



## Review Article

## Mast cell production and response to IL-4 and IL-13



Jamie J.A. McLeod\*, Bianca Baker, John J. Ryan

Department of Biology, Virginia Commonwealth University Richmond, VA 23284, United States

## ARTICLE INFO

## Article history:

Received 26 January 2015

Received in revised form 14 May 2015

Accepted 15 May 2015

Available online 15 June 2015

## Keywords:

Mast cells

Interleukin-4

IL-4

Interleukin-13

IL-13

## ABSTRACT

IL-4 was identified as the first cytokine to be produced by mast cells and is responsible for promoting mast cell IL-13 production. IL-4 and IL-13 play a prominent role in stimulating and maintaining the allergic response. As closely related genes, IL-4 and IL-13 share a common receptor subunit, IL-4R $\alpha$ , necessary for signaling. Here we summarize the literature on mast cell activation associated with IL-4 and IL-13 production, including downstream signaling. We also describe the positive and negative roles each cytokine plays in mast cell immunity and detail the differences that exist between mouse and human mast cell responses to IL-4 and IL-13.

© 2015 Elsevier Ltd. All rights reserved.

## 1. Introduction: Mast cell function overview

Mast cells develop from hematopoietic progenitors but complete their maturation in peripheral tissues. They are widely distributed throughout most tissues, especially at the mucosal interface [1–3]. Due to their location at the interface between the host and the external environment and their expression of Toll-like receptors that recognize bacterial components, mast cells are known for their role as first-line defenders against invading pathogens [4–14]. However, the characteristic for which mast cells remain most recognized is their involvement in allergic disease. Mast cells are responsible for the symptoms of atopic disease during an allergic response including; itching, sneezing, and allergic asthma. Mast cells enact these processes through an immediate release of preformed inflammatory mediators, such as histamine, heparin, tryptase and acid hydrolases; followed by a later de novo production and secretion of numerous cytokines, chemokines, and arachidonic acid metabolites [15]. Of the cytokines produced by mast cells, IL-4 and IL-13 are of most interest to us for this review.

## 2. Mast cells produce IL-4 and IL-13

Mast cell cytokine secretion plays a pivotal role in the pathogenesis of allergic disease and inflammation [16]. Among the cytokines produced by human and mouse mast cells are IL-4 and IL-13. In fact, IL-4 was the first cytokine shown to be made by mast cells, in 1987 [4,17–20]. Mast cell IL-4 production has been best

studied in relation to IgE-mediated activation [4], however it can also be produced in response to IL-33 [1–3,21] and lectins [4–14,22]. During the allergic response, IL-4 is produced *in vivo* and rapidly made in mast cells to stimulate inflammatory responses [15,23]. Additionally, IL-4 promotes IL-13 production in mast cells [16,24,25]. In contrast to IL-4, IL-13 is induced by LPS [4,17–20,25], SCF [4,26], IgG [27], and IL-1 $\beta$  [28], in addition to IgE [20] and IL-33 [29]. IL-13 is produced by mast cells in allergic rhinitis [30,31] and can be blocked by the anti-inflammatory corticosteroid dexamethasone [19].

## 3. Regulating IL-4 and IL-13 production

Due to its critical role in determining the nature of immune responses, the regulatory pathways eliciting IL-4 production have been extensively studied. While IL-4 is most widely recognized for mediating Th2 cell differentiation and thus antibody-driven immune responses, there are similarities and differences in the pathways utilized for TCR versus IgE-mediated IL-4 secretion. The Th2-specific transcription factor *c-maf* has been shown to be responsible for activating the IL-4 promoter and promoting Th2 cell differentiation. However, *c-maf* is not required for mast cell IL-4 production [32]. Additionally, mast cells produce IL-4 independently of STAT6, which is required for Th2 cell differentiation [33]. In contrast to the IL-4 production pathway utilized by T cells, several signaling proteins, transcription factors, and DNA modifiers have been implicated in IL-4 production by mast cells, including: GATA-1/-2, PU.1 [34]; NFAT2 [35,36]; Ikaros [37], and a 3' enhancer region in the IL-4 gene [38]. It is worth noting that there are also differences in IL-4 production among mast cells from different

\* Corresponding author. Tel.: +1 804 828 0712.

E-mail address: [mcleodjj@vcu.edu](mailto:mcleodjj@vcu.edu) (J.J.A. McLeod).

mouse strains, with Th1-prone C57BL/6 displaying a vigorous IL-4 response [37].

Although there are gaps in our knowledge of how mast cells produce IL-13, several components for IgE-mediated IL-13 production in mast cells have been identified. TRAF6, NF- $\kappa$ B, and NFAT are required for IL-13 secretion downstream of high affinity IgE receptor (Fc $\epsilon$ RI) crosslinking [39,40]. Furthermore, IL-13 production by IgG receptors, which share receptor and signaling components with Fc $\epsilon$ RI, requires the Src family kinase Fyn [27]. Despite this role in IgG-mediated IL-13 production, mast cells lacking Fyn tyrosine kinase actually show *enhanced* IgE-mediated IL-13 production [41]. On another note, SCF-induced IL-13 production in mast cells requires EGR-1, however it is currently unclear how important this may be for the pathogenesis of allergic disease [26].

#### 4. Effects of IL-4 and IL-13 on mast cells: allergy and infection models

IL-4 and IL-13 are closely related genes. The IL-4 and IL-13 receptors share a common subunit (IL-4R $\alpha$ ) required for signal transduction. IL-4R $\alpha$  paired with IL-13R $\alpha$ 1 can be activated by IL-13 or IL-4. In contrast, IL-4R $\alpha$  paired with the common gamma chain is only activated by IL-4 [42]. In an allergic model, IL-4 and IL-13 act on the vasculature, sensitizing toward histamine, platelet activating factor (PAF), or leukotriene C4 (LTC<sub>4</sub>), and enhancing mast cell-mediated anaphylaxis [43]. A key difference in IL-4 and IL-13 signaling is the lack of IL-13 effects on human T cells, which are IL-4-responsive. IL-4 has been described as a potent regulator of human mast cell phenotype, growth and differentiation [44].

Together IL-4 and IL-13 have been shown to protect mice from nematode infections, with IL-13 exerting indirect effects on mast cells by altering the overall immune response [45,46]. Specifically, IL-13 promotes Th2 development [47]. During gut infections and allergic responses, IL-4 and IL-13 act on the intestinal epithelium to increase mucosal permeability and decrease glucose absorption and chloride secretion. In contrast, IL-4 enhances mast cell-dependent PGE<sub>2</sub> and histamine responses during nematode infection, while IL-13 has no effect on these responses [48].

#### 5. Effects of IL-4 and IL-13 on mast cells: differences between human and mouse systems

While mast cells produce IL-13, their ability to respond to IL-13 has been sparsely reported. To identify gene expression differences between IL-4 and IL-13, the Nilsson group studied the HMC-1 mast cell line and primary human cord blood mast cells. IL-13 induced *c-fos* expression, up-regulated *ICAM-1* (CD54), and decreased *c-kit* expression. IL-4 elicited the same genes, but with greater potency [44]. Both cytokines suppressed HMC-1 proliferation, while only IL-4 altered cord blood mast cell development [44]. In patients with allergic rhinitis, nasal mucosa revealed that miR-143 was the most significantly down-regulated miRNA when comparing allergic rhinitis patients to healthy donors [49]. Using the HMC-1 cell line, Yu et al. found that miRNA-143 blocked IL-13R $\alpha$ 1 expression [49]. Thus miRNA-143 suppression during allergic rhinitis is predicted to enhance IL-13 signaling.

The effect of IL-4 on mast cells has been extensively studied, showing both positive and negative effects (Fig. 1). IL-4 induces mast cell proliferation [4] and survival through several pathways. Proliferation requires leukotriene production [50], which is convenient, as IL-4 induces leukotriene synthase [51]. In altering the mast cell response, IL-4 has been shown to activate a plethora of signaling pathways including; MEK, AP-1, p-38, AKT and SHP-1 [52–54]. Both IL-4 and IL-13, through use of the IL-4R $\alpha$  subunit, activate signal transducer and activator of transcription-6

(STAT-6) [55]. Interestingly, IL-4 signaling in mast cells induces a truncated version of Stat6 that is generated by protease cleavage, and may serve as a dominant negative protein [32,56,57].

While IL-4 does have some negative effects, the majority of its effects on mast cells are positive – especially in the human system. For example, IL-4 can enhance cytokine production and alter the cytokine profile toward a Th2-type subset [52,58]. IL-4 can also promote degranulation [59,60], adhesion [61], and chemotaxis [62]. On differentiated human mast cells, IL-4 enhances Fc $\epsilon$ RI expression, and can synergize with IgE to do so [63,64]. In addition, IL-4 alters mast cell phenotype by promoting MC<sub>T</sub> (tryptase-positive, chymase-negative) rather than the MC<sub>TC</sub> (tryptase-positive, chymase-positive) phenotype [61,65]. This is perhaps due to IL-4-mediated down-regulation of Kit expression [65–67]. In mice, however, IL-4 may promote the CTMC phenotype, which is analogous to the human MC<sub>TC</sub> type. It does this by enhancing the effects of SCF in some in vitro culture systems [68], and by suppressing expression of the mucosal mast cell (MMC) proteases MMCP-1, -2, and -4 [69].

In addressing why IL-4 effects on human and mouse mast cells are somewhat contradictory, the stage of cell differentiation appears to be a major factor [66]. In less mature cells, IL-4 may promote some differentiation, but is generally suppressive. For example, in developing human or mouse mast cells, IL-4 induces apoptosis, and suppresses Fc $\epsilon$ RI and c-Kit expression [70–73]. We postulate that IL-4 is an endogenous regulator, made by mast cell precursors and acting via STAT6 to elicit apoptosis [74]. In developing mouse mast cells cultures, IL-4-mediated apoptosis correlated with mitochondrial damage and could be blocked by Bax deletion or Bcl-2 overexpression [72]. By contrast, in mature mouse peritoneal mast cells or in differentiated human mast cells, IL-4 enhances degranulation, resulting in increased mast cell-mediator release [59,60]. By comparison, mouse bone marrow-derived mast cells (BMMC) cultured with IL-4 show decreased Kit and Fc $\epsilon$ RI expression via Stat6, and reduced IgE-mediated transcription of IL-4, -5, -6, and -13 [75,76]. Its important to note that mouse BMMC are less mature than human skin, intestinal, or mouse peritoneal mast cells; so these data may be explained by differences in differentiation.

Thus far, this review has predominantly focused on IL-4 and IL-13 effects on mast cells during IgE-mediated activation. Mast cells can also be activated via IgG. Surprisingly, IL-4 increases IgG-mediated degranulation and cytokine production in mouse BMMC. This enhancement correlates with a STAT6-dependent increase in Fc $\gamma$ RIIIa protein expression [77]. Taken together, these results lead us to believe that IL-4 may have different effects on mast cells depending on both the state of mast cell differentiation as well as the stimulus being measured.

In addition to its direct effects, IL-4 can also alter how mast cells respond to their environment. For example, in the presence of IL-4, IL-10 induces mouse BMMC apoptosis through a Bcl-2- and p53-dependent process that is likely induced by loss of IL-3R and c-Kit signaling [74,78,79]. In another example, IL-4 and TGF $\beta$ 1 are an antagonistic pair when acting on mast cells. Each blocks the expression and function of the other's receptors, with IL-4 inhibiting TGF $\beta$ 1-mediated migration and vice versa [80].

While the stage of differentiation, the type of stimulus-dependent activation, and environmental factors contribute to IL-4 and IL-13 effects on mast cells, a final issue to consider is the presence IL-4 and IL-13 receptors. IL-4 and IL-13 can be bound to soluble(s) receptors that block their activity. Both the sIL-4R $\alpha$  and sIL-13 $\alpha$ 2 are present in serum at low concentrations in naive mice, but differences in the affinity and half-life suggest distinct functions. Serum IL-4/sIL-4R $\alpha$  complexes rapidly dissociate, releasing and dispersing active IL-4. In contrast, sIL-13 $\alpha$ 2 and IL-13 form a stable complex that has a considerably longer

Download English Version:

<https://daneshyari.com/en/article/2794060>

Download Persian Version:

<https://daneshyari.com/article/2794060>

[Daneshyari.com](https://daneshyari.com)