i> <sup>W/W-v</sup>	11/15*	2/3*

Values indicate numbers of mice whose ears exhibited full thickness epidermal necrosis, and, in some cases, ulcers as assessed by histology at 5 or 10 days after challenge with DNFB (mice with necrosis/total mice).

\*  $P < 0.05$ , wild type (*Kit*<sup>+/+</sup>) mice or WT (wild type) BMCMCs→*Kit*<sup>W/W-v</sup> mice versus the corresponding mast cell-deficient *Kit*<sup>W/W-v</sup> mice or *Il10*<sup>-/-</sup> BMCMCs→*Kit*<sup>W/W-v</sup> mice. Data are from three experiments with similar results on day 5 (3–6 mice per group per experiment) or one experiment on day 10 (3–5 mice per group).

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