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Mast Cell Production and Response to IL-4 and IL-13

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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-4Rα, 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.

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 my mast cells, IL-4 and IL-13 are of most interest to us for this review.

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-1β [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].

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 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-κB, and NFAT are required for IL-13 secretion downstream of high affinity IgE receptor (FcεRI) crosslinking [39,40]. Furthermore, IL-13 production by IgG receptors, which share receptor and signaling components with FcεRI, 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].

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-4Rα) required for signal transduction. IL-4Rα paired with IL-13Rα1 can be activated by IL-13 or IL-4. In contrast, IL-4Rα 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 towards histamine, platelet activating factor (PAF), or leukotriene C4 (LTC_4), 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_2 and histamine responses during nematode infection, while IL-13 has no effect on these responses [48].

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-13Rα1 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 (Figure 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-4Rα 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 towards 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 FcεRI expression, and can synergize with IgE to do so [63,64]. In addition, IL-4 alters mast cell phenotype by promoting MC_T (tryptase-positive, chymase-negative) rather than the MC_{TC} (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_{TC} 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 FcεRI 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 FcεRI 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 FcγRIIIa 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 TGFβ1 are an antagonistic pair when acting on mast cells. Each blocks the expression and function of the other's receptors, with IL-4 inhibiting TGFβ1-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-4Rαand sIL-13α2 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-4Rα complexes rapidly dissociate, releasing and dispersing active IL-4. In contrast, sIL-13α2 and IL-13 form a stable complex that has a considerably longer half-life than uncomplexed IL-13 and appears to suppress IL-13 function, serving as a "decoy" receptor [81].

Importance of Mast Cell IL-4 & IL-13

While mast cells produce IL-4 and IL-13, the essential role of these cytokines strictly from this source has not been widely investigated. This is in contrast to mast cell-derived TNF, which has been examined in several contexts. The common approach is to reconstitute c-

Kit-mutant mice, which lack mast cells, with wild type or gene-deficient mast cells, generating a mast cell-restricted knockout mouse. Reconstituting mast-cell deficient mice with $TNF^{-/-}$ mast cells, researchers found that IL-33 induced peritoneal neutrophil infiltration was partially dependent on mast cell-derived TNF [82]. In addition, Malaviya et al found that mast cell deficient mice are unable to clear bacterial infections. Using reconstituted mast-cell deficient mice in the presence of TNF-α–specific antibody, researchers identified a significant decrease in neutrophil influx necessary for bacterial clearance [6,14]. In regards to addressing MC-derived IL-4 and IL-13's essential role in mast cell response, there is a gap in the current research. Thus far, researchers have shown that mast cells are not essential for a Th2 response defined by enhanced production of IL-4 and IgG1 antibody [83]. In addition, mast cell deficient mice reconstituted with $IL\text{-}4^{-/-}$ mast cells show that MC-derived IL-4 can promote the Th1 response, but again is not essential [37]. Future directions to determine mast cell specific IL-4 and IL-13's role in mast cell responses should employ the approaches described in the TNF experiments, using IL-4 and IL-13 deficient mast cells to reconstitute mast cell deficient mice and identify each cytokines essential role in specific mast cell responses.

While it is unclear how essential the functions of IL-4 and IL-13 on masts cells are, mast cells are known to maintain a constitutive presence of functional IL-4 and IL-13 transcripts, but not IL-4 or IL-13 cytokines. These transcripts increase under mast cell stimulation conditions, however the constitutive presence of IL-4 and IL-13 transcripts were sufficient for the rapid production of IL-4 and IL-13 cytokines seen during mast cell activation [47]. IL-13 cytokine production is enhanced during IL-33 stimulation in the absence of IgE [84]. In addition, researchers have shown that mast cell IL-33-mediated inflammation was abolished in IL-13-deficient mice [85]. These results raise the possibility that IL-33 may induce IL-13-dependent inflammation *in vivo* in part by inducing IL-13 production by mast cells [84].

Summary

Mast cells are potent sources of cytokines, able to respond to a myriad of stimuli. Their production and responsiveness to IL-4 and IL-13 is important to our understanding of allergic and inflammatory diseases. Particularly in diseases such as allergic asthma, targeting mast cell-derived cytokines may prove extremely beneficial. Currently this is done by broadly suppressive drugs, such as corticosteroids. Targeted approaches offer hope for selective therapy with fewer side effects.

References

1. Metcalfe DD, Baram D, Mekori YA. Mast cells. Physiol Rev. 1997; 77(4):1033–1079. [PubMed: 9354811]
2. Galli SJ, Kalesnikoff J, Grimbaldeston MA, Piliponsky AM, Williams CMM, Tsai M. Mast cells as 'tunable' effector and immunoregulatory cells: recent advances. Annu Rev Immunol. 2005; 23:749–786. [PubMed: 15771585]
3. Jamur MC, Grodzki ACG, Berenstein EH, Hamawy MM, Siraganian RP, Oliver C. Identification and characterization of undifferentiated mast cells in mouse bone marrow. Blood. 2005; 105(11): 4282–4289. [PubMed: 15718418]

4. Brown MA, Pierce JH, Watson CJ, Falco J, Ihle JN, Paul WE. B cell stimulatory factor-1/interleukin-4 mRNA is expressed by normal and transformed mast cells. Cell. 1987; 50(5):809–818. [PubMed: 3497723]
5. Malaviya R, Abraham SN. Mast cell modulation of immune responses to bacteria. Immunol Rev. 2001; 179:16–24. [PubMed: 11292019]
6. Malaviya R, Ikeda T, Ross E, Abraham SN. Mast cell modulation of neutrophil influx and bacterial clearance at sites of infection through TNF-alpha. Nature. 1996; 381(6577):77–80. [PubMed: 8609993]
7. Malaviya R, Gao Z, Thankavel K, van der Merwe PA, Abraham SN. The mast cell tumor necrosis factor alpha response to FimH-expressing Escherichia coli is mediated by the glycosylphosphatidylinositol-anchored molecule CD48. Proc Natl Acad Sci USA. 1999; 96(14): 8110–8115. [PubMed: 10393956]
8. Malaviya R, Abraham SN. Interaction of bacteria with mast cells. Meth Enzymol. 1995; 253:27–43. [PubMed: 7476393]
9. Malaviya R, Abraham SN. Clinical implications of mast cell-bacteria interaction. J Mol Med. 1998; 76(9):617–623. [PubMed: 9725764]
10. Marshall JS, King CA, McCurdy JD. Mast cell cytokine and chemokine responses to bacterial and viral infection. Curr Pharm Des. 2003; 9(1):11–24. [PubMed: 12570671]
11. McCurdy JD, Olynych TJ, Maher LH, Marshall JS. Cutting edge: distinct Toll-like receptor 2 activators selectively induce different classes of mediator production from human mast cells. J Immunol. 2003; 170(4):1625–1629. [PubMed: 12574323]
12. Marshall JS, McCurdy JD, Olynych T. Toll-like receptor-mediated activation of mast cells: implications for allergic disease? Int Arch Allergy Immunol. 2003; 132(2):87–97. [PubMed: 14600420]
13. Marshall JS. Mast-cell responses to pathogens: Abstract: Nature Reviews Immunology. Nat Rev Immunol. 2004
14. Echtenacher B, Männel DN, Hültner L. Critical protective role of mast cells in a model of acute septic peritonitis. Nature. 1996; 381(6577):75–77. [PubMed: 8609992]
15. Gilfillan AM, Tkaczyk C. Integrated signalling pathways for mast-cell activation. Nat Rev Immunol. 2006; 6(3):218–230. [PubMed: 16470226]
16. Plaut M, Pierce JH, Watson CJ, Hanley-Hyde J, Nordan RP, Paul WE. Mast cell lines produce lymphokines in response to cross-linkage of Fc epsilon RI or to calcium ionophores. Nature. 1989; 339(6219):64–67. [PubMed: 2469965]
17. Okayama Y, Semper A, Holgate ST, Church MK. Multiple cytokine mRNA expression in human mast cells stimulated via Fc epsilon RI. Int Arch Allergy Immunol. 1995; 107(1–3):158–159. [PubMed: 7542065]
18. Marietta EV, Chen Y, Weis JH. Modulation of expression of the anti-inflammatory cytokines interleukin-13 and interleukin-10 by interleukin-3. Eur J Immunol. 1996; 26(1):49–56. [PubMed: 8566083]
19. Fushimi T, Okayama H, Shimura S, Saitoh H, Shirato K. Dexamethasone suppresses gene expression and production of IL-13 by human mast cell line and lung mast cells. J Allergy Clin Immunol. 1998; 102(1):134–142. [PubMed: 9679857]
20. Burd PR, Thompson WC, Max EE, Mills FC. Activated mast cells produce interleukin 13. J Exp Med. 1995; 181(4):1373–1380. [PubMed: 7535336]
21. Komai-Koma M, Brombacher F, Pushparaj PN, Arendse B, McSharry C, Alexander J, Chaudhuri R, Thomson NC, McKenzie ANJ, McInnes I, Liew FY, Xu D. Interleukin-33 amplifies IgE synthesis and triggers mast cell degranulation via interleukin-4 in naïve mice. Allergy. 2012; 67(9):1118–1126. [PubMed: 22702477]
22. Hoffmann HJ, Dahl C, Schiøtz PO, Berglund L, Dahl R. Lectins interact differentially with purified human eosinophils, cultured cord blood-derived mast cells and the myeloid leukaemic cell line AML14.3D10: induction of interleukin-4 secretion is conserved among granulocytes, but is not proportional to agglutination or lectin-glycoprotein interaction. Clin Exp Allergy. 2003; 33(7): 930–935. [PubMed: 12859449]

23. Wang M, Saxon A, Diaz-Sanchez D. Early IL-4 production driving Th2 differentiation in a human in vivo allergic model is mast cell derived. Clin Immunol. 1999; 90(1):47–54. [PubMed: 9884352]
24. Toru H, Pawankar R, Ra C, Yata J, Nakahata T. Human mast cells produce IL-13 by high-affinity IgE receptor cross-linking: enhanced IL-13 production by IL-4-primed human mast cells. J Allergy Clin Immunol. 1998; 102(3):491–502. [PubMed: 9768593]
25. Varadaradjalou S, Féger F, Thieblemont N, Hamouda NB, Pleau J-M, Dy M, Arock M. Toll-like receptor 2 (TLR2) and TLR4 differentially activate human mast cells. Eur J Immunol. 2003; 33(4): 899–906. [PubMed: 12672055]
26. Li B, Berman J, Tang JT, Lin TJ. The Early Growth Response Factor-1 Is Involved in Stem Cell Factor (SCF)-induced Interleukin 13 Production by Mast Cells, but Is Dispensable for SCF-dependent Mast Cell Growth. Journal of Biological Chemistry. 2007; 282(31):22573–22581. [PubMed: 17556359]
27. Falanga YT, Chaimowitz NS, Charles N, Finkelman FD, Pullen NA, Barbour S, Dholaria K, Faber T, Kolawole M, Huang B, Odom S, Rivera J, Carlyon J, Conrad DH, Spiegel S, Oskeritzian CA, Ryan JJ. Lyn but Not Fyn Kinase Controls IgG-Mediated Systemic Anaphylaxis. The Journal of Immunology. 2012; 188(9):4360–4368. [PubMed: 22450804]
28. Lee SA, Fitzgerald SM, Huang SK, Li C, Chi DS, Milhorn DM, Krishnaswamy G. Molecular Regulation of Interleukin-13 and Monocyte Chemoattractant Protein-1 Expression in Human Mast Cells by Interleukin-1β. Am J Respir Cell Mol Biol. 2004; 31(3):283–291. [PubMed: 15191916]
29. Ryan JJ, McReynolds LJ, Keegan A, Wang LH, Garfein E, Rothman P, Nelms K, Paul WE. Growth and gene expression are predominantly controlled by distinct regions of the human IL-4 receptor. Immunity. 1996; 4(2):123–132. [PubMed: 8624803]
30. Cameron L, Hamid Q, Wright E, Nakamura Y, Christodoulopoulos P, Muro S, Frenkiel S, Lavigne F, Durham S, Gould H. Local synthesis of germline gene transcripts, IL-4, and IL-13 in allergic nasal mucosa after ex vivo allergen exposure. Journal of Allergy and Clinical Immunology. 2000; 106(1):46–52. [PubMed: 10887304]
31. Ghaffar O, Laberge S, Jacobson MR, Lowhagen O, Rak S, Durham SR, Hamid Q. IL-13 mRNA and immunoreactivity in allergen-induced rhinitis: comparison with IL-4 expression and modulation by topical glucocorticoid therapy. Am J Respir Cell Mol Biol. 1997; 17(1):17–24. [PubMed: 9224205]
32. Sherman MA, Secor VH, Brown MA. IL-4 preferentially activates a novel STAT6 isoform in mast cells. J Immunol. 1999; 162(5):2703–2708. [PubMed: 10072514]
33. Sherman MA, Secor VH, Lee SK, Lopez RD, Brown MA. STAT6-independent production of IL-4 by mast cells. Eur J Immunol. 1999; 29(4):1235–1242. [PubMed: 10229091]
34. Henkel G, Brown MA. PU.1 and GATA: components of a mast cell-specific interleukin 4 intronic enhancer. Proc Natl Acad Sci USA. 1994; 91(16):7737–7741. [PubMed: 8052653]
35. Weiss DL, Hural J, Tara D, Timmerman LA, Henkel G, Brown MA. Nuclear factor of activated T cells is associated with a mast cell interleukin 4 transcription complex. Mol Cell Biol. 1995; 16(1): 228–235. [PubMed: 8524300]
36. Hock MB, Brown MA. Nuclear Factor of Activated T Cells 2 Transactivation in Mast Cells: A NOVEL ISOFORM-SPECIFIC TRANSACTIVATION DOMAIN CONFERS UNIQUE Fc RI RESPONSIVENESS. Journal of Biological Chemistry. 2003; 278(29):26695–26703. [PubMed: 12738787]
37. Gregory GD, Raju SS, Winandy S, Brown MA. Mast cell IL-4 expression is regulated by Ikaros and influences encephalitogenic Th1 responses in EAE. J Clin Invest. 2006; 116(5):1327–1336. [PubMed: 16628252]
38. Solymar DC, Agarwal S, Bassing CH, Alt FW, Rao A. A 3′ enhancer in the IL-4 gene regulates cytokine production by Th2 cells and mast cells. Immunity. 2002; 17(1):41–50. [PubMed: 12150890]
39. Yang YJ, Chen W, Carrigan SO, Chen WM, Roth K, Akiyama T, Inoue JI, Marshall JS, Berman JN, Lin TJ. TRAF6 Specifically Contributes to Fc RI-mediated Cytokine Production but Not Mast Cell Degranulation. Journal of Biological Chemistry. 2008; 283(46):32110–32118. [PubMed: 18772140]

40. Lorentz A, Klopp I, Gebhardt T, Manns MP, Bischoff SC. Role of activator protein 1, nuclear factor-κB, and nuclear factor of activated T cells in IgE receptor-mediated cytokine expression in mature human mast cells. Journal of Allergy and Clinical Immunology. 2003; 111(5):1062–1068. [PubMed: 12743571]
41. Gomez G, Gonzalez-Espinosa C, Odom S, Baez G, Cid ME, Ryan JJ, Rivera J. Impaired Fc RI-Dependent Gene Expression and Defective Eicosanoid and Cytokine Production as a Consequence of Fyn Deficiency in Mast Cells. The Journal of Immunology. 2005; 175(11):7602–7610. [PubMed: 16301670]
42. LaPorte SL, Juo ZS, Vaclavikova J, Colf LA, Qi X, Heller NM, Keegan AD, Garcia KC. Molecular and structural basis of cytokine receptor pleiotropy in the interleukin-4/13 system. Cell. 2008; 132(2):259–272. [PubMed: 18243101]
43. Strait RT, Morris SC, Smiley K, Urban JF, Finkelman FD. IL-4 Exacerbates Anaphylaxis. The Journal of Immunology. 2003; 170(7):3835–3842. [PubMed: 12646651]
44. Nilsson G, Nilsson K. Effects of interleukin (IL)-13 on immediate-early response gene expression, phenotype and differentiation of human mast cells. Comparison with IL-4. Eur J Immunol. 1995; 25(3):870–873. [PubMed: 7705421]
45. Finkelman FD, Shea-Donohue T, Morris SC, Gildea L, Strait R, Madden KB, Schopf L, Urban JF. Interleukin-4- and interleukin-13-mediated host protection against intestinal nematode parasites. Immunol Rev. 2004; 201:139–155. [PubMed: 15361238]
46. Stem cell factor and its receptor c-Kit as targets for inflammatory diseases. Annu Rev Immunol. 2015; 533(1–3):425–456.
47. Gessner A, Mohrs K, Mohrs M. Mast cells, basophils, and eosinophils acquire constitutive IL-4 and IL-13 transcripts during lineage differentiation that are sufficient for rapid cytokine production. J Immunol. 2005; 174(2):1063–1072. [PubMed: 15634931]
48. Madden KB, Whitman L, Sullivan C, Gause WC, Urban JF, Katona IM, Finkelman FD, Shea-Donohue T. Role of STAT6 and Mast Cells in IL-4-and IL-13-Induced Alterations in Murine Intestinal Epithelial Cell Function. The Journal of Immunology. 2002; 169(8):4417–4422. [PubMed: 12370375]
49. Yu S, Zhang R, Zhu C, Cheng J, Wang H, Wu J. MicroRNA-143 Downregulates Interleukin-13 Receptor Alpha1 in Human Mast Cells. IJMS. 2013; 14(8):16958–16969. [PubMed: 23965966]
50. Jiang Y, Kanaoka Y, Feng C, Nocka K, Rao S, Boyce JA. Cutting Edge: Interleukin 4-Dependent Mast Cell Proliferation Requires Autocrine/Intracrine Cysteinyl Leukotriene-Induced Signaling. The Journal of Immunology. 2006; 177(5):2755–2759. [PubMed: 16920908]
51. Hsieh FH, Lam BK, Penrose JF, Austen KF, Boyce JA. T helper cell type 2 cytokines coordinately regulate immunoglobulin E-dependent cysteinyl leukotriene production by human cord blood-derived mast cells: profound induction of leukotriene C(4) synthase expression by interleukin 4. J Exp Med. 2001; 193(1):123–133. [PubMed: 11136826]
52. Lorentz A, Wilke M, Sellge G, Worthmann H, Klempnauer J, Manns MP, Bischoff SC. IL-4-Induced Priming of Human Intestinal Mast Cells for Enhanced Survival and Th2 Cytokine Generation Is Reversible and Associated with Increased Activity of ERK1/2 and c-Fos. The Journal of Immunology. 2005; 174(11):6751–6756. [PubMed: 15905515]
53. Feuser K, Feilhauer K, Staib L, Bischoff SC, Lorentz A. Akt cross-links IL-4 priming, stem cell factor signaling, and IgE-dependent activation in mature human mast cells. Molecular Immunology. 2011; 48(4):546–552. [PubMed: 21106245]
54. Huang Z, Coleman JM, Su Y, Mann M, Ryan J, Shultz LD, Huang H. SHP-1 regulates STAT6 phosphorylation and IL-4-mediated function in a cell type-specific manner. Cytokine. 2005; 29(3): 118–124. [PubMed: 15613279]
55. Oh CK, Geba GP, Molfino N. Investigational therapeutics targeting the IL-4/IL-13/STAT-6 pathway for the treatment of asthma. European Respiratory Review. 2010; 19(115):46–54. [PubMed: 20956165]
56. Sherman MA, Powell DR, Brown MA. IL-4 Induces the Proteolytic Processing of Mast Cell STAT6. The Journal of Immunology. 2002; 169(7):3811–3818. [PubMed: 12244176]

57. Shelburne CP, Piekorz RP, Bouton LA, Jin Chong H, Ryan JJ. MAST CELL-RESTRICTED p70 STAT6 ISOFORM IS A PRODUCT OF SELECTIVE PROTEOLYSIS. Cytokine. 2002; 19(5): 218–227. [PubMed: 12393168]
58. Lorentz A, Bischoff SC. Regulation of human intestinal mast cells by stem cell factor and IL-4. Immunol Rev. 2001; 179:57–60. [PubMed: 11292028]
59. Bischoff SC, Sellge G, Lorentz A, Sebald W, Raab R, Manns MP. IL-4 enhances proliferation and mediator release in mature human mast cells. Proc Natl Acad Sci USA. 1999; 96(14):8080–8085. [PubMed: 10393951]
60. Coleman JW, Holliday MR, Kimber I, Zsebo KM, Galli SJ. Regulation of mouse peritoneal mast cell secretory function by stem cell factor, IL-3 or IL-4. J Immunol. 1993; 150(2):556–562. [PubMed: 7678275]
61. Lorentz A, Schuppan D, Gebert A, Manns MP, Bischoff SC. Regulatory effects of stem cell factor and interleukin-4 on adhesion of human mast cells to extracellular matrix proteins. Blood. 2002; 99(3):966–972. [PubMed: 11807000]
62. Olsson N, Taub DD, Nilsson G. Regulation of Mast Cell Migration by TH1 and TH2 Cytokines: Identification of Tumour Necrosis Factor-α and Interleukin-4 as Mast Cell Chemotaxins. Scand J Immunol. 2004; 59(3):267–272. [PubMed: 15030577]
63. Yamaguchi M, Sayama K, Yano K, Lantz CS, Noben-Trauth N, Ra C, Costa JJ, Galli SJ. IgE enhances Fc epsilon receptor I expression and IgE-dependent release of histamine and lipid mediators from human umbilical cord blood-derived mast cells: synergistic effect of IL-4 and IgE on human mast cell Fc epsilon receptor I expression and mediator release. J Immunol. 1999; 162(9):5455–5465. [PubMed: 10228025]
64. Xia HZ, Du Z, Craig S, Klisch G, Noben-Trauth N, Kochan JP, Huff TH, Irani AM, Schwartz LB. Effect of recombinant human IL-4 on tryptase, chymase, and Fc epsilon receptor type I expression in recombinant human stem cell factor-dependent fetal liver-derived human mast cells. J Immunol. 1997; 159(6):2911–2921. [PubMed: 9300715]
65. Nilsson G, Miettinen U, Ishizaka T, Ashman LK, Irani AM, Schwartz LB. Interleukin-4 inhibits the expression of Kit and tryptase during stem cell factor-dependent development of human mast cells from fetal liver cells. Blood. 1994; 84(5):1519–1527. [PubMed: 7520776]
66. Thienemann F, Henz B, Babina M. Regulation of mast cell characteristics by cytokines: divergent effects of interleukin-4 on immature mast cell lines versus mature human skin mast cells. Arch Dermatol Res. 2004; 296(3)
67. Sillaber C, Strobl H, Bevec D, Ashman LK, Butterfield JH, Lechner K, Maurer D, Bettelheim P, Valent P. IL-4 regulates c-kit proto-oncogene product expression in human mast and myeloid progenitor cells. J Immunol. 1991; 147(12):4224–4228. [PubMed: 1721642]
68. Karimi K, Redegeld FA, Heijdra B, Nijkamp FP. Stem cell factor and interleukin-4 induce murine bone marrow cells to develop into mast cells with connective tissue type characteristics in vitro. Experimental Hematology. 1999; 27(4):654–662. [PubMed: 10210323]
69. Eklund KK, Ghildyal N, Austen KF, Stevens RL. Induction by IL-9 and suppression by IL-3 and IL-4 of the levels of chromosome 14-derived transcripts that encode late-expressed mouse mast cell proteases. J Immunol. 1993; 151(8):4266–4273. [PubMed: 7691943]
70. Oskeritzian CA, Wang Z, Kochan JP, Grimes M, Du Z, Chang HW, Grant S, Schwartz LB. Recombinant human (rh)IL-4-mediated apoptosis and recombinant human IL-6-mediated protection of recombinant human stem cell factor-dependent human mast cells derived from cord blood mononuclear cell progenitors. J Immunol. 1999; 163(9):5105–5115. [PubMed: 10528217]
71. Hu Z-Q, Zenda N, Shimamura T. Down-regulation by IL-4 and up-regulation by IFN-gamma of mast cell induction from mouse spleen cells. J Immunol. 1996; 156(10):3925–3931. [PubMed: 8621932]
72. Bailey DP, Kashyap M, Mirmonsef P, Bouton LA, Domen J, Zhu J, Dessypris EN, Ryan JJ. Interleukin-4 elicits apoptosis of developing mast cells via a Stat6-dependent mitochondrial pathway. Experimental Hematology. 2004; 32(1):52–59. [PubMed: 14725901]
73. Metcalfe DD, Peavy RD, Gilfillan AM. Mechanisms of mast cell signaling in anaphylaxis. J Allergy Clin Immunol. 2009; 124(4):639–46. quiz 647–8. [PubMed: 19815110]

74. Speiran K, Bailey DP, Fernando J, Macey M, Barnstein B, Kolawole M, Curley D, Watowich SS, Murray PJ, Oskeritzian C, Ryan JJ. Endogenous suppression of mast cell development and survival by IL-4 and IL-10. J Leukoc Biol. 2009; 85(5):826–836. [PubMed: 19228815]

75. Mirmonsef P, Shelburne CP, Fitzhugh Yeatman C, Chong HJ, Ryan JJ. Inhibition of Kit expression by IL-4 and IL-10 in murine mast cells: role of STAT6 and phosphatidylinositol 3′-kinase. J Immunol. 1999; 163(5):2530–2539. [PubMed: 10452990]

76. Ryan JJ, DeSimone S, Klisch G, Shelburne C, McReynolds LJ, Han K, Kovacs R, Mirmonsef P, Huff TF. IL-4 inhibits mouse mast cell Fc epsilonRI expression through a STAT6-dependent mechanism. J Immunol. 1998; 161(12):6915–6923. [PubMed: 9862725]

77. Chong HJ, Andrew Bouton L, Bailey DP, Wright H, Ramirez C, Gharse A, Oskeritzian C, Xia H-Z, Zhu J, Paul WE, Kepley C, Schwartz LB, Ryan JJ. IL-4 selectively enhances FcγRIII expression and signaling on mouse mast cells. Cell Immunol. 2003; 224(2):65–73. [PubMed: 14609572]

78. Yeatman CF, Jacobs-Helber SM, Mirmonsef P, Gillespie SR, Bouton LA, Collins HA, Sawyer ST, Shelburne CP, Ryan JJ. Combined stimulation with the T helper cell type 2 cytokines interleukin (IL)-4 and IL-10 induces mouse mast cell apoptosis. J Exp Med. 2000; 192(8):1093–1104. [PubMed: 11034599]

79. Bouton LA, Ramirez CD, Bailey DP, Yeatman CF, Yue J, Wright HV, Domen J, Rosato RR, Grant S, Fischer-Stenger K, Ryan JJ. Costimulation with interleukin-4 and interleukin-10 induces mast cell apoptosis and cell-cycle arrest: the role of p53 and the mitochondrion. Experimental Hematology. 2004; 32(12):1137–1145. [PubMed: 15588938]

80. Macey MR, Sturgill JL, Morales JK, Falanga YT, Morales J, Norton SK, Yerram N, Shim H, Fernando J, Gifillan AM, Gomez G, Schwartz L, Oskeritzian C, Spiegel S, Conrad D, Ryan JJ. IL-4 and TGF- 1 Counterbalance One Another while Regulating Mast Cell Homeostasis. The Journal of Immunology. 2010; 184(9):4688–4695. [PubMed: 20304823]

81. Khodoun M, Lewis C, Yang JQ, Orekov T, Potter C, Wynn T, Mentink-Kane M, Khurana Hershey GK, Wills-Karp M, Finkelman FD. Differences in Expression, Affinity, and Function of Soluble (s)IL-4R and sIL-13R 2 Suggest Opposite Effects on Allergic Responses. The Journal of Immunology. 2007; 179(10):6429–6438. [PubMed: 17982031]

82. Enoksson M, Moller-Westerberg C, Wicher G, Fallon PG, Forsberg-Nilsson K, Lunderius-Andersson C, Nilsson G. Intraperitoneal influx of neutrophils in response to IL-33 is mast cell-dependent. Blood. 2013; 121(3):530–536. [PubMed: 23093619]

83. Aoki I, Itoh S, Yokota S, Tanaka S, Ishii N, Okuda K, Minami M, Klinman DM. Contribution of mast cells to the T helper 2 response induced by simultaneous subcutaneous and oral immunization. Immunology. 1999; 98(4):519–524. [PubMed: 10594683]

84. Ho LH, Ohno T, Oboki K, Kajiwara N, Suto H, Iikura M, Okayama Y, Akira S, Saito H, Galli SJ, Nakae S. IL-33 induces IL-13 production by mouse mast cells independently of IgE-FcepsilonRI signals. J Leukoc Biol. 2007; 82(6):1481–1490. [PubMed: 17881510]

85. Hueber AJ, Alves-Filho JC, Asquith DL, Michels C, Millar NL, Reilly JH, Graham GJ, Liew FY, Miller AM, McInnes IB. IL-33 induces skin inflammation with mast cell and neutrophil activation. Eur J Immunol. 2011; 41(8):2229–2237. [PubMed: 21674479]

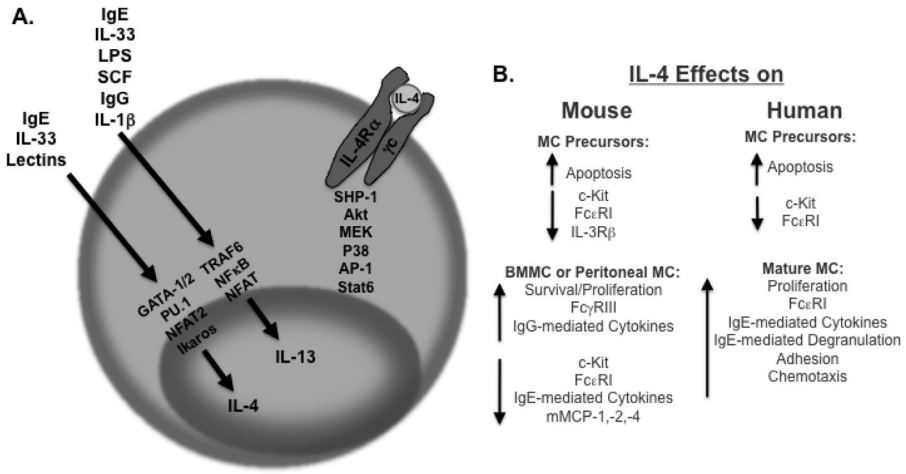

Figure 1.

(A) Summary of factors known to induce mast cell IL-4 or IL-13 expression the signaling pathways required for IL-4/IL-13 induction, and signaling pathways activated by the IL-4 receptor signaling complex. Note that signaling pathways are listed, not depicted as a linked cascade. (B) Summary of IL-4 effects on developing or mature mast cells from mouse or human origin.