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Mast cells as sources of cytokines, chemokines and growth factors

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Summary

Mast cells are hematopoietic cells that reside in virtually all vascularized tissues and that represent potential sources of a wide variety of biologically active secreted products, including diverse cytokines and growth factors. There is strong evidence for important non-redundant roles of mast cells in many types of innate or adaptive immune responses, including making important contributions to immediate and chronic IgE-associated allergic disorders and enhancing host resistance to certain venoms and parasites. However, mast cells have been proposed to influence many other biological processes, including responses to bacteria and virus, angiogenesis, wound healing, fibrosis, autoimmune and metabolic disorders, and cancer. The potential functions of mast cells in many of these settings is thought to reflect their ability to secrete, upon appropriate activation by a range of immune or non-immune stimuli, a broad spectrum of cytokines (including many chemokines) and growth factors, with potential autocrine, paracrine, local and systemic effects. In this review, we summarize the evidence indicating which cytokines and growth factors can be produced by various populations of rodent and human mast cells in response to particular immune or non-immune stimuli, and comment on the proven or potential roles of such mast cell products in health and disease.

Keywords

Chemokines; cytokines; growth factors; immunity; inflammation; mast cells

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CONFLICT OF INTEREST

The authors have no conflict of interest.

1 INTRODUCTION

Although mast cells (MCs) were described by Paul Ehrlich long ago [1], the appreciation that these cells represent a potential source of diverse cytokines, chemokines, and growth factors is a relatively recent development [2]. Early work reported the ability of neoplastic MC lines to produce certain hematopoietic cytokines [3], and subsequent studies provided evidence that both *in vitro*-derived mouse MCs and purified mouse peritoneal MCs (PMCs) could produce and secrete TNF, both in response to LPS and after activation via the FcεRI [2, 4–6]. While most of the TNF secreted by MCs appears to require induction of the corresponding mRNA upon MC activation, there is evidence that some TNF is physically associated with the secretory granules and is thereby 'preformed' and ready for more rapid release upon appropriate activation of the cells [2, 5, 6]. Human MCs were identified as a potential source of TNF shortly after the finding was reported for mouse MCs [7], and evidence was presented that these cells also could contain preformed stores of the cytokine in their granules [7].

IL-4 was reported to be a potential product of mouse MC lines in 1987 [8] and three groups subsequently reported the ability of various populations of *in vitro*-derived mouse mast cells or long term mouse MC lines to secrete IL-4 and several other cytokines in response to activation via the FcεRI [9–11] and the Burd et al. paper [11] also added a few chemokines to the growing list of cytokines which could be considered as potential products of mouse MCs.

As reviewed herein, the list of cytokines, chemokines, growth factors and mitogens which now have been identified as MC products is very long (Fig. 1, Tables 1 & 2). And while many of these were first identified, at the mRNA or protein level, in *in vitro*-derived mouse or human MCs, there is evidence that several of these can be considered to be at least potential products of native populations of mouse or human tissue MCs. However, while it can be relatively straightforward to generate evidence that MCs *might* represent a source of particular cytokines, chemokines, growth factors and mitogens, it is much more difficult to determine the biological importance of MCs as sources of such molecules, particularly in settings where multiple different immune cells and structural cells represent alternative potential sources of the same products.

In this review, we describe the evidence that MCs represent potential sources of cytokines (including chemokines), growth factors and mitogens, and mention the potential or proven roles of these products, e.g., as "pro-inflammatory" or "regulatory" cytokines; or influencing MC development, survival and/or proliferation; or functioning as mitogens or chemokines. As noted in Tables 1 & 2, much of the evidence that MCs can secrete such products is derived from studies of *in vitro*-derived mouse or human MCs, or MCs purified from mouse body fluids or mouse or human tissues. Importantly, we note that in many instances it has not yet been confirmed whether, and under which circumstances, MCs can secrete such products *in vivo*. Some of the many considerations to be kept in mind when evaluating the evidence that MCs represent potentially important sources of particular cytokines, chemokines, growth factors or mitogens are listed in Table 3.

Immunohistochemistry (IHC) has often been used to identify cytokines and growth factors in MCs in tissue sections, and the identification of such immunoreactivity is of interest (e.g.,

it can be taken to represent one line of evidence that some of the products so identified can be stored in or associated with the MC's cytoplasmic granules). However, this approach by itself can't determine the importance of MCs as a source of these molecules, which typically also can be produced by many other cell types. Moreover, in many of these "non-MC" sources of these products, the cytokines or growth factors may be rapidly secreted and therefore provide little signal for detection of cell-associated product by IHC.

Accordingly, when it is available, we have commented on more direct lines of evidence that MC production of particular cytokines, chemokines, growth factors or mitogens has relevance for understanding the roles of MCs *in vivo*. We think that the reader will appreciate that while we are still far from understanding the importance of most of these products in contributing to critical roles of MCs in physiological or pathological processes, we now have many interesting possibilities to assess, as well as increasingly powerful tools to provide more definitive answers to these questions.

2 MAST CELL-DERIVED CYTOKINES, GROWTH FACTORS, AND MITOGENS

2.1 TNF (tumor necrosis factor)

History—TNF (tumor necrosis factor/cachectin) was first described by Carswell *et al* in 1975 [12] as a factor found in the serum of bacillus Calmette-Guerin (BCG)-infected mice that induces tumor necrosis. This and several other studies showed that TNF can be released from macrophages upon endotoxin stimulation [13–15]. Later, evidence was reported that some MC lines (C57.1, 2D4, t1C9, AI, RBL-2H3, PT18) [4, 16], IL-3-maintained bone marrow-derived cells (which were reported to be "natural cytotoxic cells", but in retrospect almost certainly were MCs [17]), IL-3-derived mouse bone marrow-derived MCs (BMCMCs) and purified rat or mouse PMCs [4], rat connective type MCs [18], and human bone marrow-derived "basophils/MCs" [19] also can have a bioactivity capable of lysing certain types of tumor cell lines, such as the sarcoma WEHI-164, and that one of the factors responsible for causing such cytotoxicity had properties similar to that of TNF.

Subsequently, Gordon and Galli [5] showed that freshly isolated mouse peritoneal MCs (PMCs) constitutively express preformed TNF that can be released rapidly and can mediate TNF bioactivity. Various MCs also can exhibit enhanced TNF gene expression upon IgE-dependent activation [5, 16, 20–23], as shown by increased levels of TNF mRNA in Northern blots [5, 20, 22]. Furthermore, TNF mRNA expression and TNF production have been detected in a mouse mastocytoma cell line, MMC-1, after FcγR activation [24] as well as in an IL-3-dependent mouse mast cell line, CFTL12 [25] and in human skin MCs [23] after stimulation with substance P.

2.1.2 Preformed TNF—The ability of some populations of MCs to contain preformed TNF, which can be released rapidly from the cells upon their appropriate activation, identifies MCs as one of the first potential sources of this cytokine during innate or adaptive immune responses. Early work provided evidence that the TNF released by MCs for the first ~10 minutes after IgE-dependent stimulation was derived from a preformed pool and that at later time points TNF is secreted from a newly synthesized pool [6, 20]; findings consistent with this conclusion also were reported for human skin MCs after their exposure to UVB [26]

or anti-IgE, substance P, stem cell factor (SCF), A23187, or compound 48/80 [27]. *De novo* TNF synthesis in MCs takes several hours and appears to require mitochondrial translocation near the sites of exocytosis [28].

Evidence supporting the conclusion that MCs represent a source of "early TNF" *in vivo* was obtained in studies of immune complex peritonitis in genetically MC-deficient $Kit^{W/W\text{-}v}$ mice and the corresponding control ($Kit^{+/+}$) mice. In this model, rapid TNF secretion from MCs was thought to help to initiate inflammation by recruiting neutrophils into peritoneum [29]. Such rapidly released TNF can induce endothelial-leukocyte adhesion molecule 1 (ELAM-1), intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion protein 1 (VCAM-1) on vascular endothelial cells *in vitro* [7, 26, 30], which represents one MC-TNF-dependent mechanism for enhancing the adhesion and recruitment of neutrophils and other leukocytes to sites of MC activation. Indeed, helping to initiate local inflammation during innate and adaptive immune responses may be one of the most important functions of the TNF rapidly released from suitably stimulated MCs, and one of the major mechanisms by which MCs function as sentinels during such host responses.

The molecular mechanisms which affect the storage of TNF within MC cytoplasmic granules remain to be fully elucidated. However, there is evidence from work with rat basophil leukemia cells (RBL cells) and *in vitro*-derived mouse MCs that TNF travels from the endoplasmic reticulum (ER) to the cytoplasmic granules at least in part through N-linked glycosylation of TNF and via a mannose-6-phosphate receptor (MPR)-dependent pathway (RBL-2H3) [31]. By contrast, human MCs (LAD2 MCs and the human MC leukemia cell line, HMC-1) appear to employ a different mechanism, which does not involve glycosylation of the TNF and therefore is carbohydrate independent, and that involves a pathway by which the newly formed TNF is transiently exposed to the extracellular space and then is followed by endocytosis [32].

2.1.3 Roles of MC-derived TNF—In principle, MC-derived TNF could contribute to any biological response that is influenced by that cytokine. However, attention has focused mainly on the role of MC-derived TNF in various inflammatory responses. An early idea was that the cytotoxicity mediated by MC-derived TNF might play a role in tumor regression. However, while it has long been known (since Ehrlich's time [1]) that numbers of MCs are increased in various types of tumors (reviewed in [33]), the roles of MCs in such settings, let alone MC-derived TNF, are largely yet to be determined [33–35]. MCs have the potential to secrete a wide spectrum of cytokines, growth factors and other mediators that can have positive or negative effects on tumors and their relationship to the microenvironment (e.g., see Table 1), and TNF is just one among many such products.

By contrast, several lines of evidence indicate that MC-derived TNF can contribute to leukocyte recruitment at sites of inflammation. Studies employing a neutralizing antibody to TNF indicated that this cytokine can promote leukocyte recruitment into sites of IgE- and MC-dependent passive cutaneous anaphylaxis in mice [36, 37]. In certain delayed hypersensitivity responses elicited in the skin of mice, there is evidence that MC-derived TNF, as well as the MC-derived chemokine, macrophage inflammatory protein 2 (MIP-2), can contribute to neutrophil recruitment [38]. In antigen-induced neutrophil infiltration into the

airways of ovalbumin (OVA)-specific TCR-expressing OTII mice, there was evidence that MC-derived TNF can contribute to neutrophil recruitment in a Th17-cell dependent manner [39].

In mouse models of hapten-induced contact hypersensitivity, two groups provided evidence that MC-derived TNF can contribute to the migration of skin dendritic cells [40, 41] and airway dendritic cells [40] to the draining lymph nodes. Those findings, which indicated that MC-derived TNF can modulate DC function and thus adaptive immunity, were generated using adoptive transfer approaches to compare the function of $TNF^{+/+}$ vs. $TNF^{-/-}$ MCs *in vivo* after their engraftment into the tissues of *Kit* mutant MC-deficient mice. Recently, studies employing Mcpt5-Cre$TNF^{fl/fl}$ mice, in which TNF is specifically deleted in MCs under the control of the Mcpt5 promoter, have confirmed the findings obtained using MC-engrafted *Kit* mutant mice and identified $CD8^+$ DCs as the main target cells of MC-derived TNF in this setting [42].

Notably, Kunder et al. [43] identified a previously unknown mechanism by which MC-derived TNF can help to initiate adaptive immune responses. Specifically, Kunder et al. [43] reported evidence that the TNF associated with exteriorized MC cytoplasmic granule structures can be transported in such granules via lymphatics, thus traveling from sites of local cutaneous inflammation, in this case induced by the injection of *E. coli* bacteria into the mouse footpad, to the draining lymph nodes. This provided a mechanism to explain the group's prior observation that such MC activation by *E. coli* results in hypertrophy of the draining lymph nodes and the promotion of an adaptive immune response to the bacteria [44]. Subsequently, Gaudenzio et al. [45] reported evidence that IgE-dependent MC activation in the mouse footpad also can result in the transport of exteriorized MC cytoplasmic granules to the draining lymph nodes and the induction of their enlargement. Finally, there is also a report that, *in vitro*, TNF derived from MCs upon IgE and antigen stimulation can enhance T cell activation by increasing their expression of OX40 (also known as tumor necrosis factor receptor superfamily, member 4 [TNFRSF4] and CD134) [46]. These studies highlight the potentially diverse and non-mutually exclusive mechanisms by which MC-derived TNF can influence adaptive immunity, and we think it likely that additional mechanisms remain to be discovered.

MC-derived TNF can also influence non-immune cells. In a mouse model of oxazolone-induced contact hypersensitivity, there is evidence that MC-derived TNF can contribute to nerve elongation, perhaps via induction of nerve growth factor (NGF) production by keratinocytes [47]. Close association between MCs and nerves is often observed in inflammatory skin lesions [48–50], and further studies are needed to elucidate the molecular mechanisms which underlie functional associations between MCs, MC-derived TNF (and other MC-derived mediators) and nerves in this and other settings.

In mice, there is evidence that, after MCs are activated with IgE and antigen *in vivo* or *in vitro*, MC-derived TNF and MC-derived TGF-β1 can increase type I collagen production in fibroblasts [51, 52]. Fibrosis can occur as part of the tissue remodeling associated with allergic asthma and atopic dermatitis, and many other settings characterized by chronic inflammation. It will be of interest to determine in such settings the extent to which MCs

represent important sources of TNF, TGF-β1, and other products that may drive or regulate various aspects of these complex tissue responses.

Given how many factors may potentially influence MC phenotype and function, including the cells' ability to produce cytokines (Table 1), and how many other immune and non-immune cell types can participate in complex inflammatory or immune responses, through production of cytokines and many other mechanisms, it is not surprising that the importance of MCs as sources of particular cytokines may vary depending on the specific setting being analyzed. This is illustrated by the history of attempts to analyze the roles of MCs and MC-derived TNF in a commonly used mouse model of sepsis: cecal ligation and puncture (CLP). In work employing MC-engrafted genetically MC-deficient *Kit*$^{W/W\text{-}v}$ mice, Echtenacher et al. [53] reported that MCs can contribute to enhanced survival during CLP and that administration of a neutralizing antibody (Ab) to TNF could diminish this effect. In a study employing MC-engrafted genetically MC-deficient *Kit*$^{W/W\text{-}v}$ mice that was published back-to-back with the Echtenacher et al. [53] report, Malaviya et al. [54] provided additional evidence for a role for MC-derived TNF in enhancing survival in another model of bacterial infection in mice. Subsequent mechanistic work indicated that activation of MCs either by products of complement activation [55, 56] or via toll-like receptors (TLRs), particularly TLR4 [57], can contribute to MC activation for TNF production during CLP and perhaps other forms of bacterial infection. The observation that IL-4-pretreated human cord blood MCs can produce TNF upon LPS or PGN (peptidoglycan) stimulation [58] highlighted the potential clinical relevance of the mouse studies.

Subsequent work employing MC-engrafted *Kit*$^{W/W\text{-}v}$ mice confirmed that MCs can enhance survival during the model of CLP tested, and that repetitive administration of the Kit ligand and MC growth factor, stem cell factor (SCF) can also do so [59]. However, SCF treatment also significantly enhanced survival after CLP in TNF-deficient mice, showing that this effect can occur independently of TNF, whether of MC or non-MC origin [59]. Later work provided evidence that the role of MCs, and MC-derived TNF, can vary depending on both the severity of the CLP model being tested and mouse strain background [60].

Analysis of MC-engrafted *Kit*$^{W/W\text{-}v}$ mice confirmed that engrafted MCs can enhance survival of *Kit*$^{W/W\text{-}v}$ mice during a model of moderately severe CLP, but that was not true in mice subjected to a severe model of CLP [60]. However, experiments employing MC-engrafted genetically MC-deficient *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice indicated that the beneficial role of MCs in this setting can occur independently of MC-derived TNF [60]. By contrast, work in MC-engrafted *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice indicated that MC-derived TNF can increase mortality during severe CLP and also can enhance bacterial growth and hasten death after intraperitoneal inoculation of *Salmonella typhimurium* [60]. Finally, Piliponsky, et al. [61] reported that MC-derived TNF can be degraded by mouse mast cell protease 4 (mMCP-4) *in vitro* and that the reduction of TNF levels by mMCP-4 *in vivo* can help to limit inflammation and promote survival in mice subjected to a moderately severe model of CLP.

Taken together, these findings support the hypothesis that, depending on the circumstances (including mouse strain background, the nature of the mutation resulting in the MC deficiency, and type and severity of the infection), MCs can have either no detectable effect

or even opposite effects on survival during bacterial infections. As discussed in detail elsewhere [62–64], a caveat about these findings is that much of the work reviewed above was performed using mice that were MC-deficient because of mutations affecting c-*kit* structure or expression, and such mice have multiple phenotypic abnormalities in addition to their profound MC deficiency.

In summary, current evidence indicates that MC-derived TNF can contribute to the initiation and amplification of inflammation, particularly in its early stages, during certain innate and adaptive immune responses, and that TNF (particularly that associated with exteriorized MC cytoplasmic granules) also may contribute to the development of certain adaptive immune responses. However, MC-derived TNF may be a two-edged sword, which in some settings contributes more substantially to pathology than to host defense.

2.2 IL-1β

IL-1β is an important pro-inflammatory cytokine that can be involved in various inflammatory diseases. The IL-1 family is a target for treating inflammatory and autoimmune diseases and multiple molecules/biologics are currently being clinically investigated, some of which have demonstrated efficacy (reviewed in [65]).

In vitro studies indicate that MCs can produce IL-1β upon stimulation via the FcεRI [11, 66], FcγRs [66], calcium ionophore [66], LPS and ATP (Adenosine 5′-triphosphate), or R837 [67, 68]. Moreover, there is evidence that MC-derived IL-1β can contribute to the development of various models of arthritis [69, 70], and skin inflammation [67, 68] in mice *in vivo*.

2.3 IL-2

IL-2 can have effects on many immune cells, and is especially important for Treg cell development and homeostasis [71]. The critical sources of IL-2 in the skin have been unclear, but recent work indicates that MCs represent one source, along with T cells. Mouse peritoneal- or bone marrow-derived cultured MCs produce IL-2 upon activation with IgE and antigen *in vitro* [72]. In a model of oxazolone-induced contact hypersensitivity (CHS), MC expansion occurred both at the site of pathology in the skin and in the spleen, and spleen MCs exhibited increased production of IL-2 [72]. Moreover, engraftment of wild type (WT) but not IL-2-deficient MCs into the skin of genetically MC-deficient $Kit^{W\text{-}sh/W\text{-}sh}$ mice suppressed inflammation at sites of oxazolone-induced CHS, and, in the absence of MC-derived IL-2, the ratio of activated to Treg cells at the site of skin pathology was increased [72]. This work indicates that, in these models, MC-derived IL-2 can contribute to the immune suppression of oxazolone-induced CHS.

MC IL-2 production also has been reported to contribute to the expansion of Treg T cells which contribute to immune suppression in a mouse model of IL-33-induced airway inflammation [73]. By contrast, Moretti et al [74] recently reported evidence for a positive feedback loop involving MC IL-2 production that can contribute to lung pathology in a mouse model of cystic fibrosis. Specifically, they reported that IL-9 can induce enhanced production of IL-2 by lung MCs, which is associated with expansion of CD25+ group 2 innate lymphoid cells (ILC2s) and subsequent activation of Th9 T cells. It will be of interest

to extend these findings, as well as other work which has suggested potential roles of MC-derived IL-2 in immune responses, using mice in which IL-2 is selectively ablated in MCs.

2.4 IL-3

IL-3 has been well characterized as a cytokine which supports MC and basophil differentiation, growth, survival, and expansion [75–79]. IL-3 is dispensable in mice for MC and basophil production, in that IL-3-deficient mice have numbers of MCs and basophils similar to those in WT controls (at least when the mice have been maintained under standard conditions in specific pathogen-free colonies), but it is essential for normal expansion of numbers of blood basophils and intestinal and spleen MC populations during infections with certain parasites [78]. At least certain MC populations can produce IL-3 upon IgE-mediated stimulation [9–11] and in some cases even when IgE is tested in the absence of specific antigen [80]. Such MC production of IL-3 thus might constitute an autocrine signal for promoting MC survival and growth *in vivo*, and MC-derived IL-3 (together with other MC-derived cytokines with similar or overlapping effects) also might promote the recruitment, development, and survival of additional myeloid cells.

2.5 IL-4

IL-4 is the paradigmatic cytokine involved in type-2 immune responses and plays a critical role in the development of Th2 cells and subsequent allergic reactions. Mouse MC lines were first identified as a source of IL-4 in 1987 (first described in Brown et al [8], reviewed in [81, 82]), and MCs can produce IL-4 upon IgE-mediated stimulation or in response to calcium ionophore [83, 84], IL-33 (in mouse MCs [85]) or certain lectins (in human cord blood MCs [86]). LPS or PGN didn't induce IL-4 in certain human MCs *in vitro* [87] but LPS or PGN can induce the cytokine, at least at the mRNA level, in a strain-specific manner in mouse MCs [88] and PGN can induce secretion of IL-4 protein from mouse bone marrow-derived MCs [57].

IL-4 immunoreactive MCs can be detected using IHC in biopsies of patients with allergic rhinitis, asthma, or atopic dermatitis [89–92]. Furthermore, the number of such IL-4 immunoreactive MCs can be increased in biopsies of allergic subjects compared to healthy controls [93]. IL-4 immunoreactive MCs also were detected in human skin mast cells isolated from patients with atopic dermatitis [91] and after anti-IgE stimulation [23], but were not detected in the skin of healthy control subjects [27].

Later research provided several lines of evidence indicating that basophils can represent a more important source of IL-4 than MCs [94–96]. Using IL-4 reporter mice, Gessner et al. [83] showed that MCs, basophils, and eosinophils can express constitutive IL-4 transcript, but the secretion of IL-4 is stimulus-dependent, findings which are consistent with those of earlier studies [8, 9, 97, 98]. It was shown recently that ILC2s can produce some IL-4 in humans, but not in mice [99, 100]. In addition to being a cytokine of potential MC origin, IL-4 is also known to influence MC function and differentiation/growth [101–104].

2.6 IL-5

IL-5 is a well-known type-2 cytokine with important effects on eosinophils [105, 106]. Both mouse and human MCs can produce IL-5 upon IgE-mediated stimulation [11, 107–109] or upon

their activation with IL-33 [110], or with LPS or PGN [57, 58]. MCs that are immunoreactive for IL-5 can be demonstrated in human duodenal [111], bronchial [93], and nasal biopsies [90]. Like other type-2 cytokines, IL-5 can have priming effects on MCs [112]. It has recently been recognized that ILC2 cells represent a potentially important source of IL-5, both in mice and humans [113–115]. These interesting findings further complicate efforts to determine whether IL-5 derived from MCs has any important non-redundant functions in inflammation or immunity. Moreover, MCs potentially can influence immune responses involving ILCs because MCs can both be activated by IL-33 and can inactivate IL-33, a cytokine which also has important effects on ILC2 cells [113–116].

2.7 IL-6

IL-6 is a pleiotropic cytokine which is produced during a variety of inflammatory responses (reviewed in [117, 118]), and which is considered a therapeutic target in certain autoimmune and inflammatory disorders [119–121]. Many immune cells can produce IL-6, and MCs can produce IL-6 in response to IgE-dependent stimulation [9, 11, 122], LPS [122], substance P [123], IL-1 [124], or IL-33 [73, 125]. Human airway MCs can exhibit IL-6 immunoreactivity by IHC, suggesting that MC-derived IL-6 might contribute to the pathogenesis of asthma or allergic rhinitis [90, 93]. Although early studies in *Kit* mutant MC-deficient mice implicated MC–derived IL-6 (and IFNγ) in the promotion of mouse models of atherogenesis [126] and in diet-induced obesity and glucose intolerance [127], later work with a *Kit*-independent MC-deficient mouse strain ($Cpa3^{Cre/+}$) detected no role for MCs in diet-induced or genetic ($Lep^{Ob/Ob}$ background) models of obesity [128]. Such findings indicate that the interpretation of the results of the earlier studies may have been confounded by the use in these models of $Kit^{W\text{-}sh/W\text{-}sh}$ mice, which have increased levels of neutrophils compared to the corresponding wild type mice, as well as other MC-independent phenotypic abnormalities [62, 63, 129]. MCs not only represent a potentially important source of relatively large amounts of IL-6, but can in turn be influenced by this cytokine, e.g., IL-6 supports MC growth and is used in growth media to generate human MCs *in vitro* [130, 131].

2.8 IL-9

IL-9 is a pleiotropic cytokine, as reviewed in [132]. IL-9 is produced by and can influence a variety of immune cells. In addition to the well-known IL-9 source, Th9 T cells [133, 134], MCs also can produce IL-9 upon stimulation with ionomycin or IgE/Ag, alone or combination with IL-1, IL-10 or SCF [135–137]. It has recently been reported that a subpopulation of mucosal MCs (MMCs), perhaps representing immature stages in the MMC lineage, can produce large amounts of IL-9 that in turn may contribute to the pathology of IgE-mediated food allergy in a mouse model [138]. Many reports indicate that IL-9 is involved in various examples of type 2 immunity, including host defenses against parasitic infections and the pathogenesis of allergic diseases. In such contexts, ILC2s also can represent critical producers of IL-9 [139, 140].

MCs express the receptor for IL-9 [141] and IL-9 stimulation can alter patterns of MC gene expression [142, 143], suggesting that IL-9 produced by MCs has the potential to exert autocrine effects on these cells. IL-9 can enhance the growth of mouse BMCMCs, either

alone or synergistically with IL-3 [144], and IL-9 also can enhance the growth of human MC progenitors [141].

In vivo, IL-9 transgenic mice exhibit expansion of MMCs, including those in airway and intestinal sites [145], and can exhibit enhanced expulsion of the nematode *Trichuris muris* [146, 147]. IL-9 also promotes MC production of TGF-β1 and studies in transgenic mice indicate that IL-9 can increase numbers of MCs in models of allergic inflammation [148, 149]. IL-9 overexpression in transgenic mice also can result in MC hyperplasia associated with airway inflammation and bronchial hyperresponsiveness [150] as well as intestinal mastocytosis which is thought to contribute to food allergy [151]. By contrast, IL-9-deficient mice have impaired pulmonary mastocytosis and diminished goblet cell hyperplasia in a model of *S. mansoni* infection compared to wild type mice [152]. It has been reported that IL-9 from Tregs can contribute to recruitment and/or proliferation of MCs in the development of skin allograft tolerance [153] and in Treg-induced immune suppression in models of nephritis [154].

2.9 IL-10

IL-10 is an anti-inflammatory and regulatory cytokine which can be secreted by many kinds of immune cells including Th1, Th2, Th17, Treg, and $CD8^+$ T cells, B cells, dendritic cells, macrophages, NK cells, eosinophils, neutrophils, basophils and MCs, as well as non-immune cells including keratinocytes (reviewed in [155, 156]). MCs can secrete IL-10 upon LPS or lipid A stimulation and its production can be synergistically enhanced with IgE crosslinking [107]. *In vitro*-derived mouse BMCMCs also can secrete IL-10 via activation of FcγRIII [157].

There is substantial evidence that many immune responses, including allergic reactions, can be regulated by IL-10 secreted from Tregs (reviewed in [155, 158]). However, it now appears that MC IL-10 production also can contribute to immune regulation, at least in certain model systems. Based in part on studies of $Kit^{W/W\text{-}v}$ or $Kit^{W\text{-}sh/W\text{-}sh}$ mice (that can be called "*Kit*-dependent MC-deficient mice") which had been engrafted with MCs derived from WT or IL-10-deficient mice, Grimbaldeston et al. [157] reported that mast cell-derived IL-10 can limit the severity of severe cutaneous contact hypersensitivity (CHS) reactions. In this setting, *in vivo* and *in vitro* studies indicated that MC activation via IgG1 and FcγRIII may represent a more important mechanism for triggering MC IL-10 production than IgE crosslinking.

Later, Dudeck et al. [159], working with strains of MC-deficient mice that had normal c-*kit*, (i.e., "*Kit*-independent MC-deficient mice") reported that, in their models of CHS, MCs promoted the intensity of the reactions rather than having a suppressive effect. The latter findings were in accord with prior work indicating that, in some settings, MCs [38, 159–162] and IgE [160] can have effects that amplify the local expression of CHS responses, and it was suggested that the disparate results reported by Grimbaldeston et al. [157] may have reflected the effects of some of the MC-independent abnormalities which were present in the *Kit*-dependent MC-deficient mice used in that study.

However, inspection of the figures in the two papers indicated that, in addition to using different strains of MC-deficient mice, the two groups were studying CHS responses of

different severity and duration. This is important, in that Gimenez-Rivera et al. [163] recently reported additional evidence, derived from studies using a different model of CHS tested in both "*Kit*-dependent" and "*Kit*-independent" MC-deficient mice, that MCs can limit the features of this model CHS. Indeed, many different CHS models have been examined with various types of MC-deficient mice, and the results obtained could be interpreted to indicate that, depending on the circumstances, MCs can enhance, suppress, or have no detectable effects on the features of the tested model [164].

In part to address the "controversy" regarding the different conclusions of the studies by Grimbaldeston et al [157] and Dudeck et al [159], Reber et al [165] developed a new a fluorescent imaging approach that enables selective *in vivo* labeling (with sulforhodamine 101-coupled avidin [Av.SRho]) and tracking of MC secretory granules by real-time intravital 2-photon microscopy in living mice, and permits the identification of such MCs as a potential source of cytokines in different disease models (Figure 2). Specifically, Reber et al. [165] injected Av.SRho i.d. into ear pinnae of IL-10-GFP mice expressing a GFP tracker under the control of the *Il10* promoter [166], to monitor simultaneously both MC secretory granules and activation of *Il10* gene transcription.

Before hapten (DNFB) challenge (day 0), no Av.SRho$^+$ dermal MCs were positive for GFP, suggesting that, at least under those baseline conditions, the *Il10* gene was not substantially activated (Figure 2, B and C). However, a clear GFP signal (i.e., emission of green fluorescence detectable above the green autofluorescence of the dermis) was detected in ~40% of Av.SRho$^+$ MCs as soon as 1 day after hapten (DNFB) challenge, a percentage that remained stable for the next 2 days (Figure 3, B and C). By quantifying the total number of IL-10-GFP$^+$ cells at sites of CHS, and assessing how many of these cells were Av.SRho$^+$ MCs, Reber et al [165] observed a progressive increase over time in the total number of IL-10-GFP$^+$ cells, with the highest numbers 2 days after DNFB challenge (Figure 3, B and D), a finding which is consistent with previous reports describing the kinetics of infiltration of Treg cells at sites of CHS [167]. IL-10-GFP$^+$ Av.SRho$^+$ dermal MCs represented up to ~55% of all detected IL-10-GFP$^+$ cells at day 1, but only ~10%–20% at days 2 and 3 after DNFB challenge (Figure 3, B, D, and E).

Taken together, these results indicate that dermal MCs are one of the first immune cells to produce IL-10 at sites of severe CHS, before the substantial infiltration of other IL-10–producing immune cells. By contrast, Reber et al [165] reported that, in a mild model of CHS, in which studies in *Cpa3-Cre$^+$; Mcl-1$^{fl/fl}$* (*Kit*-independent) MC-deficient mice [168] indicated that MCs promoted the development of inflammation and epidermal hyperplasia (see Supplemental Figure 3 in Reber et al 2017 [165]), intravital microscopy detected only minimal, if any, changes from baseline levels of MC *Il10* gene expression (see Supplemental Figure 4 in Reber et al 2017 [165]).

Confirming the findings of Grimbaldeston et al. [157] in *Kit*-mutant mice, two types of *Kit*-independent MC–deficient mice, *Cpa3-Cre$^+$; Mcl-1$^{fl/fl}$* [168] and *Mcpt5-Cre$^+$; DTA* [159] mice, exhibited significantly enhanced ear swelling and epidermal hyperplasia compared with the values in their respective littermate controls [165]. However, while *Kit$^{W\text{-}sh/W\text{-}sh}$* mice exhibited an ~200% increase in ear swelling on day 5 of the reaction as compared with their littermate

controls, this difference was less pronounced in *Kit*-independent MC-deficient mice at the same time point (~120% increase in *Cpa3-Cre*$^{+}$*; Mcl-1*$^{fl/fl}$ mice and ~50% increase in *Mcpt5-Cre*$^{+}$*; DTA* mice). Reber et al. [165] suggested that these findings are consistent with the conclusion that MCs can have effects that can substantially limit features of this model of severe CHS in each of the 3 examined mouse strains, but that additional phenotypic abnormalities in *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice beside their MC deficiency probably also contribute to the exacerbation of severe CHS responses in this strain.

To assess the potential role of MC-derived IL-10 in this model of severe CHS, Reber et al [165] tested mice in which the *Il10* gene was floxed out specifically in connective tissue–type MCs by generating *Mcpt5-Cre*$^{+}$*; Il10*$^{fl/fl}$ mice (Figure 3A). Dermal MCs were present in similar numbers in the ear pinnae of *Mcpt5-Cre*$^{+}$*; Il10*$^{fl/fl}$ mice, in which connective tissue–type MCs are deficient for IL-10, and littermate control *Mcpt5-Cre*$^{-}$*; Il10*$^{fl/fl}$ mice (Figure 3, C and D). However, Reber et al. [165] found that the *Mcpt5-Cre*$^{+}$*; Il10*$^{fl/fl}$ mice exhibited significantly enhanced ear swelling and epidermal hyperplasia compared with the littermate control mice (Figure 3, B, C, and E). Notably, the enhancement of both the tissue swelling and the epidermal thickness associated with the reactions observed in *Mcpt5-Cre*$^{+}$*; Il10*$^{fl/fl}$ mice was less pronounced than that observed in the *Kit*-independent MC-deficient mice, suggesting that MCs might help to limit these features of this acute model of severe CHS by both IL-10–dependent and IL-10–independent mechanisms [165].

In addition to having the potential to regulate the intensity of CHS, studies in mice in which IL-10 was specifically deleted in MCs indicate that MC-derived IL-10 can suppress the adaptive immune response and thereby result in enhanced persistence of bacteria in a mouse model of bladder infection of *Escherichia coli* [169]. MC-derived IL-10 also can suppress germinal center formation by affecting T follicular helper (Tfh) cell function [170]. Evidence derived from studies in *Kit*-dependent MC-deficient mice suggests that MC-derived IL-10 also can limit the cutaneous pathology associated with chronic UVB irradiation [157] and can suppress graft versus host disease (GVHD) in a mouse model independently of Treg [171]. However, to our knowledge, the latter two findings have not yet been assessed in tests of *Kit*-independent MC-deficient mice.

The studies reviewed above indicate that MC-derived IL-10 indeed can contribute to the suppression of certain adaptive immune responses in mice, with beneficial consequences in the case of a model of severe CHS [165] but with detrimental effects in a model of bladder infection with *E. coli* [169]. The findings of Reber et al [165] also support the conclusion that the same MC population, in this case mouse dermal MCs, can exhibit markedly different levels of *Il10* gene expression, with upregulation of expression occurring rather rapidly in response to the induction of a severe CHS reaction. Clearly, further studies are needed to clarify the roles of MC-derived IL-10 in various immune responses.

2.10 IL-11

IL-11 is multifunctional cytokine that belongs to IL-6 cytokine family. Indeed, by structure, IL-11 is the cytokine that is most closely related to IL-6 and they share gp130 as a component of their receptors (reviewed in [172–174]). Various functions are also shared among IL-6 cytokine family members, and IL-11, which can promote thrombopoiesis, is used to

prevent the development of chemotherapy-induced thrombocytopenia [172, 174, 175]. IL-11 can be produced by many kinds of cells including leukocytes, epithelial cells, and fibroblasts, and is thought to be involved in the pathogenesis of asthma, airway hyperresponsiveness, and lung inflammation [176–178]. One report indicated that human umbilical cord blood-derived MCs can produce IL-11 in response to an IgE-mediated stimulus [179]. However, the importance of MCs as a potential source of IL-11 remains to be determined.

2.11 IL-12

IL-12 is important for the induction of Th1 responses and for stimulating IFNγ production from Th1 cells and NK cells [180, 181]. IL-12-deficient mice are severely susceptible to bacterial and viral infections, and IL-12 is important for mounting adequate cellular immune responses to intracellular pathogens. One of the causes of vulnerability to pathogens is impaired IL-12 production from various immune cells in response to pathogen-derived products such as LPS. Besides activating IL-12 production in dendritic cells and macrophages, LPS (but not IgE-mediated stimulation) can stimulate IL-12 production in MCs [87, 182]. SCF-derived mouse BMCMCs express IL-12 mRNA but not IL-3-derived mouse BMCMC [183]. Moreover, IL-12 can induce production of IFNγ in rat PMCs [184], raising the possibility that IL-12 might have autocrine effects on MCs.

2.12 IL-13

IL-13 is an important cytokine in type-2 immune responses, with functions that partially overlap with those of IL-4 [185–187]. Human and mouse MCs produce IL-13 upon stimulation with IgE and antigen [107, 137, 188, 189], PMA (phorbol 12-myristate 13-acetate) and ionomycin [188, 190], LPS or PGN [57, 58, 107], or IL-33 [73, 125, 191, 192]. Human MCs produce IL-13 upon IL-1β stimulation [190] and mouse MC IL-13 production by IgE/Ag stimulation can be enhanced in the presence of IL-1β [135]. SCF can induce IL-13 production in mouse MCs [193].

IL-13 is also produced by many other cell types including T cells, basophils, eosinophils, and epithelial cells. A series of studies now suggest that ILC2-derived IL-13 plays a critical role in host defense to infections with certain parasites and in the pathogenesis of type-2 immune responses [185, 194, 195]. Further research is needed to understand the importance of MC production of IL-13, especially in those in settings in which many other cell types also elaborate this product.

2.13 IL-16

IL-16 is a pro-inflammatory cytokine that can act as a chemoattractant for T cells, eosinophils, monocytes, dendritic cells, and MCs (reviewed in [196]). In addition to functioning as a MC chemoattractant via its binding to CD9 [197], IL-16 also can promote maturation and differentiation of human umbilical cord blood-derived MCs when administered together with SCF [198]. Qi et al [198] also showed that IL-16-treated human cord blood-derived $CD3^{-}/CD4^{+}/CD117^{+}$ cells, which contained cells the authors called “mast cells/basophils”, are less susceptible to HIV infection. It has been reported that IL-16 can be produced without any stimulation in human CBMCs [199] and that IL-16 mRNA can be detected constitutively in human intestinal MCs [200]. IL-16 also has been detected by IHC in

tryptase^{+} MCs present in bronchial biopsies from normal subjects as well as from patients with asthma [201].

2.14 IL-33

IL-33 is recognized as an important alarmin secreted by damaged or necrotic cells, particularly vascular endothelial and epithelial cells [202–205]. IL-33 has been implicated in the activation of ILC2s in the settings of infections and allergic diseases [205]. MCs constitutively express the IL-33 receptor ST2, therefore they can respond to IL-33. MCs can produce a variety of cytokines and chemokines upon IL-33 stimulation, including TNF [191, 192], IL-2 [73], IL-4 [85], IL-5 [191], IL-6 [191], IL-10 [191], IL-8 [206], IL-13 [125, 191, 206], granulocyte-macrophage colony-stimulating factor (GM-CSF) [191], CXCL8 [191], CCL1 [191], CCL2 [191], CCL17 [191], and CCL22 [191] (also see the sections on each of these products). Moreover, *in vitro* studies indicate that IL-33 can act on CD34^{+} cells to facilitate MC maturation and differentiation [191], both physiologically and in the setting of chronic myeloid leukemia [207]. Recent evidence has identified mouse BMCMCs as a potential source of IL-33 [110, 208], as well as a target of this cytokine. MCs also can be involved in the activation of IL-33 by converting full-length IL-33 into more active mature forms with either chymase or tryptase [209, 210]. Finally, MC chymase (mMCP-4 or human chymase) can further degrade 17.5 kDa active IL-33 into a biologically inactive form [211, 212].

2.15 EGF (epidermal growth factor)

Epidermal growth factors stimulate proliferation and differentiation of various cells including fibroblasts, endothelial cells, and epithelial cells [213]. Human MCs in the thyroid are EGF positive by IHC [214] and freshly isolated human dermal MCs are positive for heparin-binding EGF-like growth factor (HB-EGF) mRNA by RT-PCR [215].

2.16 FGF2 (fibroblast growth factor 2)/bFGF (basic fibroblast growth factor)

MC-derived FGF2 is considered to be a potential pro-angiogeneic factor [216]. Immunoreactivity for FGF2 has been detected by IHC in MCs in human fibrotic lung tissue, rheumatoid synovia, and skin hemangiomas [217], in human thyroid MCs [214], and in rat PMCc [34], and MCs containing FGF2 in a granule-associated form with heparan sulfate were detected in human skin using a binding assay with biotinylated FGF2 [218]. Secretion of FGF2 has been reported for human dermal MCs and HMC-1 cells [215]. There is a report that IL-17A can increase the secretion of FGF2 from human CD133^{+} progenitor derived cultured MCs [219]. In addition to FGF2, other factors with mitogenic activity on fibroblasts, including FGF7 and FGF10 are also can be detected in human dermal MCs [215].

The importance of FGF2 production by MCs *in vivo* is not yet understood. However, Wroblewski et al. [220] have suggested that one reason VEGF-targeted therapy becomes less effective is that MCs re-activate angiogenesis in part by secreting FGF2.

2.17 GM-CSF

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a cytokine which facilitates the development of granulocytes and macrophage from precursors in bone marrow [221]. MCs can produce GM-CSF upon IgE-mediated stimulation [10, 11, 109, 222], or after

exposure to LPS [222], PGN [222], zymosan [222], or Pam3Cys [222]. Mucosal mast cells in the airways of asthmatic patients can exhibit GM-CSF immunoreactivity [111], indicating that MC-derived GM-CSF might participate in the pathogenesis of allergic diseases, for example by promoting eosinophil survival. There is evidence that MC-derived GM-CSF can contribute, together with TNF, to the migration of graft-derived dendritic cells to lymph nodes by enhancing their survival and thereby contributing to the development of peripheral tolerance [41].

2.18 IFN-γ

IFN-γ is considered a paradigmatic Th1 cytokine [223]. mRNA for IFN-γ can be upregulated upon IgE-mediated or ionophore stimulation of rat PMCs and certain mouse MC lines [9, 11, 108]. Gupta et al. [184] later detected IFN-γ protein in rat PMCs after IL-12 stimulation, but not after IgE-mediated activation. We discuss above, in the section on IL-6, recent work [128] that has called into question the interpretation of prior work indicating that MC–derived IL-6 and IFN-γ may be important in the promotion of atherogenesis [126] or diet-induced obesity and glucose intolerance [127].

IFN-γ can influence MCs directly, since MCs can express the receptor for IFNγ [189, 224]. Varied effects of IFN-γ on MCs have been reported, including both positive and negative effects. For example, IFN-γ can inhibit the growth and/or induce apoptosis in mouse BMCMCs [224, 225] and in human bone marrow-derived MCs [226]. IFN-γ can inhibit serotonin release from mouse PMCs [227] and also can inhibit IL-4 mediated enhancement of serotonin/arachidonate release upon IgE and antigen stimulation [228]. IFN-γ can inhibit MC-associated cytotoxicity by inhibiting TNF release from rat PMCs [229].

By contrast, other studies showed that IFNγ can promote the survival of, and histamine release from, human umbilical cord blood-derived MCs [230], or have no effect on the degranulation of human peripheral blood-derived MCs [231] or human MCs derived *in vitro* from intestinal MCs [232]. Human (peripheral blood progenitor-derived) cultured mast cells can express functional Toll-like receptor 4 only when they have been preincubated with IFNγ. The profile of cytokines which these MCs can express in response to LPS is unique compared to other stimuli. For example, they can produce far more TNFγ [233]. Studies using BMCMCs derived from wild type (WT) mice or IFNγR-deficient mice showed that IFN-γ can significantly increase the release of histamine, IL-6, and IL-13 by IgE+antigen-stimulated WT BMCMCs, whereas treatment of the cells with IFN-γ alone was without effect [189]. The ability of IFN-γ to enhance dose-dependently the IgE+antigen-induced mast cell production of IL-13 is of particular interest, since IL-13 is thought to contribute to the development of asthma through such effects as promoting subepithelial fibrosis (in part by upregulating synthesis of arginase-1), increasing mucus secretion, and eliciting airway hyperresponsiveness (AHR) [234].

The varied results obtained in studies of effects of IFN-γ on MCs might reflect, at least in part, differences in the effects of IFN-γ on different populations of MCs. For example, IFNγ inhibited histamine and TNF release from rat PMCs, but had no detectable effect on rat intestinal MCs [235]. Exposure of human MCs to IL-4, IL-5, and IFNγ during growth and differentiation generally downregulated MC numbers and function, but when these cytokines

were administered to mature human peripheral blood-derived MCs, IFN-γ and IL-5 had no effects on degranulation and cell division, but IL-4 induced division and potentiated FcεRI-mediated degranulation [104]. Furthermore, IFN-γ decreased proliferation, without affecting apoptosis, in human intestinal MCs cultured in the presence of optimal concentrations of SCF or SCF and IL-4 [232]. However, in the absence of growth factors or at suboptimal concentrations of SCF, IFN-γ promoted survival through inhibition of MC apoptosis [232].

Both mouse and human studies suggest that effects of IFN-γ on MCs may importantly influence multiple aspects of the pathology of certain forms of asthma, particularly those associated with high levels of neutrophil infiltration of the airways and certain forms of severe asthma [189, 236–238]. However, in such settings, MCs are more likely to represent important targets of IFN-γ rather than critical sources of this cytokine.

2.19 NGF

NGF is a neurotropic polypeptide with effects which regulate the development, growth, survival, and function of central and peripheral neurons (reviewed in [239, 240]). As mentioned in the section on TNF, close anatomical associations between MCs and nerves have long been recognized [48–50]. NGF is one of the key factors to link these two cell types, and was the first mitogen to be identified as able to directly or indirectly promote MC development *in vivo*, in this case in neonatal but not adult rats [241]. NGF can support rat PMC survival [242], the development by mouse BMCMCs of features of “connective tissue type MCs” [243], and the growth of rat PMCs [241, 244]. Furthermore, NGF can induce degranulation of rat skin MCs [245] and PMCs [246–249] and can induce chemotaxis in rat PMCs [250]. Moreover, correlations have been reported for numbers of MCs and levels of NGF mRNA levels in bronchial biopsies from patients with asthma [251], vernal keratoconjunctivitis [252], or systemic sclerosis [253].

However, there are reports indicating that NGF has few if any direct effects on some populations of human MCs [254, 255], but can influence human basophils [255, 256]. On the other hand, it has been reported that the HMC-1 leukemic MC line and human CBMCs can express functional receptors for NGF [257, 258] and that NGF can support the development and differentiation of some types of human MCs (HMC-1 and CBMCs) [259, 260]. Tam et al. [258] identified mRNA transcripts of full-length tyrosine kinase-containing *trkA*, *trkB*, and *trkC* neurotrophin receptor genes in HMC-1 cells and, by flow cytometry, HMC-1 cells exhibited expression of TrkA, TrkB, and TrkC receptor proteins containing full-length tyrosine kinase domains. Highly purified populations of human lung MCs expressed mRNAs for *trkA*, *trkB* and *trkC*, whereas preparations of human umbilical cord blood-derived MCs expressed mRNAs for *trkA* and *trkC*, but not *trkB*. Populations of the latter cells also exhibited significantly higher numbers of chymase-positive MCs after the addition of NGF to their culture medium for 3 weeks [258]. HMC-1 cells expressed mRNAs for NGF, brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT-3), the cognate ligands for TrkA, TrkB, and TrkC, whereas NGF and BDNF transcripts were detectable in human umbilical cord blood MCs [258].

Taken together, the findings of Nilsson et al. [257] and Tam et al. [258], and subsequent work [259, 261], indicate that at least some populations of human MCs can express functional TrkA

receptors and suggest that NGF may be able to promote certain aspects of MC development and/or maturation in humans. These studies, and reports that rodent rat PMCs can contain and secrete NGF [262], indicate that MCs may represent a potential source of neurotrophins.

2.20 PDGF (platelet-derived growth factor)

PDGF is an important mitogen that can contribute to angiogenesis by facilitating the growth of blood vessels [263–265]. By IHC, PDGF positive MCs are increased in the areas of thyroid tissue regeneration in patients with subacute thyroiditis [214], suggesting a role in tissue repair, as well as in Graves' ophthalmopathy, an autoimmune inflammatory disease of the periorbital and orbital tissues [266]. Mouse MCs also can produce PDGF after co-culture with cardiac myocytes or fibroblasts, and it has been suggested that such MC-derived PDGF can contribute to the pathogenesis of atrial fibrillation [267].

2.21 SCF (stem cell factor)

The KIT ligand, SCF is essential for normal MC differentiation, growth, and survival [268–271]. Non-hematopoietic cells such as endothelial cells or fibroblasts are considered to be more important sources of SCF than are hematopoietic cells [272–274]. However, human MCs have been reported to exhibit SCF immunoreactivity in their granules [275–279]. SCF mRNA and/or protein has been reported in human skin and lung mast cells and human PBMCs and CBMCs [275, 277, 278]. SCF production by MCs may have autocrine effects on MCs, and/or paracrine effects on other cell types, under physiological conditions or in settings of pathology, such as during some forms of mastocytosis [278, 280].

2.22 TGF-β1

Transforming growth factor type-β (TGF-β) has many biological activities, and is thought to be a particularly important contributor to fibrosis, angiogenesis, and tissue repair. In addition, TGF-β can influence T cells, including Th17 and Treg cells (reviewed in [281–285]), as well as B cells, dendritic cells, NK cells, neutrophils, eosinophils, and MCs (reviewed in [192, 284–287]).

MCs can be a source of TGF-β1 [51, 288], and can secrete TGF-β1 upon IgE and antigen stimulation [51]. *In vitro* evidence obtained from mice suggests that, along with MC-derived TNF, MC-derived TGF-β1 can enhance the production of type-I collagen by fibroblasts [51]. Evidence from IL-9 blockade in mouse cystic fibrosis model suggests that TGF-β1 derived from MCs (and other cells) stimulated with IL-9 can contribute to the pathogenesis of cystic fibrosis [74].

Similar to TNF, TGF-β1 has been shown to be secreted rapidly by MCs [288, 289] and to be stored in MC cytoplasmic secretory granules together with chymase 1 [289]. Human cord blood-derived MCs constitutively express TGF-β1, but its expression is not upregulated after calcium ionophore stimulation [290].

Many reports indicate that TGF-β1 can suppress the functions of diverse immune cells, including MCs [192, 286, 291], and it has been proposed that MC-derived TGF-β1 can suppress MC functions in an autocrine [292] or paracrine manner. TGF-β1 can inhibit the release of

multiple mediators upon IgE-mediated stimulation of MCs, including release of histamine and TNF in rat PMCs [292], IL-6 and TNF in mouse BMCMCs [192, 286], IL-6 in human skin-derived MCs [286], and β-hexosaminidase, TNF, GM-CSF, IL-13, and IL-6 in SCF cultured MCs derived from human skin [293]. Co-exposure to TGF-β1 can also inhibit the IL-33-induced release of multiple mediators from mouse BMCMCs including TNF, MCP-1, IL-6, IL-13, and MIP-1α [192]. There is evidence that TGF-β1 can have autocrine effects which inhibit the proliferation of mouse BMCMCs [294] and cultured mouse PMCs [294, 295]. One mechanism by which TGF-β1 may suppress the IgE-dependent activation of some MC populations is its ability to reduce levels of expression of FcεRI on the MC surface [296].

In vivo administration of TGF-β1 can inhibit immediate and delayed type hypersensitivity reactions, although this might reflect indirect effects rather than actions specifically on MCs [297]. On the other hand, there are reports that TGF-β1 either can enhance mediator production in certain types of MCs *in vitro* [298, 299] and *in vivo* [300] or have no effect in BMCMCs *in vitro* [294]. For example, Ganeshan and Bryce [298] found that membrane-bound TGF-β1 on Tregs can promote IL-6 production from mouse BMCMCs, whereas, by contrast, Tregs can inhibit MC degranulation through OX40/OX40L [301].

Finally, the cytoplasmic granule-stored MC protease, chymase (from human skin [302] or stomach [303] or rat PMCs [289]) can generate active TGF-β1 from its inactive latent form. *In vivo* studies with chymase inhibitors (in hamsters [303], rats [304] and in mice [305, 306]), as well as work in mMCP4-deficient mice (which genetically lack the mouse chymase most like the human enzyme)[307], have suggested possible direct or indirect effects of chymase in the pathogenesis of fibrotic diseases. However, the extent to which any such effects of chymase reflect its ability to activate latent TGF-β1 (derived from MCs or other sources) remains to be determined. Also, it seems likely that TGF-β1's bioactivity, e.g., as an enhancer or suppressor of various MC functions, may depending on the particular types of MCs in that microenvironment, as well as other local factors that can influence the cytokine's bioactivity or biodistribution.

2.23 VEGF (vascular endothelial growth factor)/VPF (vascular permeability factor)

Angiogenesis is critically important in normal development and tissue homeostasis and repair, and can contribute to diverse forms of pathology, e.g., tumor development and metastasis, psoriasis, rheumatoid arthritis, and wet macular degeneration [308, 309]. Observational studies have implicated MCs in angiogenesis in various settings and one of the most important MC products which may contribute to such roles is thought to be VEGF [216].

The molecule now called VEGF was initially discovered as a component of a guinea pig tumor ascites that can markedly enhance cutaneous vascular permeability *in vivo*, the bioactivity which was the basis of its initial name, vascular permeability factor (VPF) [310–313]. VPF later was found to be identical to VEGF, which was cloned and characterized in 1989 [314]. The initially described VPF/VEGF, now called VEGF-A, is one of five members of the VEGF family in mammals, that also includes placental growth factor (PGF), VEGF-B, VEGF-C and VEGF-D [315, 316]. VEGF-A is a pro-angiogenetic factor which can enhance the angiogenesis process by promoting endothelial cell proliferation and migration,

and, as its alternative name (VPF) indicates, VEGF-A also can potently enhance vascular permeability, with a molar potency roughly 1000 times that of histamine [311–313].

Many normal and neoplastic cell types can secrete VEGF, and two groups provided evidence that MCs should be added to that list [317, 318]. Moreover, there is evidence that MCs can constitutively contain VEGF as a preformed, heparin-binding factor [34, 317, 318] and can secrete this protein after stimulation by diverse triggers, including IgE and antigen (this was the first evidence that secretion of VEGF could be induced in an antigen-specific way in any cell type), PMA, A23187, or SCF [317], substance P or IL-1 (with enhanced release when either agent was tested together with IL-33 [319]), corticotropin-releasing hormone [320], IL-17A [219], or live *Staphylococcus aureus* bacteria [321]. It also has been shown that human CBMCs and purified lung MCs can constitutively express VEGF-A isoforms (VEGF-A_{121} and VEGF-A_{165} in CBMCs; VEGF-A_{121}, VEGF-A_{165} and VEGF-A_{189} in purified human lung MCs), VEGF-B, VEGF-C and VEGF-D, and their receptors (VEGFR1 and VEGFR2) [322, 323], indicating the potential involvement of such MC-derived products in angiogenesis and lymphangiogenesis [324]. VEGF can act as a chemoattractant for certain MCs *in vitro* [325] and *in vivo* [326], suggesting a mechanism by which VEGF can have autocrine or paracrine effects on this lineage.

Given the large number of other cell types that also can produce VEGF, it may be difficult to identify settings in which MCs represent important or non-redundant sources of this cytokine. IgE-associated disorders represent one potential setting of this kind, in that relatively few cells other than MCs express the FcεRI, and it has been reported that VEGF immunoreactive MCs are increased in the airways of asthmatic patients compared to controls [327–329].

There are also several reports that MCs can be immunoreactive for VEGF in certain tumors including laryngeal squamous cell carcinoma [330], malignant melanoma [331], and non-Hodgkin lymphoma [332], suggesting their possible involvement of MC-derived VEGF in tumor-associated angiogenesis. Evidence has been reported based on tests of several tumor models, using both *Kit*-dependent and *Kit*-independent MC-deficient mice, that MCs can contribute to tumor-related angiogenesis and other features of tumor progression [333–335]. MCs are increased in the areas of thyroid tissue regeneration in patients with subacute thyroiditis, and such MCs can exhibit immunoreactivity for VEGF, bFGF, PDGF, TGF-β1 and EGF [214]. In mice, several lines of evidence indicate that low-dose irradiation can promote tissue revascularization at least in part through MC production of VEGF [336]. However, this point needs to be investigated further, ideally by employing mice in which VEGF production can be selectively ablated in MCs.

3 MAST CELL-DERIVED CHEMOKINES

Chemokines are cytokines which have chemotactic activities on various immune cells [337–339]. Chemokines play important roles in the development and homeostasis of the immune system and in the pathogenesis of inflammatory responses, including those associated with diverse disorders including allergic and autoimmune diseases, infections, and cancer [338, 340–342]. Beyond inducing chemotaxis, chemokines can also activate immune

cells, including MCs, and play a critical role during HIV infection [343]. Therefore chemokines are considered potential therapeutic targets in many diseases [344–346].

The first identification of MCs (in this case *in vitro*-derived mouse MCs and mouse MC lines) as a potential source of certain chemokines, specifically CCL1, CCL2, CCL3, and CCL4 mRNA, was in 1989 [11]. Since then, various populations of mouse or human MCs, most often representing *in vitro*-derived MCs [347], have been identified as potential sources of a now very long list of these molecules (Table 2). Given: 1) the vast number of biological responses in which chemokines are involved, 2) the large number of chemokines which MCs have at least the potential to produce, 3) the long list of stimuli (including IgE in the absence of known specific antigen [348]) which can elicit chemokine production by MCs (Table 2), in some cases without inducing substantial MC degranulation, and 4) the large number of other cell types which also represent a potential source of these mediators, it will be challenging to attempt to identify situations in which MCs represent important non-redundant sources of these molecules.

In fact, there is relatively little work attempting to identify MCs as sources of chemokines *in vivo* and we are not aware of any published work reporting results of experiments in mice in which individual chemokines have been deleted selectively in MCs. Until experiments of that type are performed, MCs may be best regarded as *potentially* important sources of certain chemokines in health and disease, especially in those settings in which relatively selective MC activation occurs (e.g., by IgE and specific antigen); but in many settings in which chemokines have been implicated, MCs may not represent critical non-redundant producers of these mediators.

CONCLUSION

The long and growing list of cytokines, chemokines and growth factors which have been identified in analyses of various populations of rodent and human MCs offers great scope for the imagination concerning the potential roles of MCs as important sources of these products in health and disease. However, to date, all of the cytokines, chemokines and growth factors identified in MCs also can be produced by other (and often many other) cell types.

Moreover, as described herein, many of these potentially MC-derived products have been identified in analyses of *in vitro*-derived MCs, and it remains to be shown whether and to what extent, and it which settings, native populations of MCs *in vivo* represent important or even non-redundant sources of these molecules. Finally, as we have discussed, there appears to be substantial variation in the types of products which MCs can produce and in the signals that can elicit production of these molecules, based on animal species, type and anatomical location of MCs, stage of MC development, and current (and perhaps past) exposure of MCs to inflammatory or immune responses. Different MC populations also will vary in the extent to which they can produce and release mediators, such as their granule-stored proteases, which have the capacity to biochemically activate and/or degrade, or otherwise regulate levels of, cytokines, chemokines or growth factors of MC or non-MC origin.

In light of these considerations, defining the *actual* roles of MC-derived cytokines, chemokines and growth factors in health and disease will require the application of more definitive tools than those used in the past to identify MCs as *potential* sources of these products. The good news is that a large number of new approaches for analyzing the importance of MCs as sources of such products already have been described (Table 4). We anticipate that the thoughtful application of such new methods will enable us to identify many settings in which the production of particular cytokines and growth factors, by particular MC populations, makes a real difference in the initiation, amplification or regulation of biological responses that contribute importantly to the maintenance of health or to features of disease. Such work also may help to identify new therapeutic targets in at least some of the disorders in which MCs play an important role.

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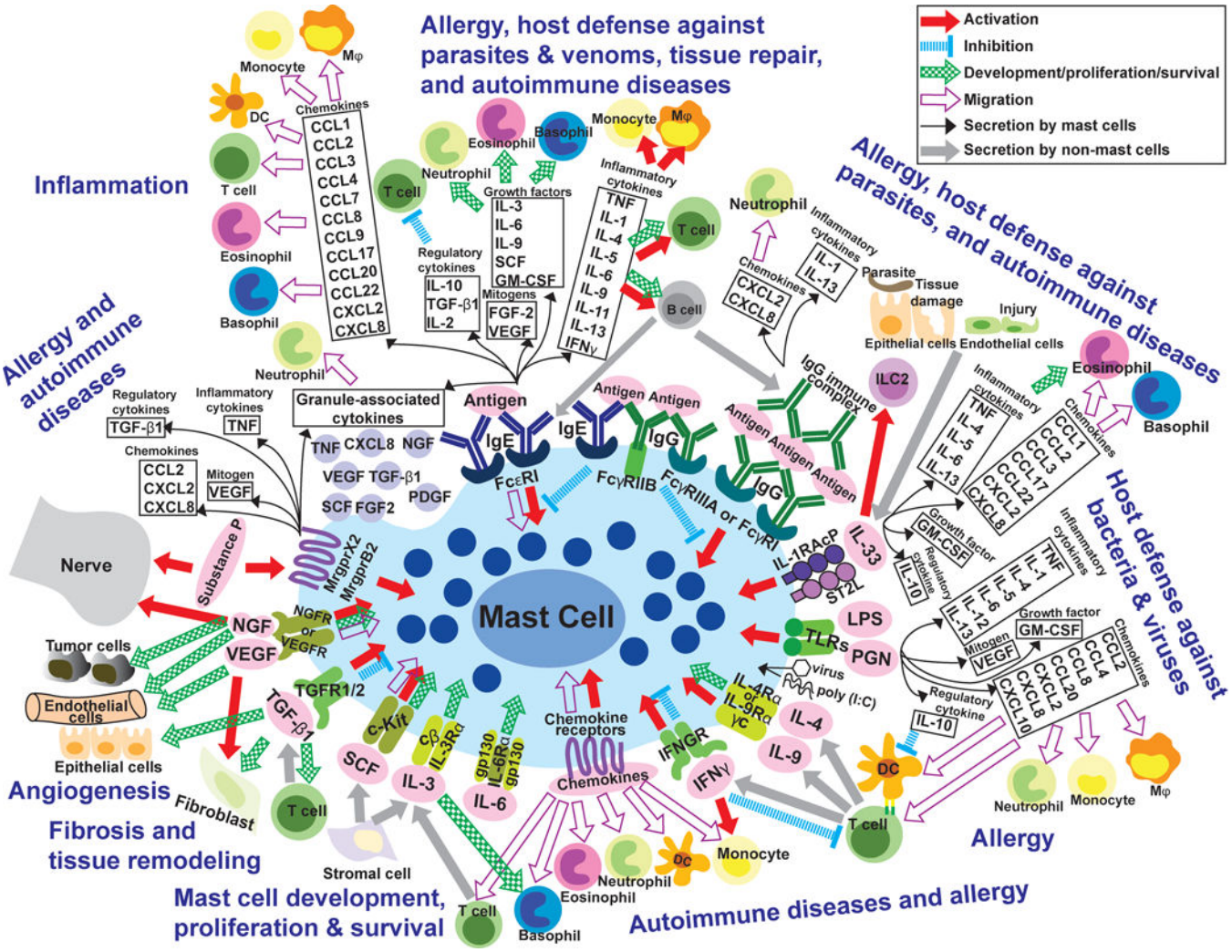

Figure 1. Highly simplified overview of the diverse stimuli and potential consequences of mast cell activation and secretion of cytokines, chemokines and growth factors

Mast cells (MCs) can be activated through various receptors when they are exposed to the corresponding ligands (e.g., in pink ovals). This can induce MC activation (red arrows), inhibition (blue dotted lines), or migration (purple open arrows), influence MC development/proliferation/survival (green patterned arrows), and/or induce MCs to secrete many cytokines, chemokines and growth factors (black arrows and related boxes). Grey arrows depict secretion of products from cells other than MCs. Depending on the type of stimulus/stimuli, as well as the type/phenotype of the MCs, such activated MCs also may secrete many other stored and/or newly synthesized mediators (not shown). In adaptive immune responses (e.g., elicited by parasites, animal venoms or allergens), MCs can be activated when IgE bound to surface FcεRI receptors is crosslinked by bi- or multivalent antigens, or when immune complexes (IgG-ICs) bind to FcγRs. In some settings, for example in mouse BMCMCs, co-ligation of FcεRI with inhibitory FcγRIIb receptors can down-regulate MC activation [349, 350]. FcγRI is a high affinity receptor induced in human MCs by IFNγ stimulation *in vitro* [231] or in the IFNγ enriched environment of skin MCs in the setting of psoriasis [351]. However, this FcγRI expression is observed in humans not in mice. Upon

antibody/antigen-mediated stimulation, MCs can synthesize and secrete a panel of factors as indicated in the black boxes. In turn, those factors can influence other immune and non-immune (structural) cells and contribute to pathogenesis of various types of allergic reactions and perhaps autoimmune disorders, such as some forms of arthritis, as well as to host defense against venoms or parasites. Many of the immune and structural cells depicted are comprised of functionally distinct subtypes (e.g., T cells, DCs, macrophages, fibroblasts, nerves) and the effects of particular MC products on such cells may vary importantly depending on the target cell subtype (not shown). In some settings, such MC-derived products also may contribute to tissue repair and remodeling, both through effects on structural cells and by regulating aspects of the inflammatory/immune response. Antibody/antigen-mediated stimulation also can induce MCs to secrete preformed mediators such as histamine, serotonin (in rodents, primarily), proteoglycans, and proteases (not shown), as well as certain cytokines and growth factors which can be granule-associated (black boxes and the purple granules underneath), as well as many lipid mediators including cysteinyl leukotrienes and certain prostaglandins (not shown). IL-33, which is produced by endothelial/epithelial cells in sites of tissue damage, can stimulate MCs to secrete many factors (indicated in the black boxes) with diverse potential effects on other immune and non-immune cells that can contribute to the pathogenesis of allergies and to host defense. Products of pathogens such as LPS (lipopolysaccharide) and PGN (peptidoglycan), poly (I:C), and certain viruses can directly activate MCs through TLRs (toll-like receptors), resulting in the secretion of a variety of factors (as indicated in black boxes); depending on the setting, this could contribute to host defense and/or disease (e.g., there is a well-established clinical association between certain viral infections and exacerbations of asthma). During Th2 cell-associated immune responses, IL-4 or IL-9 from T cells or from immature cells in the MC lineage can activate MCs and promote their development/proliferation. IFNγ can deliver positive or negative signals to MCs, probably depending on species of animal, MC subpopulation, and setting (such as a disease or a particular beneficial host response). MCs can migrate in response to certain chemokines, but MCs also can be activated by chemokines. IL-3 and SCF (stem cell factor) are representatives of factors which support MC development, proliferation and/or survival (others include, depending on the MCs, IL-4, IL-6, IL-9, and NGF). IL-3 can have similar effects on basophils. NGF (nerve growth factor), VEGF (vascular endothelial growth factor), FGFs (fibroblast growth factors), and TGF-β1 (transforming growth factor type-β) can contribute to the development of fibrosis or angiogenesis, and there is some evidence indicating that these factors, like TNF (tumor necrosis factor), can be constitutively stored in the granules of some MCs. These factors also can influence MCs (as indicated with arrows). Substance P is a product of certain neurons that can potently activate some types of MCs, which in turn can secrete preformed mediators that may include granule-associated cytokines (as indicated in the black boxes). Bidirectional interactions between certain nerve cells and MCs have been studied extensively, and there is considerable interest in the potential importance of such nerve-MC interactions in health and disease. Finally, it should be kept in mind that proteases released from activated MCs can degrade TNF [61], IL-1β [352], IL-18 [353], IL-33 [209, 211], SCF [354], CCL5 and CCL11 [355], CCL26 [356], and likely other factors shown in the figure, and this may represent an important mechanism by which MCs can control the intensity and duration of the biological effects of such factors. Please see Tables 1 and 2 for additional information

about how variation in MC subtype may influence the extent to which these cells can produce and/or respond to the factors shown in the figure.

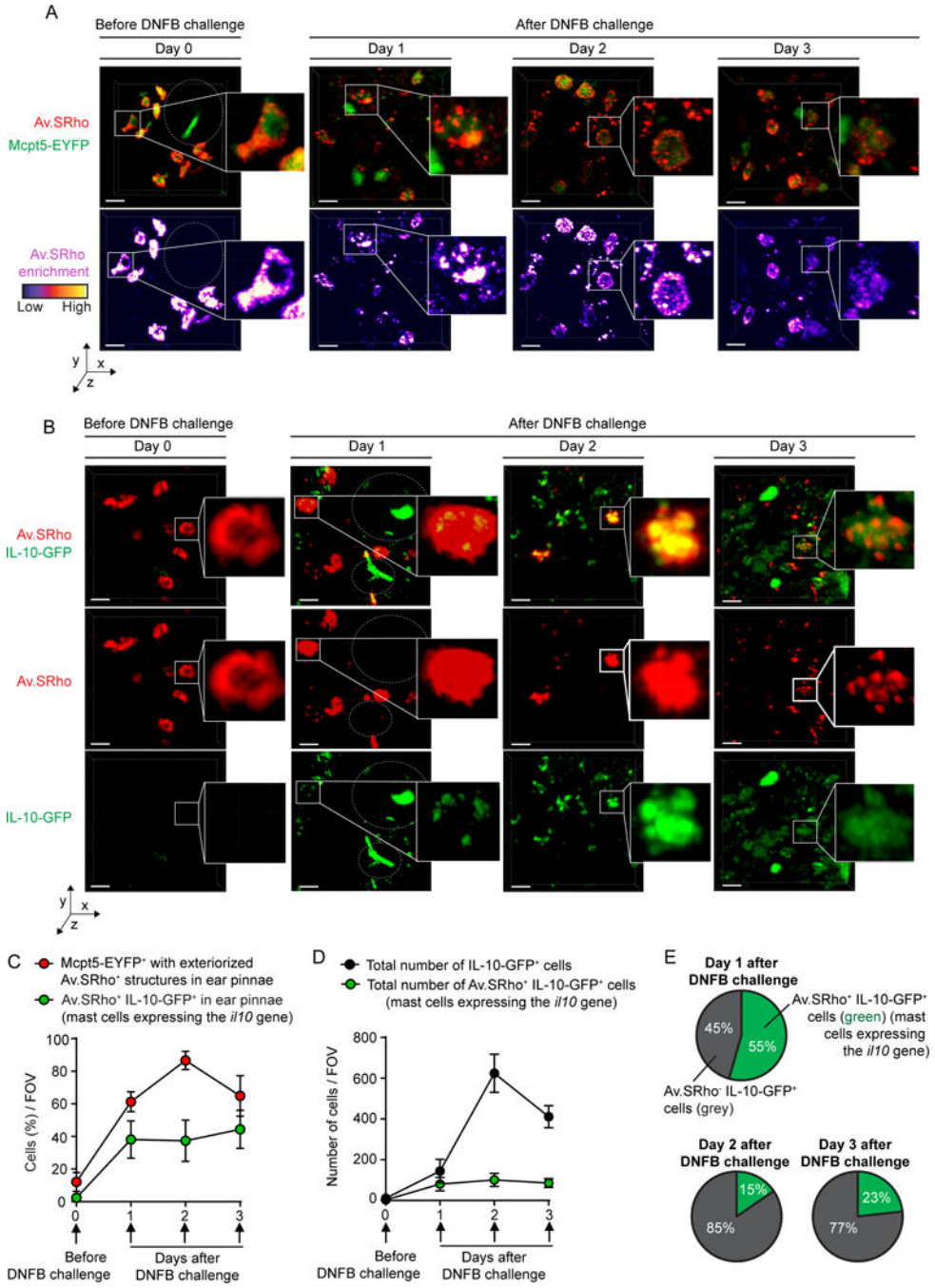

Figure 2. Longitudinal imaging of mast cell (MC) degranulation and *Il10* gene activation in a model of severe cutaneous contact hypersensitivity (CHS)

Sulforhodamine 101–coupled avidin (Av.SRho; 5 μg) was injected intradermally (i.d.) into the ear pinna of mice. One week later, the mice were treated as described in [165] to induce a severe 1-fluoro-2,4-dinitrobenzene–induced (DNFB-induced) contact hypersensitivity (CHS) reaction. (**A**) Longitudinal monitoring of the release of Av.SRho^{+} granules by dermal MCs at the site of CHS using intravital 2-photon microscopy. Representative 3D photographs of the ear pinna before DNFB challenge or at day 1, 2, or 3 after DNFB challenge. Upper panel: merged fluorescence of Av.SRho (red) and Mcpt5-EYFP (green).

Lower panel: Av.SRho fluorescence (pseudocolor scale). Dashed white circles identify hair follicles. (**B**) Longitudinal monitoring of both the release of dermal MC Av.SRho$^+$ granules and activation of *Il10* gene transcription (IL-10-GFP, as detected by emission of GFP fluorescent signal) at the site of CHS using intravital 2-photon microscopy. Representative 3D photographs of the ear pinna before DNFB challenge or at day 1, 2, or 3 after DNFB challenge. Upper panel: merged fluorescence of Av.SRho (red) and IL-10-GFP (green). Middle panel: Av.SRho (red) fluorescence. Lower panel: IL-10-GFP (green) fluorescence. White lines identify the magnified areas and dashed white circles identify hair follicles. Scale bars: 20 μm. (**C**) Percentage of Mcpt5-EYFP$^+$ cells with exteriorized Av.SRho$^+$ structures (i.e., degranulated dermal MCs, red circles) and of Av.SRho$^+$ IL-10-GFP$^+$ cells (i.e., representing MCs expressing the *Il10* gene, green circles) per field of view (FOV) in ear pinnae. (D) Total number of Av.SRho$^+$ IL-10-GFP$^+$ cells (MCs expressing the *Il10* gene, green circles) per FOV in ear pinnae and total number of IL-10-GFP$^+$ cells in ear pinnae (black circles). (E) Percentage of Av.SRho$^+$ IL-10-GFP$^+$ cells (i.e., representing MCs expressing the *Il10* gene, green) and of Av.SRho$^-$IL-10-GFP$^+$ cells (i.e., representing other cell types expressing the *Il10* gene, gray) among total IL-10-GFP$^+$ cells in ear pinnae per FOV. Mean ± SEM; data (n = 3 per group) are pooled from the 3 independent experiments performed (each done with 1 mouse per group), each of which gave similar results. (This is Figure 3 from [165].)

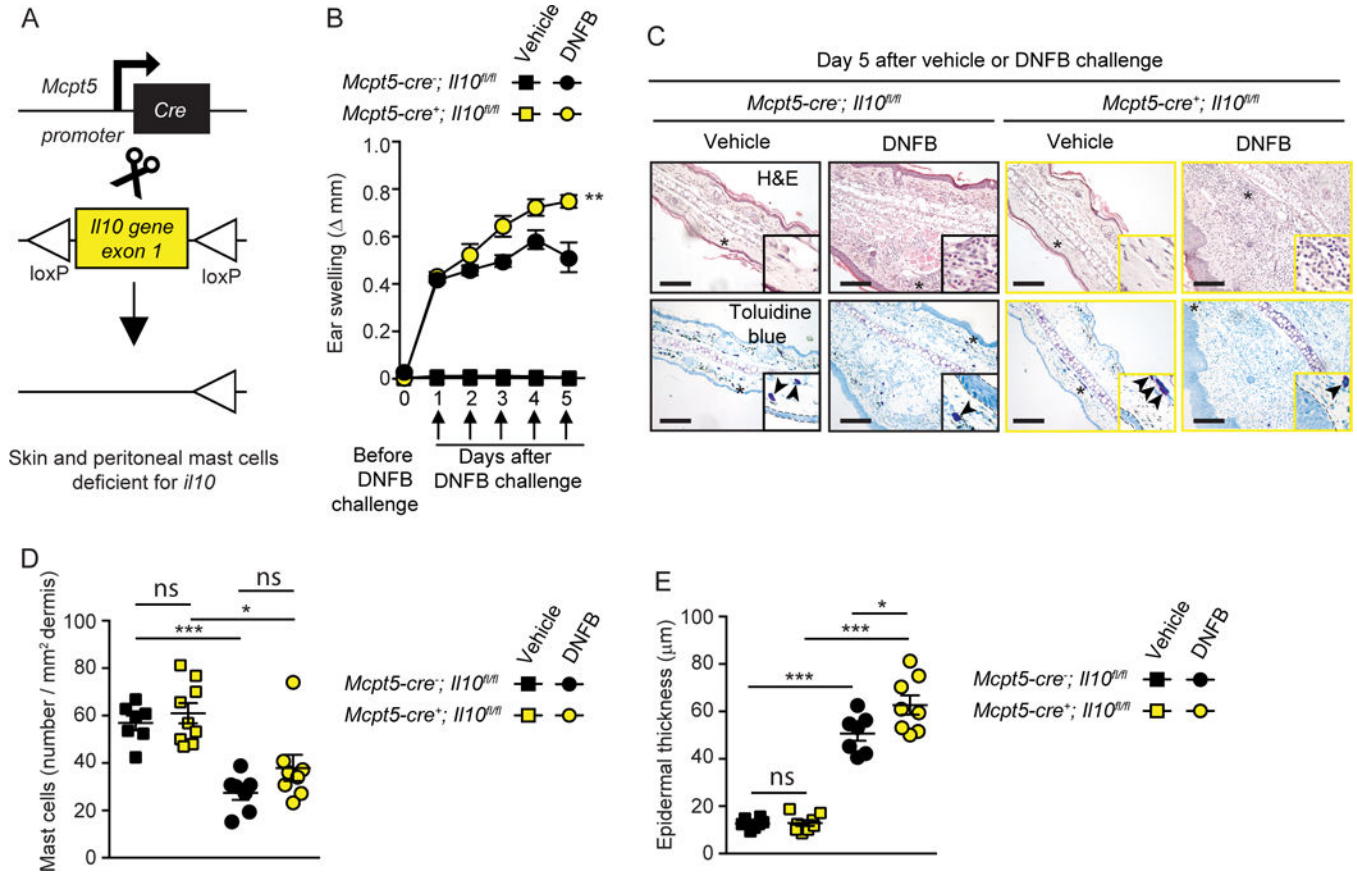

Figure 3. Mast cell (MC) production of IL-10 limits inflammation and epidermal hyperplasia in a model of severe cutaneous contact hypersensitivity (CHS)

Mice were treated as described in [165] to elicit a 1-fluoro-2,4-dinitrobenzene–induced (DNFB-induced) severe CHS reaction. (A) Breeding strategy to obtain *Mcpt5-Cre*$^{+}$; *Il10*$^{fl/fl}$ (MC IL-10 deficient) mice. (B) Changes (Δ) in ear thickness over time after challenge with vehicle (squares) or DNFB (circles) in *Mcpt5-Cre*$^{+}$; *Il10*$^{fl/fl}$ (MC IL-10 deficient, yellow) or *Mcpt5-Cre*$^{-}$; *Il10*$^{fl/fl}$ (MC IL-10 sufficient, black) mice. (C) Photomicrographs of representative H&E (upper panel) and toluidine blue (lower panel) stained sections of ear pinnae of mice sacrificed 5 days after challenge. Asterisks indicate areas shown at higher magnification (×60) in insets, arrowheads indicate MCs, and dashed white lines in insets depict epidermis. (D) Number of MCs/mm^2 dermis and (E) epidermal thickness 5 days after vehicle (squares) or DNFB (circles) challenge in *Mcpt5-Cre*$^{+}$; *Il10*$^{fl/fl}$ (MC IL-10 deficient, yellow) or *Mcpt5-Cre*$^{-}$; *Il10*$^{fl/fl}$ (MC IL-10 sufficient, black) mice. Scale bars: 200 μm. Mean ± SEM; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; (B) 2-way ANOVA; (D and E) 2-tailed, unpaired *t* test. Data (n = 6–12 mice per group) are pooled from the 3 independent experiments performed (each done with n = 2–4 mice per group), each of which gave similar results. (This is Figure 5 from [165].)

Table 1

Mast cell-derived Cytokines, Growth Factors & Mitogens

Factor	Stimulus	Product (if not the protein)	Mast cell type(s)	References
TNF	Anti-IgE, IgE/Ag		Mouse BMCMCs, PMCs, cell lines	2, 5, 6, 51
	Constitutive		Human skin	7
	Morphine sulfate		Human skin	7
	Anti-IgE		Human skin	21
	Anti-IgE		Human lung	22
	Substance P		Human skin	23
	Anti-IgE		Human skin	27
	SCF		Human skin	27
	A23187		Human skin	27
	Compound 48/80		Human skin	27
	Substance P		Human skin	27
	UVB		Human skin	26
	LPS		Mouse BMCMCs, rat PMCs	357, 358
	PGN		Mouse BMCMCs	57, 222
	LPS		Mouse BMCMCs	57, 222
	LPS or PGN		IL-4 pretreated human CBMCs	58
IL-1β	IgE/Ag		Mouse BMCMCs, cell lines	11
	IgG receptor crosslinking: anti-FcγRII/III (2.4G2)+anti-rat F(ab')2		Mouse BMCMCs	66
	IgE/Ag		Mouse BMCMCs	66
	Ionophore		Mouse BMCMCs	66
	Constitutive		Mouse *in vivo*	70
	Constitutive		Mouse *in vivo*	69
	LPS+ATP or R837		Mouse BMCMCs	67, 68
	LPS, PGN, Zymosan, PamCys		Human CBMCs	222
	LPS, PGN		Mouse BMCMCs	57
IL-2	IgE/Ag or PMA+ ionomycin		Mouse BMCMCs, PDMCs	72
	IL-33		Mouse BMCMCs	73
	IL-9		Mouse lung MCs	74
IL-3	IgE/Ag		Mouse BMCMCs	10
	IgE/anti-IgE	mRNA	Human BM-derived	109
	Constitutive		Human gastroduodenal	111
IL-4	Constitutive	mRNA, bioactivity	Mouse cell lines	8
	IgE/Ag		Mouse BMCMCs	84

Factor	Stimulus	Product (if not the protein)	Mast cell type(s)	References
	Ionophore	mRNA is constitutive; protein is detected after stimulation	Mouse BMCMCs	83
	IgE/Ag or ionophore		Mouse cell lines	9
	PGN		Mouse BMCMCs	57
	LPS	mRNA	Mouse BMCMCs	88
	Constitutive		Human nasal, bronchial, skin	89–92
	Anti-IgE		Human skin	23
	IL-33		Mouse PMCs	85
IL-5	IgE/Ag or ionophore	mRNA	Mouse cell lines	9
	IgE/Ag or ionophore	mRNA	Mouse BMCMCs, cell lines (Cl.MC/9, Cl.MC/C57.1)	11
	Anti-IgE	mRNA	Rat PMCs	108
	IgE/anti-IgE		Human bone marrow-derived	109
	IgE/Ag or LPS		Mouse BMCMCs	107
	IL-33	mRNA	Mouse BMCMCs	110
	IL-33		Human PBMCs, CBMCs	191
	LPS or PGN		Human CBMCs	58
	PGN		Mouse BMCMCs	57
	Constitutive		Human airway	90, 92
	Constitutive		Human gastroduodenal	111
IL-6	IgE/Ag or ionophore		Mouse BMCMCs, cell lines	11
	IgE/Ag or ionophore		Mouse cell lines	9
	Anti-IgE or LPS		Rat PMCs	122
	Constitutive		Mouse BMCMCs	359
	Constitutive		Human bronchial, nasal	90, 93
	Constitutive		Mouse *in vivo*	126
	Constitutive		Mouse *in vivo*	127
	IL-33		Human PBMCs, CBMCs	191
IL-9	IgE/Ag		Mouse BMCMCs	135
	IgE/Ag or ionophore		Mouse BMCMCs	137
	IL-1β		Mouse BMCMCs	136
IL-10	LPS, lipid A +/− IgE/Ag		Mouse BMCMCs	107
	IL-33		Human PBMCs, CBMCs	191
IL-11	Anti-IgE		Human CBMCs	179
IL-12	LPS+IFNγ		Mouse BMCMCs	182
	LPS+SCF		Human PBMCs	87
	Constitutive	mRNA	SCF derived-BMCMCs	183

Factor	Stimulus	Product (if not the protein)	Mast cell type(s)	References
IL-13	IgE/Ag or ionomycin or PMA	mRNA and bioactivity	Mouse BMCMCs, C1.MC/C57.1 cell line	188
	LPS or PGN		Human CBMCs	58
	LPS or PGN		Mouse BMCMCs	57
	LPS or Lipid A		Mouse BMCMCs	107
	IL-33		Mouse BMCMCs	73, 125, 192
	IL-33		Human PBMCs, CBMCs	191
	SCF		Mouse BMCMCs	193
	IgG receptor crosslinking		Mouse BMCMCs	360
	IL-1β		Human CBMCs	190
	TSLP		Human CBMCs	361
IL-16	Constitutive		Human BM-derived & lung	199
IL-33	IgE/Ag		Mouse BMCMCs	110
	PMA+ ionomycin	mRNA	Mouse BMCMCs	208
EGF			Human thyroid	214
bFGF/FGF-2	Constitutive		Human dermal	215
	Constitutive		Human cutaneous	362
	Constitutive		Human lung and skin	217
	Constitutive		Human thyroid	214
	Constitutive		Rat PMCs	34
	IL-17A		Human PBMCs	219
	Constitutive		Mouse BMCMCs	220
	Constitutive		Human skin	218
GM-CSF	IL-33		Human PBMCs, CBMCs	191
	LPS, PGN, Zymosan, PamCys		Human CBMCs	222
	IgE or IL-33		Mouse BMCMCs	41
	IgE/Ag		Mouse BMCMCs	10
	IgE/Ag	mRNA	Mouse cell lines	11
	IgE/anti-IgE		Human BM-derived	109
	Constitutive		Human gastroduodenal	111
	P. aeruginosa		Human CBMCs	363
IFNγ	IL-12		Rat PMCs	184
	Anti-IgE	mRNA	Rat PMCs	108
	IgE/Ag	mRNA	Mouse cell lines	11
	Ionophore	mRNA	Mouse cell lines	9
	Anti-IgE	mRNA	Rat PMCs	108
	Constitutive		Mouse *in vivo*	126
	Constitutive		Mouse *in vivo*	127

Factor	Stimulus	Product (if not the protein)	Mast cell type(s)	References
NGF	Constitutive		Rat PMCs	262
	Constitutive	mRNA	Human CBMCs	257
PDGF			Human thyroid	214
	Coculture with cardiac myocytes or fibroblasts		Mouse BMCMCs	267
SCF	Constitutive		Human lung and skin	275
	Constitutive, IgE/anti-IgE, ionophore		Human skin, CBMCs, PBMCs	277
	Anti-IgE		Human lung and skin	278
	Constitutive		Human cardiac	276
	Constitutive		Human mastocytosis in bone marrow	279
TGF-β1	IgE/Ag		Mouse BMCMCs, cell lines, mouse PMCs	51
	Constitutive, phorbol ester		Dog mastocytoma	288
	Compound 48/80		Rat PMCs	289
	N/A		Human CBMCs	290
	IL-33		Mouse BMCMCs	73
	IL-9		Mouse lung MCs	74
VEGF/VPF	Constitutive		Human skin	318
	Constitutive		Rat small intestine	364
	IgE/Ag, PMA, A23187, SCF		BMCMCs	317
	PMA		Mouse PMCs	317
	Anti-IgE		Human CBMCs	317
	Substance P, IL-1, Substance P+ IL-33, IL-1+ L-33		Human CBMCs	319
	Corticotropin-releasing hormone		Human CBMCs	320
	Constitutive		Mouse *in vivo*	336
	Constitutive		Human thyroid	214
	Constitutive		Rat PMCs	34
	Constitutive		Human, in laryngeal squamous cell carcinoma	330
	Constitutive		Human, in malignant melanoma	331
	Constitutive	mRNA	Human, in non-Hodgkin lymphoma	332
	IL-17A		Human PBMCs	219
	Live *S. aureus*		Mouse PMCs	321

BMCMCs: Mouse bone marrow-derived cultured mast cells (these are reported by many groups as “BMMCs” – referring to “bone marrow-derived mast cells”, but we prefer BMCMCs to refer to such cells as this is more specific and emphasizes that the cells have been derived *in vitro*.

CBMCs: Human umbilical cord blood-derived mast cells

PBMCs: Human peripheral blood-derived mast cells

PMCs: Peritoneal mast cells (from mice or rats, as noted)

PDMCs: Peritoneal-derived cultured mast cells.

Constitutive: There is evidence, such as from IHC or detection of mRNA, that the analyzed mast cells can constitutively express that factor under “baseline” conditions.

In the Product column: Detected product was the protein unless “mRNA” is listed, which indicates that the mRNA for that product was identified, but not yet the protein.

In the References column: Papers listed include first reports and/or those with key data.

Table 2

Mast cell-derived Chemokines

Factor	Stimulus	Product (if not the protein)	Mast cell type(s)	References
CCL1	IgE/Ag	mRNA	Mouse cell lines	11
	IL-33		Human PBMCs or CBMCs	191
	IgE/Ag or IL-33	mRNA	Mouse BMCMCs	365, 366
	IgE/Ag		Mouse liver-derived	367
	IgE/Ag		Human skin	365
CCL2	IgE/Ag	mRNA	Mouse cell lines	11
	IgE/Ag or IL-33		Mouse BMCMCs, Human skin	192
	PMA/ionophore, IgE/anti-IgE, IL-1β		Human CBMCs	190
	IL-33		Human PBMC or CBMCs	191
	Poly(I:C)		Human CBMCs	368
CCL3	IgE/Ag	mRNA	Mouse cell lines	11
	IgE/Ag		Mouse liver-derived	367
	IL-33		Mouse BMCMCs	192
	IgG receptor crosslinking		Mouse BMCMCs	360
	Anti-IgE		Human CBMCs	369
CCL4	IgE/Ag	mRNA	Mouse cell lines	11
	In vivo		Mouse skin	370
	Poly(I:C)		Human CBMCs	368
	Dengue virus + Anti-dengue Ab		Human CBMCs	371
	RSV		Human CBMCs	372
CCL5			Human skin	373
	Dengue virus + Anti-dengue Ab		Human CBMCs	371
	RSV		Human CBMCs	372
CCL7	IgE/Ag		Mouse BMCMCs	374
	Anti-FcεRIα Ab	mRNA	Human PBMCs	375
CCL8	LPS	mRNA	Human PBMCs	233
	IgE/Ag or PMA/ionophore	mRNA	Mouse cell lines	376
CCL9	IgE/Ag		Mouse liver-derived	367
CCL11			Human skin	373
CCL17	IL-33		Human PBMCs or CBMCs	191
	Anti-FcεRIα Ab	mRNA	Human PBMCs	375
		mRNA	Human skin	377
CCL20	Anti-FcεRIα Ab	mRNA	Human PBMCs	375
	P. aeruginosa		Human CBMCs	363

Factor	Stimulus	Product (if not the protein)	Mast cell type(s)	References
CCL22	IL-33		Human PBMCs or CBMCs	191
	Anti-FcεRIα Ab	mRNA	Human PBMCs	375
		mRNA	Human skin	377
human CXCL2	Anti-IgE		Human skin	378
	IgG immune complexes		Human synovium-derived	379
	Anti-IgE, SCF, Substance P, Compound 48/80 or A23187		Human skin	27
	LPS+SCF		Human PBMCs	87
mouse CXCL8	Anti-IgE	mRNA	Rat PMCs	108
	IL-33		Human PBMC or CBMC	191
	Poly(I:C)		Human CBMCs	368
	Substance P or ionomycin		Human CBMCs	380
CXCL10	Poly(I:C)		Human CBMCs	368
	RSV		Human CBMCs	372

BMCMCs: Mouse bone marrow-derived cultured mast cells (these are reported by many groups as “BMMCs” – referring to “bone marrow-derived mast cells”, but we prefer BMCMCs to refer to such cells as this is more specific and emphasizes that the cells have been derived *in vitro*.

CBMCs: Human umbilical cord blood-derived mast cells.

PBMCs: Human peripheral blood-derived mast cells.

PMCs: Peritoneal mast cells (from mice or rats, as noted).

In the Product column: Detected product was the protein unless “mRNA” is listed, which indicates that the mRNA for that product was identified, but not yet the protein.

In the References column: Papers listed include first reports and/or those with key data.

Table 3

Principles of MC biology to keep in mind when assessing the importance of MCs as sources of cytokines, chemokines and growth factors*.

- *In vivo*, MCs can be heterogeneous in multiple aspects of phenotype and function, depending on animal species, anatomical location, stage of development or maturity, and influence of genetic and microenvironmental factors (reviewed in [381–383]).
- Many other factors also may influence MC phenotype and function *in vivo*, including effects of age, sex, circadian rhythms, various forms of stress and concurrent metabolic, inflammatory or immune responses, and disease processes.
- MCs are potentially long-lived and are responsive to diverse systemic or local signals which can influence their phenotype and function, including those related to having undergone prior activation events.
- Some biological responses are associated with substantial expansion and/or contraction of MC populations, and this may result in tissues containing MCs in various stages of development or maturation and such cells may vary in phenotype and function.
- MC populations which are generated *in vitro* may differ in important features from native MC populations *in vivo*.
- Processes of purifying MCs from bodily fluids and, especially, tissues may alter aspects of MC phenotype and function, including their ability to make or respond to cytokines, chemokines and growth factors.

*All of these factors may influence the MC's ability to produce cytokines, chemokines and growth factors, and/or to produce and secrete proteases and other factors that can influence the structure and bioactivity of these molecules.

Table 4

New approaches for analyzing MC production of cytokines, chemokines and growth factors.

- Constitutive or inducible genetic ablation or reduction, in all MCs or in particular subpopulations of MCs, of individual or multiple cytokines, chemokines, or growth factors (or of receptors for such products, or of other MC products, such as proteases, which may regulate levels and activity of cytokines, chemokines, or growth factors) [42, 159, 165, 384].
- Real time simultaneous imaging of MC activation and gene expression in normal or diseased tissues *in vivo* [165].
- Single cell analysis of MC mRNA, products, and metabolites (either *ex vivo* or *in situ*).
- Advances in approaches to generate and analyze mice of diverse genetic backgrounds, which can be used to assess the extent to which genetic background can influence the importance of MC production of particular products in specific settings [385–387].
- Advances in the ability to use more definitive experimental approaches to analyze the effects of microbiomes and their metabolites, as well as exposure to UV light, environmental toxins and other environmental factors, on the capacity of MCs to produce, regulate or respond to cytokines, chemokines and growth factors.