

Regulation of Mast Cell Development by Inflammatory Factors

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Abstract: Mast cells are potent effectors playing a key role in IgE-associated hypersensitivity reactions, allergic disorders, inflammation and protective immune responses. Mast cell development *in vivo* occurs mainly in non-hematopoietic microenvironments and increased mast cell numbers can be seen in various inflammatory diseases and pathologic conditions. SCF (also known as *kit* ligand or KitL) and *c-kit* signaling are essential for both human and murine mast cell development, while IL-3 is required for murine mast cell hyperplasia that occurs in response to various stimuli. Besides SCF and IL-3, the cytokines IL-4, IL-9, IL-10 and IL-13 are also called mast cell growth factors due to their actions synergistically promoting mast cell proliferation and differentiation in the presence of SCF or IL-3. These cytokines alone however are unable to support neither the proliferation nor survival of mast cells. Most research has focused on examining the direct effects of the above cytokines on mast cells or their precursors. However, it is difficult to explain the process of mast cell development only in terms of the above mast cell growth factors. A series of experiments in our laboratory and by others has revealed that inflammatory mediators and cytokines, as triggers or regulators, are also crucial for mast cell development. This review summarizes recent progress in our understanding of how various inflammatory factors regulate mast cell development, with particular focus on the effects of prostaglandin E (PGE), TNF- α , IL-6, IFN- γ and an unknown apoptosis-inducing factor produced by IL-4-stimulated macrophages.

Keywords: Mast cell development, mast cell growth factor, inflammatory factors, prostaglandin E, IL-4, IL-6, IFN- γ , TNF- α .

INTRODUCTION

The mention of mast cells may first evoke the firmly established negative image because of their key role in IgE-associated hypersensitivity reactions, such as anaphylactic shock. This "bad reputation" of mast cells is rehabilitated by current knowledge that mast cells play a critical role not only in allergic diseases but also in protective and homeostatic functions of the immune system. Mast cell-deficient mice (W/W^u) have diminished innate immune responses against bacterial infections, which are restored after reconstitution of the mice by mast cell transplantation [1,2]. Mast cell-derived tumor necrosis factor (TNF)- α has been described as an immunoprotective factor of mast cells to efficiently recruit neutrophils to the infected tissues [1-3]. However, this conclusion has been challenged by the fact that TNF- α is not a mast cell-restricted cytokine and the number of TNF- α -expressing lipopolysaccharide (LPS)-responsive macrophages in the lungs and peritoneal cavities of bacteria-infected mice greatly exceeds the number of mast cells [4]. Recently, mouse mast cell protease (mMCP)-6 was reported to be the most important factor responsible for the role of mast cells in bacterial infections. Mice lacking this neutral protease cannot efficiently clear *Klebsiella pneumoniae* from their peritoneal cavities [4,5]. Mast cells are potential immunoregulatory cells which contribute to the initiation, development, expression, and regulation of acquired immune responses by producing not only multiple cytokines but also many pro-inflammatory mediators [6-10]. Since a number of reviews on the biological functions of mast cells have been published recently [10-15], this review instead focuses on some new understandings of mast cell development.

Mast cells are derived from CD34⁺/*c-kit*⁺ multipotent hematopoietic progenitor cells that exit the bone marrow and migrate into virtually all tissues throughout the body, where they undergo final maturation in response to local microenvironmental factors. Compared to the very limited numbers of mast cell-committed progenitors in the bone marrow, blood, normal spleen and other lymphoid organs, more mast cell progenitors can be found in the intestine [16]. The mast cell-committed progenitors are unable to be identified as mast cells by their morphology or histochemistry because they lack high-affinity IgE receptors and have few secretory granules [17-20]. It is only under certain physiological and/or pathological conditions that these precursor cells begin

to proliferate and differentiate into morphologically identifiable mast cells. For *in vitro* study, various sources, such as bone marrow cells, splenic cells, peritoneal cells, peripheral/cord blood cells and purified cells with specific markers, such as CD34⁺/*c-kit*⁺, can be used to develop mast cells.

In 1981, several laboratories simultaneously reported that apparently pure populations of mast cells could be generated by culturing murine hematopoietic cells in conditioned media derived from mitogen-activated T cells, cloned Ly-1⁺2⁺ inducer T cells, or WEHI3B cells [21-25]. The culture systems used to develop mast cells are usually based on either a liquid culture version or a semi-solid culture version using methylcellulose. Since 1981, such methods have generally been used to develop murine mast cells *in vitro* [26,27]. The cytokine responsible for mast cell proliferation and differentiation in conditioned media was later proved to be interleukin (IL-) 3 [28,29], the well-known growth factor for almost all cell lineages at early stages of differentiation. However, human mast cells, unlike those of rodent origin, cannot be supported by IL-3 alone, due to a lack of IL-3 receptors on their surface [30]. Fibroblasts were found to be able to maintain the phenotype and viability of the rat mast cells *in vitro* [31]. Coculture of IL-3-dependent mouse mast cells with fibroblasts resulted in a phenotypic change of the mast cells [32]. Research into the mechanism of the above phenomena led to the finding of another crucial mast cell growth factor: stem cell factor (SCF; also known as *kit* ligand or KitL) and its receptor, *c-kit* [33-39], which are also responsible for the anemia and mast cell deficiency in *Sl/Sl^d* and W/W^u mice [40-44]. SCF is essential for human mast cells. Withdrawal of SCF from both human and murine mast cell cultures, and withdrawal of IL-3 from the latter, can result in mast cell apoptosis [45,46]. However, in IL-3-knockout mice the number of tissue mast cells appears unaltered [47], and *in vitro* conditions, mast cells can develop from hematopoietic cells of *Sl/Sl^d* and W/W^u mice in the presence of IL-3 [48]. It is now clear that SCF and *c-kit* signaling is indispensable for both human and murine mast cell development, while IL-3 is required for murine mast cell hyperplasia that occurs in response to various stimuli. Relatively stable numbers of mast cells within connective and mucosal tissues are maintained by the constitutive expression of SCF in its membrane-bound and soluble forms by stromal cells (such as fibroblasts, epithelial cells, endothelial cells, bronchial smooth muscle cells) and by the expression of *c-kit* on mast cells at all stages of differentiation. Besides SCF and IL-3, the Th2 cytokines IL-4 [49,50], IL-9 [51], IL-10 [52] and IL-13 [53], also play critical roles in mast cell development by synergistically promoting the actions of SCF and IL-3 on mast cell proliferation

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and differentiation. However, the Th2 cytokines alone are unable to support neither the proliferation nor survival of mast cells.

In spite of accumulating evidence, it is difficult to explain the process of mast cell proliferation and differentiation only in terms of the above-mentioned growth factors, because mast cell development *in vivo* occurs primarily in tissues with non-hematopoietic microenvironments and mast cell hyperplasia can be seen in various inflammatory sites. Chemokines are important for regulating the recruitment to and tissue retention of mast cells and their committed progenitors. Many chemokine receptors have been confirmed to be expressed by mast cells [54,55]. It has also been well documented that β -chemokines play important roles in driving the terminal differentiation of mast cell precursors in mucosal tissues and in providing priming or costimulatory signals required for mast cell activation [56]. The distribution of mast cells *in vivo* also suggests the importance of inflammatory mediators on mast cell development. Mast cells are found adjacent to respiratory and intestinal mucosal surfaces and are spread throughout the skin, peritoneal cavity and musculature. That is, mast cells are situated at sites where different types of primary infections and inflammatory stimulation are initiated. It can be speculated that inflammatory mediators provide a favorable microenvironment for mast cell growth. In return, mast cells, as potent effectors, play a critical role in inflammation and protective immune responses by releasing pre-formed vasoactive amines, prostaglandins, cytokines and chemokines that collectively induce or enhance a local or systemic inflammatory response [7,11-13, 26]. However, most research on mast cell development has focused on mast cell growth factors, while the effects of various inflammatory and microenvironmental factors, which lack the promoting activity on mast cell growth, have received less attention. A series of experiments in our laboratory and others has revealed that some inflammatory factors, which act as triggers or regulators, are also crucial for mast cell development although they are not mast cell growth factors [57-64]. In this review, we emphasize these recent findings of how various inflammatory factors regulate mast cell development and survival with a particular focus on the effects of prostaglandin E (PGE), TNF- α , IL-6, interferon (IFN) γ and an unknown apoptosis-inducing factor produced by IL-4-stimulated macrophages.

PGE AND MAST CELL DEVELOPMENT

We unexpectedly observed the phenomenon that large numbers of mast cells could be developed by the long-term culture of mouse spleen cells without the addition of any exogenous IL-3 [57,58]. Further experiments revealed that the source of fetal calf serum used was important and could be classified into mast cell-inducing and mast cell non-inducing sera. Contaminating LPS in the mast cell-inducing sera was responsible for the mast cell development, and confirmed by the detection of LPS in the sera and by the addition of LPS to the mast cell non-inducing sera [59]. We found that all supernatants recovered from long-term cultures with either mast cell-inducing or mast cell non-inducing sera, contained IL-3 endogenously produced by splenic T cells. The addition of rIL-3 into the cultures with mast cell non-inducing sera failed to develop mast cells. When endogenous IL-3 was depleted, by adding neutralizing antibody to cells grown in mast cell-inducing sera, mast cell development was completely inhibited. These results indicate that IL-3 alone is not the only requirement for mast cell development, although IL-3 is essential. Some inflammatory factors induced by LPS-mediated stimulation are also crucial.

PGE₂ is a well-known inflammatory factor induced by LPS-mediated stimulation and is mainly produced by macrophages, follicular dendritic cells and fibroblasts as previously reviewed [65]. On this basis we thus investigated the role of PGE in mast cell development. When indomethacin, an inhibitor of PGE synthesis, was added to the cultures, the activity of LPS in mast cell development

was inhibited. Furthermore, both PGE₁ and PGE₂ induced mast cell development in a dose- and time-dependent manner when added into splenic cell cultures with mast cell non-inducing sera. Indomethacin failed to inhibit mast cell development induced by exogenous PGE, while exogenous PGE antagonized the indomethacin-induced inhibition of mast cell development in the presence of LPS [60]. This activity of PGE was mediated through the second messenger cAMP, since not only PGE, the physiologic stimulant for the production of cAMP [65], but also dibutyryl cAMP, an analogue of cAMP, induced mast cell development in the presence of endogenous IL-3 [60]. In agreement with the action of PGE, cholera toxin, the non-physiologic stimulant for production of cAMP [66], also promoted mast cell development from mouse spleen [60] and bone marrow cells [67,68]. Saito *et al.* established a method to develop human mast cells from umbilical cord blood cells with a combination of SCF, IL-6 and PGE [69]. The above reports show that for mast cell development, IL-3 or SCF requires the co-operation of PGE or other stimulants, which can elevate the production of the second messenger cAMP in long-term cultures.

The exact mechanism by which PGE promotes mast cell development remains unclear. PGE alone or in combination with either IL-3 or SCF does not promote the growth of mast cell lines and purified mast cells. Both the direct and indirect effects of PGE on mast cell development can be considered as possible mechanisms. Firstly, given that many cell types are present in the mast cell cultures particularly in the first week they are established, it is possible that PGE regulates mast cell development in an indirect manner by inducing bystander cells to produce factors like IL-3, IL-9, IL-10, and/or SCF that then act directly on mast cells. PGE has been well studied as an immunosuppressant, since it can inhibit the proliferation and function of many kinds of cells including T cells, B cells, NK cells and macrophages. PGE has also been confirmed to selectively inhibit Th1 cells but not Th2 cells [65,70,71]. Selective inhibition of some suppressive cells or cytokine production may favor mast cell development. Granulocyte-macrophage colony-stimulating factor (GM-CSF) has been proposed as such a cytokine. PGE may inhibit the proliferation of macrophages by blocking GM-CSF secretion and, thereby, indirectly promote mast cell development [69]. Secondly, PGE may act directly on progenitor cells or mast cell precursors and thereby elevate intracellular cAMP. The second messenger cAMP then co-operates with the signal of IL-3 or SCF for the differentiation of such cells at early stages. The expression of EP₁, EP₂, EP₃ and EP₄ receptors for PGE₂ on mast cells [72,73] together with the result showing that mast cell development was also induced by dibutyryl cAMP seems to support this explanation.

TNF- α AND MAST CELL DEVELOPMENT

Large amounts of TNF- α are released in response to LPS and other bacterial products both *in vivo* and *in vitro*. As a well-known inflammatory factor produced mainly by macrophages, TNF- α plays a critical role in systemic inflammation. TNF- α is also produced by a broad variety of other cell types including neutrophils, lymphoid cells, endothelial cells and fibroblasts. Interestingly, TNF- α is also involved in mast cell development. We previously reported that exogenous TNF- α and endogenous IL-3 co-operatively induced large numbers of mast cells from the culture of mouse spleen cells [62]. This finding is corroborated by a recent report showing that TNF- α is necessary for mast cell development from murine bone marrow cells [74]. The importance of TNF- α in mast cell development is also supported by the *in vivo* observation showing that peritoneal mast cell numbers in TNF- α -knockout mice were reduced 50% compared to their wild-type littermates [74].

Nevertheless, the mechanisms involved in the two systems are different because of the different cell sources and microenvironments for mast cell proliferation and differentiation. In our system, macrophages may be one of the responsive cells of

TNF- α , since removal of macrophages greatly reduced the mast cell development induced by TNF- α . The action of TNF- α was inhibited by indomethacin, an inhibitor of prostaglandin synthesis [62]. These results indicate that TNF- α may stimulate macrophages to produce PGE₂ which then indirectly triggers mast cell development as discussed in the previous section. In the system reported by Wright *et al.* they compared mast cell development from bone marrow cells of TNF- α -knockout mice with their wild-type littermates in the presence of exogenous IL-3 and SCF. They confirmed that IL-3-induced and Mac-1-positive cell-produced TNF- α is an obligatory factor for developing mast cells since total mast cell numbers from the culture of bone marrow cells of TNF- α -knockout mice were only 6% of their wild-type counterpart. The failure of TNF- α -deficient bone marrow cells to survive for more than 3 weeks when cultured in IL-3 and SCF was responsible for this phenomenon while the defect was reversed by adding soluble TNF- α . The TNF- α -deficiency resulted in mast cell apoptosis which occurred with changes in mitochondrial membrane potential and caspase activation due to loss of IL-3 signalling [74].

IL-6 AND MAST CELL DEVELOPMENT

IL-6 is one of the most important mediators of fever and of the acute phase response and is a multifunctional pro-inflammatory cytokine secreted mainly by T cells and macrophages. IL-6 is actually the major cytokine produced by activated mast cells [75-77], although mast cells may produce more than 30 cytokines and chemokines. In our murine system, IL-6 promoted mast cell development from splenic cells in a liquid culture [62]. Endogenous IL-3 is essential for co-operation with exogenous IL-6 because mast cells did not develop from the splenic cells of nude mice which lack T cells able to produce IL-3. However, SCF is not essential for IL-6-triggered mast cell development since large numbers of mast cells were developed from the splenic cells of *W/W^v* mice. In a semi-solid culture with as few as 1000 cells/ml, however, IL-6 failed to promote the action of rIL-3 for mast cell growth and rIL-3 + rIL-6 induced the same number of mast cells as rIL-3 alone. These results indicate that IL-6-triggered mast cell development is an indirect process. PGE and IFN- γ may be the secondary mediators because both indomethacin and neutralizing antibody against IFN- γ inhibited the mast cell development induced by IL-6 from the liquid culture of splenic cells [62].

In the human system, IL-6 shows discrepancies in its effects on mast cell development. IL-6 in combination with SCF and PGE was reported to be a requisite for promoting mast cell development from umbilical cord blood, peripheral blood, bone marrow and fetal liver cells [20,69,78] and to be an anti-apoptotic factor in cultures of cord-derived mononuclear cells and CD34⁺ cells [79,80]. On the other hand, another study has demonstrated that addition of IL-6 into the liquid culture of CD34⁺ cord blood cells resulted in a significant reduction of SCF-dependent mast cell development [81]. The authors postulated that this IL-6-mediated inhibition of mast cell growth might be due, in part, to the suppression of *c-kit* expression at the precursor level. The exposure of cultured mast cells to SCF + IL-6 also caused substantial increases in cell size, frequency of chymase-positive cells and intracellular histamine levels compared with values obtained with SCF alone [81].

Based on the above results, we propose that the direct effects of IL-6 on mast cells and their precursors are inhibition of their proliferation and promotion of their differentiation. However, when IL-6 is added to cultures with mixed cell populations, such as umbilical cord blood, peripheral blood, bone marrow, fetal liver cells and murine splenic cells, the indirect effect of IL-6 may dominate the fate of mast cell precursors and result in the development of large numbers of mast cells. Further research is needed to identify the exact process and the secondary factors induced by IL-6 stimulation.

IL-1 AND MAST CELL DEVELOPMENT

IL-1 failed to induce mast cell development from cultures of mouse splenic cells despite the presence of endogenous IL-3 [62]. Compared with the roles of PGE, TNF- α and IL-6 in mast cell development using the same system, it is difficult to explain this negative result because IL-1 is known to stimulate PGE and IFN- γ production [65,82]. However, IL-1 is a strong stimulator of Th2 cells to produce IL-4 [83,84]. The IL-1-induced elevation of IL-4 seen in the cultures may result in the failure to induce mast cell development by IL-1, because IL-4 is a critical inhibitor of mast cell development (although IL-4 itself is a well-known mast cell growth factor, as will be discussed below in the section 'IL-4 and Mast Cell Development').

Recently, it has been reported that IL-1 α promotes mast cell proliferation when mouse mast cells derived from bone marrow cells are co-cultured on a NIH/3T3 fibroblast monolayer. The addition of neutralizing antibodies against IL-3, IL-4 and IL-10 in this system did not inhibit the promoting action of IL-1 α . This activity of IL-1 α was significantly reduced when mast cells were prepared from *W/W^v* mice (which lack a functional *c-kit*), or when NIH/3T3 fibroblasts were substituted with *Sl/Sl^v*-derived fibroblasts (which lack membrane-bound SCF). These results indicate that IL-1 α stimulates mast cell growth *via* a fibroblast-dependent mechanism although flow cytometric analysis revealed no enhancement of SCF expression on fibroblasts following stimulation with IL-1 α [85]. Consistent with our previous reports on LPS, PGE, IL-6 and TNF- α [59,60,62], indomethacin inhibited the effect of IL-1 α -induced mast cell growth in the mast cell/fibroblast co-culture system [85]. Therefore, IL-1 α -triggered and fibroblast-produced PGE₂ in co-operation with membrane-bound SCF on fibroblasts is responsible for enhancement of mast cell growth by IL-1 α .

IFN- γ AND MAST CELL DEVELOPMENT

It is well known that the Th1 cytokine IFN- γ suppresses murine [86-88] and human [78,89,90] mast cell development and activation [91-93]. A recent report has shown that IFN- γ induced apoptosis in developing mast cells in a STAT-1-dependent manner, when IFN- γ was added to the culture of murine bone marrow cells in the presence of IL-3 and SCF [94]. In contrast to the above reports, we found that mast cell development from the cultures of mouse splenic cells was directly proportional to IFN- γ levels in the supernatants recovered on days 2 and 4. In the cultures with mast cell non-inducing serum and without exogenous IL-3 and SCF, rIFN- γ induced mast cell development in a dose-dependent manner. Time course studies showed the importance of adding IFN- γ into the cultures during the early phase of culture (i.e. on days 0 and 2 of a 12-day culture). When endogenous IFN- γ (present at the early phase of culture) was neutralized by anti-IFN- γ antibody, all stimulants (including LPS, rIFN- γ , rIL-10, PGE₂ and dibutyryl cAMP) failed to induce mast cell development. The above results reveal that IFN- γ is crucial for the survival and/or differentiation of splenic mast cell precursors, although IFN- γ itself is not a mast cell growth factor [61]. This conclusion was further supported by our investigation into the mechanisms of strain-dependent development of mast cells from mouse splenocytes [63]. During a 12-day culture, mast cell development from splenic cells was not triggered by PGE or dibutyryl cAMP when the splenic cells were isolated from C57BL/6N and DBA/1 mice, but mast cells did develop when the splenic cells were from C3H/HeN, BALB/c and ICR mice. A lack of endogenous IFN- γ in the initial two days of the culture period was responsible for the failure to develop mast cells. This was confirmed by detecting IFN- γ levels in splenic cell cultures and by adding neutralizing anti-IFN- γ antibody and rIFN- γ into the cultures. Th1 cells in the spleens of C57BL and DBA/1 mice were much more sensitive to PGE and dibutyryl cAMP than Th1 cells from other inbred mice strains, thereby resulting in the complete

inhibition of IFN- γ production in those cultures. Furthermore, the different sensitivities of Th1 cells to PGE and dibutyryl cAMP were confirmed to be dependent on the different levels of IL-12 p40 monomers or homodimers in the splenic cell cultures. As the endogenous specific inhibitors of IL-12 p70 (heterodimers of p40 and p35), large amounts of IL-12 p40 in the splenic cell cultures of C57BL and DBA/1 mice enhanced the ability of PGE and dibutyryl cAMP to inhibit IFN- γ production by antagonizing the activity of IL-12 p70 [63]. These results indicate that strain-dependent development of mast cells from mouse splenocytes is related to endogenous IFN- γ levels that are regulated by PGE, dibutyryl cAMP, IL-12 p70 and IL-12 p40.

In a culture of pure human mast cells generated from cultures of umbilical cord blood mononuclear cells in the presence of SCF and IL-6, Yanagida *et al.* showed that mast cells underwent apoptosis after withdrawal of SCF and IL-6. The addition of IFN- γ into the cultures suppressed apoptosis and prolonged cell survival in a dose-dependent manner. This survival-promoting effect of IFN- γ was blocked by neutralizing antibodies against both IFN- γ and IFN- γ receptor. The mast cells were further confirmed to bear IFN- γ receptors on their surface [95]. These findings suggest that IFN- γ may directly act on human mast cells *via* specific receptors in certain aspects of inflammatory reactions.

The exact mechanisms for the discrepancy in reports related to the effects of IFN- γ on mast cell development are not clear. Different culture systems, cell sources and even initial cell numbers as well as the balance between direct and indirect effects of IFN- γ on mast cell precursors may be responsible for the contradictory conclusions.

IL-4 AND MAST CELL DEVELOPMENT

IL-4 is a multifunctional Th2 cell-associated cytokine that, through STAT6-dependent signaling, plays a critical role in the

regulation of immune responses [96-98]. The role of IL-4 in allergic inflammation is not limited to its capacity to induce the production of allergen-specific IgE antibodies *via* the class-switch effect. IL-4, together with other Th2 cytokines as IL-9, IL-10 and IL-13, are also known mast cell growth factors responsible, at least in part, for mast cell hyperplasia. Since initial reports [49,50], the ability of IL-4 to promote both proliferation and differentiation of either murine or human mast cells has been well documented and reviewed [14,99-101].

We unexpectedly found that the number of mast cells that developed from mouse spleen cells was inversely proportional to IL-4 levels in cultures. Addition of rIL-4 dose-dependently suppressed mast cell development induced by rIFN- γ , rIL-10, LPS, PGE and dibutyryl cAMP. The suppressive action of IL-4 was completely diminished by the addition of neutralizing anti-IL-4 antibody [61]. Reports from other laboratories also support our conclusion; IL-4 inhibits SCF-dependent mast cell development from various sources of progenitors, especially in the early phase of culture [80,90,102-105].

One possible mechanism is that IL-4 directly acts on mast cells and their precursors at various stages of their differentiation and results in suppression of their development. This explanation is supported by some reports showing IL-4-induced inhibition of *c-kit* expression on mast cells [90,102,104]. Human rIL-4 has been reported to induce apoptosis of cord blood-derived mast cells [80,106]. In murine systems, IL-4 alone, or in combination with IL-10, has been reported to directly elicit apoptosis of developing mast cells from bone marrow cells [105,107,108]. Importantly, however, the cells used in these studies were from mixed populations, and the influence of indirect effects of IL-4 was not considered.

We confirmed in our system that IL-4 and IL-13 can suppress mast cell development from mouse spleen, bone marrow and peritoneal cells by an indirect process that is dependent on the presence

Table 1. Cytokines Regulating Mast Cell Development and Survival

Promotion	
IFN- γ	Promotes mast cell development from mouse splenic cells [61,63] and promotes survival of human mast cells [95]
IL-1 α	Triggers PGE ₂ production and then indirectly promotes mast cell development in cooperation with membrane-bound SCF expressed by fibroblasts [85]
IL-3	Murine mast cell growth factor [28,29]
IL-4	Mast cell growth factor [49,50]
IL-5	Cofactor for the proliferation of human mast cells [20,78]
IL-6	Triggers mast cell development from mouse splenic cells [62] and promotes human mast cell development as cofactor of SCF [20,69,78]
IL-9	Mast cell growth factor [51]
IL-10	Mast cell growth factor [52]
IL-12	Promotes murine mast cell development in an IFN- γ -dependent [61,63] and -independent way [115]
IL-15	Prevents mouse mast cell apoptosis [116]
IL-16	Induces the chemotaxis and activation of human and murine mast cells [117]
NGF	Cofactor of IL-3 for murine mast cell development [118] and promotes the survival of human mast cells synergistically with SCF [119]
SCF	Crucial growth factor for murine and human mast cells [31-46]
TGF- β	Promotes mast cell functions [111,112]
TNF- α	Triggers mast cell development from mouse splenic cells [62] and bone marrow cells [74]
TPO	Promotes SCF-dependent human mast cell development [120]
Suppression	
GM-CSF	Promotes macrophage proliferation and indirectly inhibits mast cell development [69]
IFN- γ	Inhibits mast cell development [78,86-90] and activation [91-93] and induces mast cell apoptosis [94]
IL-4	Inhibits mast cell development [61,80,90,102-105] and induces mast cell apoptosis [64,80,105-108]
IL-6	Reduces SCF-dependent human mast cell development from CD34 ⁺ cord blood cells [81]
IL-10	Induces mast cell apoptosis [105,108,121]
IL-13	Induces mast cell apoptosis [64]
TGF- β	Suppresses mast cells proliferation [64] and induces mast cell apoptosis [113]
TRAIL	Induces human mast cell apoptosis [114]

of macrophages. When peritoneal cells from macrophage-deficient *op/op* mice were stimulated with rIL-3, rSCF and rIL-4, mast cell development was not suppressed by IL-4, but was greatly promoted. Mast cells underwent apoptosis when exposed to supernatants collected from cultures of IL-4-stimulated peritoneal cells, due to the IL-4-induced production of an apoptosis-inducing factor in the cultures. This effect of IL-4 was shown to be dependent on STAT6 signaling because IL-4 and IL-13 did not suppress mast cell development from the spleen and peritoneal cells of STAT6^{-/-} mice. Moreover, supernatants from cultures of IL-4- and IL-13-stimulated peritoneal cells of STAT6^{-/-} mice did not exhibit apoptosis-inducing activity [64].

Our studies have characterized a novel IL-4-dependent mechanism that can contribute to mast cell homeostasis. The fact that IL-4 induces the production of this apoptosis-inducing factor from macrophages offers some insight into why IL-4 can promote mast cell growth under certain circumstances but can also promote mast cell apoptosis and suppress mast cell development in other settings. The precise molecular identification of this mast cell apoptosis-inducing factor may be of considerable interest.

OTHER CYTOKINES REGULATING MAST CELL DEVELOPMENT

Besides the confirmed mast cell growth factors SCF, IL-3, IL-4, IL-9, IL-10 and IL-13, many cytokines have been reported to affect, either positively or negatively, mast cell development as summarized in Table 1. Among them, transforming growth factor (TGF)- β is a well-known suppressive factor of various types of cells [109] and can influence mast cell apoptosis [110] and functions [111,112]. Recently, it was reported that TGF- β 1 is a potent apoptotic inducer of mast cells derived from mouse bone marrow cells, peritoneal cells and human skin cells. The cell death seen appears to be caused by TGF-mediated repression of IL-3 receptor expression, thus leading to mitochondrial damage and activation of an apoptotic cascade acting *via* p53 and caspases [113]. Under the conditions tested in our experiments, TGF- β did antagonize the activities of IL-3 and SCF on mast cell growth and development. However, mast cell lines and purified mast cells did not undergo apoptosis after exposure to TGF- β . Also, a neutralizing antibody against TGF- β did not eliminate the apoptosis-inducing activity of supernatants collected from the cultures of IL-4-stimulated peritoneal cells.

TNF-related apoptosis inducing ligand (TRAIL) has recently been reported to be an apoptosis-inducing factor for human mast cells. Human mast cell leukemia cell line HMC-1 and human mast cells were confirmed to express TRAIL receptors and activation of them resulted in caspase 3-dependent apoptosis [114]. By RT-PCR analysis, it was confirmed that IL-4 did not significantly stimulate the expression of TRAIL mRNA in our system. Neutralizing antibody against TRAIL also did not abolish the apoptosis-inducing activity of the supernatants recovered from the cultures of IL-4-stimulated peritoneal cells [64], indicating that the IL-4-induced and macrophage-produced apoptosis-inducing factor of mast cells is not TRAIL. By using deficient mice, neutralizing antibodies and recombinant cytokines, we also confirmed that the IL-4-induced apoptosis is not related to the well-known apoptosis-inducing factors Fas, Fas ligand, TNF- α or perforin [64].

CONCLUSION

Mast cell development involves a particularly complex process entailing a cytokine milieu and a tissue-specific microenvironment consisting of various cell types, such as T cells, fibroblasts, endothelial cells, macrophages and even mast cells themselves. The cytokine milieu includes not only mast cell growth factors, such as SCF, IL-3, IL-4, IL-9, IL-10 and IL-13, but also many mediators

released in inflammatory responses, such as IFN- γ , IL-1, IL-6, IL-12, TNF- α and TGF- β . Such cytokines orchestrate the recruitment, activation and apoptosis of mast cells *via* both up- and down-regulation. Different culture systems, cell sources, mouse strains and even initial cell numbers are also critical and may result in different and even contradictory conclusions. The effect of a cytokine on undifferentiated mast cells may be considerably different from its effect on mature mast cells. Furthermore, human mast cells and murine mast cells may respond differently to a given cytokine. To clarify such confusing and contradictory results, it is essential to recognize the properties of each *in vitro* and *in vivo* system used to develop mast cells. The effects of a factor on mast cell development can be divided into either direct or indirect action, and the final result may depend on the balance between the two actions. Generally, the direct effect of a stimulant can be ascertained from data derived from semi-solid culture system seeded with limiting numbers of pure cell populations. Conversely, data need to be analyzed carefully when derived from liquid cultures seeded with relatively large numbers of cells of mixed populations, as results are typically confounded by diverse, indirect effects caused by the stimulant on mast cell development. A typical example we have shown is that IL-4 displays both a direct effect as a mast cell growth factor and an indirect effect as a trigger for macrophages to produce an, as yet unknown, apoptosis-inducing factor of mast cells.

ABBREVIATIONS

cAMP	=	Cyclic AMP
CD	=	Cluster of differentiation
GM-CSF	=	Granulocyte-macrophage colony-stimulating factor
IFN	=	Interferon
LPS	=	Lipopolysaccharide
NGF	=	Nerve growth factor
PGE	=	Prostaglandin E
rIL-	=	Recombinant interleukin
SCF	=	Stem cell factor
STAT	=	Signal transducers and activators of transcription
Th1(2)	=	Type 1 (2) T helper cells
TGF	=	Transforming growth factor
TNF	=	Tumor necrosis factor
TPO	=	Thrombopoietin
TRAIL	=	TNF-related apoptosis inducing ligand

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