Published in final edited form as:
Curr Opin Allergy Clin Immunol. 2014 February ; 14(1): 7–12. doi:10.1097/ACI.0000000000000019.

樹突細胞 c-kit 信號傳導和適應性免疫：對上呼吸道的影響

Dendritic cell c-kit signaling and adaptive immunity: implications for the upper airways

Timothy B. Oriss[a], **Nandini Krishnamoorthy**[b], **Prabir Ray**[a,c], and **Anuradha Ray**[a,c]

[a]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

[b]Brigham and Women's Hospital, Harvard Institute of Medicine, Boston, Massachusetts

[c]Department of Immunology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

Abstract

Purpose of review—Binding of the receptor tyrosine kinase, c-kit, to its ligand, stem cell factor (SCF), mediates numerous biological functions. Important roles for c-kit in hematopoiesis, melanogenesis, erythropoiesis, spermatogenesis, and carcinogenesis are well documented. Similarly, activation of mast cells and eosinophils by c-kit ligation has long been known to result in degranulation with concomitant release of pro-inflammatory mediators including cytokines. This review will highlight a recently discovered function of c-kit in regulating the adaptive immune responses with relevance to allergic diseases.

Recent findings—Recent studies in a number of laboratories including our own highlight the previously unappreciated functions for c-kit in immunological processes. Increased expression of c-kit and its ligand, SCF, on dendritic cells by Th2/Th17-inducing stimuli leads to c-kit activation and immune skewing toward these subsets and away from Th1 responses. Treatment of dendritic cells with inhibitors of c-kit activation such as imatinib mesylate (Gleevec) induces breach of T-cell tolerance, skewing of responses toward Th1, and activation of natural killer cells.

Summary—Taken together, these observations suggest that the c-kit/SCF axis may be a useful target for redirecting deleterious immune responses in various disease settings, including allergic diseases that are often associated with Th2 and Th17 responses.

Keywords

adaptive immunity; c-kit; dendritic cells; SCF

Correspondence to Anuradha Ray, PhD, NW628 MUH, 3459 Fifth Avenue, Pittsburgh, PA 15213, USA. Tel: +1 412 802 3191; fax: +1 412 692 3219; raya@pitt.edu.

Conflicts of interest

The authors declare no conflicts of interest.

This work was supported by the U.S. National Institutes of Health grants HL 077430 and AI 048927 (to A.R.), AI 093116 and AI 100012 (to P.R.), and HL 113956 (to A.R. and P.R.).

INTRODUCTION

The gene encoding the receptor tyrosine kinase, c-kit, was cloned in the late 1980s [1–3]. Like other tyrosine kinase receptors, the extracellular domain of c-kit facilitates the binding of ligand and the cytoplasmic domain transduces signals [2–5]. The c-kit ligand, stem cell factor (SCF), is encoded by the Steel (Sl) locus on chromosome 12 and 10 in humans and mice, respectively [6,7]. SCF exists as a 165 amino acid soluble product (sSCF) or as a 220 amino acid membrane-bound form (mSCF) [8–10]. Proteolytic cleavage of mSCF can yield sSCF [11,12].

c-Kit signaling has profound effects on the biological functions such as spermatogenesis, melanin formation, and erythropoiesis [13,14]. Mutations in c-kit leading to aberrant signaling have been particularly well documented in the case of certain tumors, identifying it as an attractive target for intervention [15■,16■■]. Expression of mSCF versus sSCF has different biological ramifications as evident in our previous [17] and ongoing studies (Oriss et al., unpublished observation). Some cell types can co-express c-kit and SCF, suggesting a self-regulated enhancement of receptor expression [14]. In spite of the significant accumulation of literature related to the c-kit/SCF axis across multiple cell types and biological processes involving varied signaling/regulatory pathways [18■■], our recent work demonstrated previously unappreciated role of this axis in the peripheral immune system with potential applications in immunological therapeutic strategies.

c-KIT HAS IMPORTANT FUNCTIONS IN DIFFERENT CELL TYPES INCLUDING DENDRITIC CELLS

Although highly expressed on hematopoietic stem cells (HSCs) [19,20], most mature cell types lose c-kit, whereas a few such as mast cells, natural killer (NK) cells, and some types of dendritic cells retain its expression [6,14]. c-kit has critical developmental importance, as mice lacking c-kit expression die within 10 days of birth [21]. It appears necessary for myeloid cell development, although it is some-what dispensable for lymphopoiesis [22]. The function of c-kit in mast cell biology is particularly well established [23]. In contrast, SCF is expressed by a wide variety of cells. Although c-kit and SCF can be co-expressed by the same cell type [14,17], HSCs only express c-kit [14,24–26]. Therefore, c-kit$^+$ HSCs engage SCF on other cell types such as stromal fibroblasts during hematopoiesis.

There is a paucity of research on the role of c-kit in dendritic cell biology. Investigations of c-kit function in dendritic cells have lagged because in-vitro development of bone-marrow-derived dendritic cells (BMDCs) from HSCs earmarked c-kit as being stem-cell-specific. These studies [27–29] reported decreased c-kit expression upon dendritic cell development and maturation in line with the general profile of c-kit loss upon HSC differentiation. In fact, tissue dendritic cells do show minimal expression of this receptor. However, Zitvogel and colleagues initially demonstrated that c-kit expression on dendritic cells modulates NK cell function by increasing their cytolytic and IFN-γ-secreting functions. Importantly, it was clearly demonstrated that dendritic cells, rather than mast cells, are the pharmacological target of Gleevec *in vivo* [30]. The demonstration of c-kit functionality in mature, activated

dendritic cells with respect to dendritic cell cytokine production for the first time highlighted an important regulatory role of this molecule in adaptive immune responses [17].

Various lineages of myeloid-type dendritic cells arise from the c-kit-expressing bone marrow precursors [31]. c-Kit blockade reportedly can block full maturation of dendritic cells and macrophages from progenitors [32,33]. Our work has shown that expression of c-kit and SCF by dendritic cells is upregulated by Th2/Th17-inducing stimuli, but not Th1-inducing stimuli [17]. We have shown that c-kit expression promotes IL-6 production by dendritic cells, which in turn supports both Th2 and Th17 development. BMDCs, spleen dendritic cells, and lung dendritic cells upregulated c-kit upon treatment with cholera toxin or house dust mite (HDM) antigen, and this was associated with IL-6 production. Sorted c-kit-expressing dendritic cells induced greater production of Th2/Th17 cytokines from naïve $CD4^+$ T cells than c-kit-negative cells. Furthermore, c-kit-negative dendritic cells promoted the production of the Th1 cytokine, IFN-γ, even following cholera toxin or HDM treatment [17].

We also found that c-kit was important for dendritic cell expression of Jagged-2, a Notch ligand. This is particularly important regarding Th2 generation as although IL-6 promotes the Th2 phenotype, it is not considered a Th2-skewing cytokine. Jagged-2, on the other hand, by virtue of its binding to Notch1 or Notch 2 on T cells, has been associated with Th2 differentiation, although the precise role of the Jagged ligands, 1 and 2, in this regard needs additional investigation [34,35]. Mice with a c-kit mutation were deficient in Jagged-2 and IL-6 expression, leading to reduced Th2/Th17 immune responses [17]. Most significantly, c-kit-deficient dendritic cells were unable to induce experimental airway inflammation upon adoptive transfer into naïve animals.

THE BIOLOGICAL RAMIFICATIONS OF SOLUBLE VERSUS MEMBRANE-BOUND FORM OF STEM CELL FACTOR

mSCF has signaling properties, distinct from sSCF, resulting in varied biological functions [36,37]. Association of c-kit with sSCF results in transient activation of the receptor, whereas mSCF prevents its internalization, thus promoting sustained downstream signaling [38,39]. Expression of mSCF is thought to predominate, suggesting that cell –cell interactions underlie many of the biological functions of c-kit. For example, expression of c-kit is found on most HSCs and their renewal is promoted by SCF^+/c-kit^- fibroblasts [24–26]. Additionally, expression of both is altered during injury, infection, and inflammation, reinforcing the concept that selective expression of both is key in the maintenance of homeostasis. mSCF also provides better support for mast cells than sSCF [40], which is additionally true for $CD34^+$ progenitors. The brain produces high levels of sSCF [10], but upon brain injury, mSCF elevation is important not only for recruiting neural stem cells to the site, but also for activating c-kit, thus contributing to the repair process [41]. We showed that lung dendritic cells in naïve mice express a low level of c-kit, but the expression of both c-kit and mSCF is significantly elevated by allergens causing persistent downstream signaling [17]. Given that both receptor and ligand can be expressed simultaneously under specific conditions, it is critical that co-expression is minimized to prevent inadvertent activation under homeostasis. By the same token, such interactions are an integral part of

development and repair after tissue injury, and must be stringently regulated to prevent adverse effects such as oncogenesis. Given that most studies suggest a role for mSCF in chronic c-kit signaling, it would be interesting to determine how production of mSCF vs. sSCF is regulated in the immune system. This type of information will allow modulation of c-kit signaling by targeting SCF. Gleevec, which inhibits c-kit signaling, also targets other receptor tyrosine kinases and, there-fore, SCF is a more desirable target.

CYCLIC AMP: THE INTRACELLULAR MESSENGER IN c-KIT/STEM CELL FACTOR-INDUCED BIOLOGICAL FUNCTIONS

Recent studies demonstrated a role for the intra-cellular second messenger, cyclic AMP (cAMP), in the expression of both c-kit and SCF. In several cancer cell lines, elevated cAMP, induced by agents such as forskolin, is associated with increased expression of c-kit [42–45]. However, elevated c-kit mediated by cAMP is not solely restricted to tumor cells as was revealed in our study [17] of allergen-induced c-kit expression in dendritic cells. In dendritic cells, increased c-kit expression in response to both cholera toxin and HDM was inhibited by a cAMP antagonist [17]. Similarly, treatment with forskolin or cholera toxin promoted c-kit expression in human ovarian carcinoma cell lines, which constitutively express SCF [45]. In keeping with the antiproliferative effects of cAMP, increased intracellular cAMP in these cells inhibited cell proliferation independently of c-kit expression. Interestingly, cAMP also directly activates the SCF promoter in Sertoli cells. An unidentified cAMP-induced factor binds the SCF promoter resulting in increased SCF expression [46]. As c-kit plays an important role in the development of various cell types, cAMP may play a dual role in upregulating c-kit/SCF expression and promoting cell differentiation.

c-KIT SIGNALING IN DENDRITIC CELLS AND CYTOKINE BALANCE

An immune response is a highly orchestrated event involving several key players and cross-regulated pathways, which are essential for mounting a balanced innate and adaptive response toward a foreign antigen or a danger signal generated within the host.

Induction of an immune response mediated by dendritic cells is inherently tied to the nature of the antigen and the cytokine response it elicits in dendritic cells and in other cell types that help T-cell priming. IL-12 production favors Th1 development, but a low level of IL-12 facilitates Th2 [47] or Th17 response [48] depending on the stimulus. Although mechanisms to subvert a Th1 response involve direct inhibition of IL-12, the pathways that promote a Th2 response are very diverse. This diversity likely contributes to the challenge in developing immunologically based therapies for allergies or asthma. Unlike IL-12, a counterpart cytokine released from dendritic cells that uniquely promotes Th2 response has not been identified. IL-6 produced by dendritic cells in response to allergens or adjuvants such as cholera toxin [49,50] has been shown to be a strong stimulus for the development of a Th17 response [51,52]. Dendritic-cell-produced IL-23, however, is essential for commitment to the Th17 phenotype [53,54]. It remains to be seen whether the production of IL-23, like that of IL-6 [17], is also regulated by the c-kit/SCF axis.

It is important to note that in our study, cholera toxin and HDM promoted the expression of c-kit on lung dendritic cells and neither of these Th2/Th17-promoting stimuli has been shown to elicit responses via TLRs. This is significant as it assigns specificity to c-kit for the induction of Th2/Th17 responses, given that a potent Th1-promoting agent like CpG oligodeoxynucleotide (ODN) was unable to upregulate the expression of c-kit on dendritic cells [17]. Low level of c-kit in naïve lung dendritic cells coupled with reduced expression following stimulation with CpG ODN suggests an evolutionary protection aimed at preventing the unwarranted immune responses. Inhibition of c-kit function via Gleevec reversed the established tolerance to tumors by significantly elevating IL-12 levels in dendritic cells, thereby promoting T-cell IFN-γ production highlighting the immunomodulatory function of c-kit [55]. This observation suggested a possible role for c-kit-triggered phosphoinositide 3 (PI3) kinase activation in inhibiting TLR-mediated IL-12 production [55].

Activation of PI3 kinase is an important event for Th2/Th17 responses via c-kit signaling in dendritic cells. PI3 kinase serves the dual purpose of blocking IL-12 and promoting IL-6 production [56]. This positive feedback loop is amplified as IL-6 is also known to antagonize IL-12 [57,58] and mice deficient in IL-6 have increased IFN-γ production from T cells [58]. Reduced levels of AKT phosphorylation in dendritic cells from c-kit mutant mice [17] and the established importance of the PI3 kinase pathway in promoting Notch-mediated signaling in the setting of various tumors [59] led us to speculate that the PI3 kinase pathway is an important regulator of Notch ligand expression in dendritic cells. It seems likely that PI3 kinase activation promotes the expression of Jagged-2 favoring a Th2 response and the inhibition of this pathway facilitates the expression of the Th1-promoting Notch ligand, delta-4 [35,59,60]. Conversely, CD40 activation on dendritic cells by Th1-inducing agents like LPS or CpG ODN specifically promotes IL-12 production [61]. It is important to note that signaling events downstream of CD40 remain to be better elucidated, although studies have dissected the key molecules involved in IL-12 production. For example, dampening of PI3 kinase coupled with low-level AKT phosphorylation promotes IL-12 [56]. Mice deficient in PI3-kinase activation have increased IL-12 production, which leads to deleterious effects like development of inflammatory bowel disorder [62,63]. Hence, it is possible that a mechanism by which CD40 mediates a Th1 response is by negatively regulating PI3 kinase, thereby promoting IL-12. Again, this implies that activation of c-kit in dendritic cells by allergen or cholera toxin promotes the activation of PI3 kinase thus inhibiting IL-12 production [17], while simultaneously promoting IL-6 [17,56,64,65]. Synergistic cooperation between the PI3 kinase pathway and Src kinases has been associated with c-kit signaling [66], which may play a role in promoting IL-6 and limiting IL-12 production. Collectively, data from our studies and those of others show a central role for c-kit signaling in dendritic cells as a switch in regulating the IL-6/IL-12 cytokine balance, thereby influencing the nature of the adaptive immune response.

c-KIT AND IMPLICATIONS IN UPPER AIRWAY DISEASE

A great deal has been written regarding the involvement of c-kit in a number of disease conditions [15■,18■■]. Not surprisingly, given the importance of c-kit in mast cell functions, much of the literature on c-kit is focused on the role mast cells play in relation to

the efficacy of c-kit-targeted interventions. The c-kit/SCF axis in mast cells is known to be active in wound healing, and the condition of mastocytosis actually represents an abnormal manifestation of this normal process [29]. Other conditions characterized by mast cell accumulation such as allergic rhinitis, asthma, and rheumatoid arthritis respond favorably to the blockade of c-kit/SCF via agents such as Gleevec or neutralizing antibodies [14]. A part of the beneficial effects of Gleevec or of neutralizing antibodies can be attributed to the inhibition of production of inflammatory mediators by mast cells, as well as by eosinophils, which are also important in the pathogenesis of asthma [67–72]. It is interesting to note in this context that cigarette smoke exposure downregulates c-kit expression in developing mast cells and among other cytokines also inhibits the production of IL-6 by these cells [73■■]. Undoubtedly, c-kit has an important role in the mast cell development and function that impacts allergic responses. However, our description of a regulatory effect of mSCF-triggered persistent c-kit signaling on cytokine balance in dendritic cells highlights a central role of this molecule in the priming of an allergen-specific T-cell response, which would ultimately contribute to building allergen-specific memory T cells [17]. Therefore, inhibition of c-kit signaling should have long-term effects beyond acute beneficial effects stemming from inhibition of mast cell/eosinophil degranulation and production of inflammatory mediators. Given that the expression of mSCF can be modulated by proteases [11,12], cleavage of mSCF might be expected to reduce Th2/Th17 responses.

CONCLUSION

It is interesting to speculate about what it might mean for the efficacy of dendritic-cell-based biologic therapies involving cells which do or do not express c-kit, or variants thereof [16■■] to redirect the immune response in a manner tailored to the particular disease. In contrast, the idea of regulating SCF in order to modulate c-kit signaling in the context of the airways is completely untapped. Steinman [74] wrote about the multifaceted, multifunctional nature of dendritic cells as being essentially a largely untapped reserve of promise for the development of vaccines and other dendriticcell-based biological disease-modifying strategies. Clearly, the major challenges are how to bring observations made at the bench to the bedside. In this regard, we highlight the c-kit/SCF module as a promising target against which to direct future therapies for allergic diseases such as asthma and rhinitis.

Acknowledgments

None.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■■ of outstanding interest

1. Besmer P, Murphy JE, George PC, et al. A new acute transforming feline retrovirus and relationship of its oncogene v-kit with the protein kinase gene family. Nature. 1986; 320:415–421. [PubMed: 3007997]
2. Qiu FH, Ray P, Brown K, et al. Primary structure of c-kit: relationship with the CSF-1/PDGF receptor kinase family – oncogenic activation of v-kit involves deletion of extracellular domain and C terminus. EMBO J. 1988; 7:1003–1011. [PubMed: 2456920]
3. Yarden Y, Kuang WJ, Yang-Feng T, et al. Human proto-oncogene c-kit: a new cell surface receptor tyrosine kinase for an unidentified ligand. EMBO J. 1987; 6:3341–3351. [PubMed: 2448137]
4. Schlessinger J. Cell signaling by receptor tyrosine kinases. Cell. 2000; 103:211–225. [PubMed: 11057895]
5. Blume-Jensen P, Hunter T. Oncogenic kinase signalling. Nature. 2001; 411:355–365. [PubMed: 11357143]
6. Besmer P. The kit ligand encoded at the murine Steel locus: a pleiotropic growth and differentiation factor. Curr Opin Cell Biol. 1991; 3:939–946. [PubMed: 1726043]
7. Geissler EN, Liao M, Brook JD, et al. Stem cell factor (SCF), a novel hematopoietic growth factor and ligand for c-kit tyrosine kinase receptor, maps on human chromosome 12 between 12q14.3 and 12qter. Somat Cell Mol Genet. 1991; 17:207–214. [PubMed: 1707188]
8. Flanagan JG, Chan DC, Leder P. Transmembrane form of the kit ligand growth factor is determined by alternative splicing and is missing in the Sld mutant. Cell. 1991; 64:1025–1035. [PubMed: 1705866]
9. Toksoz D, Zsebo KM, Smith KA, et al. Support of human hematopoiesis in long-term bone marrow cultures by murine stromal cells selectively expressing the membrane-bound and secreted forms of the human homolog of the steel gene product, stem cell factor. Proc Natl Acad Sci USA. 1992; 89:7350–7354. [PubMed: 1380155]
10. Huang EJ, Nocka KH, Buck J, et al. Differential expression and processing of two cell associated forms of the kit-ligand: KL-1 and KL-2. Mol Biol Cell. 1992; 3:349–362. [PubMed: 1378327]
11. Majumdar MK, Feng L, Medlock E, et al. Identification and mutation of primary and secondary proteolytic cleavage sites in murine stem cell factor cDNA yields biologically active, cell-associated protein. J Biol Chem. 1994; 269:1237–1242. [PubMed: 7507105]
12. Longley BJ, Tyrrell L, Ma Y, et al. Chymase cleavage of stem cell factor yields a bioactive, soluble product. Proc Natl Acad Sci USA. 1997; 94:9017–9021. [PubMed: 9256427]
13. Ali S, Ali S. Role of c-kit/SCF in cause and treatment of gastrointestinal stromal tumors (GIST). Gene. 2007; 401:38–45. [PubMed: 17659849]
14. Reber L, Da Silva CA, Frossard N. Stem cell factor and its receptor c-Kit as targets for inflammatory diseases. Eur J Pharmacol. 2006; 533:327–340. [PubMed: 16483568]
15. Liang J, Wu YL, Chen BJ, et al. The c-kit receptor-mediated signal transduction and tumor-related diseases. Int J Biol Sci. 2013; 9:435–443. [PubMed: 23678293]

■. This study provides detailed information about the role of c-kit signaling pathways, specifically related to tumor cells. A brief discussion of interventional strategies for the treatment of c-kit$^+$ cancers is also included

16. Phung B, Steingrimsson E, Ronnstrand L. Differential activity of c-kit splice forms is controlled by extracellular peptide insert length. Cell Signal. 2013; 25:2231–2238. [PubMed: 23880320]

■■. Mutations in c-kit have been well described that result in increased intracellular signaling activity (i.e. ‘gain-of-function’ mutations). This work describes two isoforms of c-kit differing by only a tetrapeptide domain in the extracellular region of the molecule with consequences in multiple downstream effects. The existence of such isoforms with varying functional activity could have implications outside of the tumor biology field, in allergy and asthma, for example

17. Krishnamoorthy N, Oriss TB, Paglia M, et al. Activation of c-kit in dendritic cells regulates T helper cell differentiation and allergic asthma. Nat Med. 2008; 14:565–573. [PubMed: 18454155]
18. Lennartsson J, Ronnstrand L. Stem cell factor receptor/c-kit: from basic science to clinical implications. Physiol Rev. 2012; 92:1619–1649. [PubMed: 23073628]

■■. This extensive review provides a detailed discussion of small molecule inhibitors that are currently being used to target c-kit function

19. Cambareri AC, Ashman LK, Cole SR, et al. A monoclonal antibody to a human mast cell/myeloid leukaemia-specific antigen binds to normal haemopoietic progenitor cells and inhibits colony formation in vitro. Leuk Res. 1988; 12:929–939. [PubMed: 3146004]
20. Ashman LK, Cambareri AC, To LB, et al. Expression of the YB5.B8 antigen (c-kit proto-oncogene product) in normal human bone marrow. Blood. 1991; 78:30–37. [PubMed: 1712644]
21. Russell ES. Hereditary anemias of the mouse: a review for geneticists. Adv Genet. 1979; 20:357–459. [PubMed: 390999]
22. Ogawa M, Matsuzaki Y, Nishikawa S, et al. Expression and function of c-kit in hemopoietic progenitor cells. J Exp Med. 1991; 174:63–71. [PubMed: 1711568]
23. Grimbaldeston MA, Chen CC, Piliponsky AM, et al. Mast cell-deficient W-sash c-kit mutant Kit W-sh/W-sh mice as a model for investigating mast cell biology in vivo. Am J Pathol. 2005; 167:835–848. [PubMed: 16127161]
24. Bowie MB, Kent DG, Copley MR, et al. Steel factor responsiveness regulates the high self-renewal phenotype of fetal hematopoietic stem cells. Blood. 2007; 109:5043–5048. [PubMed: 17327414]
25. Ikuta K, Weissman IL. Evidence that hematopoietic stem cells express mouse c-kit but do not depend on steel factor for their generation. Proc Natl Acad Sci USA. 1992; 89:1502–1506. [PubMed: 1371359]
26. Nocka K, Buck J, Levi E, et al. Candidate ligand for the c-kit transmembrane kinase receptor: KL, a fibroblast derived growth factor stimulates mast cells and erythroid progenitors. EMBO J. 1990; 9:3287–3294. [PubMed: 1698611]
27. Feng B, Inaba M, Lian Z, et al. Development of mouse dendritic cells from lineage-negative c-kit(low) pluripotent hemopoietic stem cells in vitro. Stem Cells. 2000; 18:53–60. [PubMed: 10661572]
28. Lian Z, Feng B, Sugiura K, et al. c-kit<low Pluripotent hemopoietic stem cells form CFU-S on day 16. Stem Cells. 1999; 17:39–44. [PubMed: 10215400]
29. Orfao A, Garcia-Montero AC, Sanchez L, et al. Recent advances in the understanding of mastocytosis: the role of KIT mutations. Br J Haematol. 2007; 138:12–30. [PubMed: 17555444]
30. Borg C, Terme M, Taieb J, et al. Novel mode of action of c-kit tyrosine kinase inhibitors leading to NK cell-dependent antitumor effects. J Clin Invest. 2004; 114:379–388. [PubMed: 15286804]
31. Del Rio ML, Rodriguez-Barbosa JI, Bolter J, et al. $CX3CR1^{+}$ $c\text{-}kit^{+}$ bone marrow cells give rise to $CD103^{+}$ and $CD103^{-}$ dendritic cells with distinct functional properties. J Immunol. 2008; 181:6178–6188. [PubMed: 18941208]
32. Appel S, Boehmler AM, Grunebach F, et al. Imatinib mesylate affects the development and function of dendritic cells generated from $CD34^{+}$ peripheral blood progenitor cells. Blood. 2004; 103:538–544. [See comment]. [PubMed: 14504105]
33. Dewar AL, Domaschenz RM, Doherty KV, et al. Imatinib inhibits the in vitro development of the monocyte/macrophage lineage from normal human bone marrow progenitors. Leukemia. 2003; 17:1713–1721. [PubMed: 12970769]
34. Amsen D, Blander JM, Lee GR, et al. Instruction of distinct CD4 T helper cell fates by different notch ligands on antigen-presenting cells. Cell. 2004; 117:515–526. [PubMed: 15137944]
35. Amsen D, Antov A, Flavell RA. The different faces of Notch in T-helper-cell differentiation. Nat Rev Immunol. 2009; 9:116–124. [PubMed: 19165228]
36. Brannan CI, Lyman SD, Williams DE, et al. Steel-Dickie mutation encodes a c-kit ligand lacking transmembrane and cytoplasmic domains. Proc Natl Acad Sci USA. 1991; 88:4671–4674. [PubMed: 1711207]
37. Massague J, Pandiella A. Membrane-anchored growth factors. Annu Rev Biochem. 1993; 62:515–541. [PubMed: 8394682]
38. Kurosawa K, Miyazawa K, Gotoh A, et al. Immobilized anti-KIT monoclonal antibody induces ligand-independent dimerization and activation of Steel factor receptor: biologic similarity with membrane-bound form of Steel factor rather than its soluble form. Blood. 1996; 87:2235–2243. [PubMed: 8630383]
39. Miyazawa K, Williams DA, Gotoh A, et al. Membrane-bound Steel factor induces more persistent tyrosine kinase activation and longer life span of c-kit gene-encoded protein than its soluble form. Blood. 1995; 85:641–649. [PubMed: 7530502]

40. Mierke CT, Ballmaier M, Werner U, et al. Human endothelial cells regulate survival and proliferation of human mast cells. J Exp Med. 2000; 192:801–811. [PubMed: 10993911]
41. Sun L, Lee J, Fine HA. Neuronally expressed stem cell factor induces neural stem cell migration to areas of brain injury. J Clin Invest. 2004; 113:1364–1374. [PubMed: 15124028]
42. Hou L, Panthier JJ, Arnheiter H. Signaling and transcriptional regulation in the neural crest-derived melanocyte lineage: interactions between KIT and MITF. Development. 2000; 127:5379–5389. [PubMed: 11076759]
43. Leslie MC, Bar-Eli M. Regulation of gene expression in melanoma: new approaches for treatment. J Cell Biochem. 2005; 94:25–38. [PubMed: 15523674]
44. Poole DP, Van Nguyen T, Kawai M, et al. Protein kinases expressed by interstitial cells of Cajal. Histochem Cell Biol. 2004; 121:21–30. [PubMed: 14658070]
45. Shaw TJ, Keszthelyi EJ, Tonary AM, et al. Cyclic AMP in ovarian cancer cells both inhibits proliferation and increases c-KIT expression. Exp Cell Res. 2002; 273:95–106. [PubMed: 11795950]
46. Grimaldi P, Capolunghi F, Geremia R, et al. Cyclic adenosine monophosphate (cAMP) stimulation of the kit ligand promoter in Sertoli cells requires an Sp1-binding region, a canonical TATA box, and a cAMP-induced factor binding to an immediately downstream GC-rich element. Biol Reprod. 2003; 69:1979–1988. [PubMed: 12904318]
47. Kapsenberg ML. Dendritic-cell control of pathogen-driven T-cell polarization. Nat Rev Immunol. 2003; 3:984–993. [PubMed: 14647480]
48. Khayrullina T, Yen JH, Jing H, et al. In vitro differentiation of dendritic cells in the presence of prostaglandin E2 alters the IL-12/IL-23 balance and promotes differentiation of Th17 cells. J Immunol. 2008; 181:721–735. [PubMed: 18566439]
49. De Jong EC, Vieira PL, Kalinski P, et al. Microbial compounds selectively induce Th1 cell-promoting or Th2 cell-promoting dendritic cells in vitro with diverse th cell-polarizing signals. J Immunol. 2002; 168:1704–1709. [PubMed: 11823500]
50. Kalinski P, Lebre MC, Kramer D, et al. Analysis of the $CD4^+$ T cell responses to house dust mite allergoid. Allergy. 2003; 58:648–656. [PubMed: 12823126]
51. Acosta-Rodriguez EV, Napolitani G, Lanzavecchia A, et al. Interleukins 1beta and 6 but not transforming growth factor-beta are essential for the differentiation of interleukin 17-producing human T helper cells. Nat Immunol. 2007; 8:942–949. [PubMed: 17676045]
52. Bettelli E, Carrier Y, Gao W, et al. Reciprocal developmental pathways for the generation of pathogenic effector Th17 and regulatory T cells. Nature. 2006; 441:235–238. [PubMed: 16648838]
53. Ghoreschi K, Laurence A, Yang XP, et al. Generation of pathogenic T(H)17 cells in the absence of TGF-beta signalling. Nature. 2010; 467:967–971. [PubMed: 20962846]
54. McGeachy MJ, Chen Y, Tato CM, et al. The interleukin 23 receptor is essential for the terminal differentiation of interleukin 17-producing effector T helper cells in vivo. Nat Immunol. 2009; 10:314–324. [PubMed: 19182808]
55. Wang H, Cheng F, Cuenca A, et al. Imatinib mesylate (STI-571) enhances antigen-presenting cell function and overcomes tumor-induced $CD4^+$ T-cell tolerance. Blood. 2005; 105:1135–1143. [PubMed: 15454486]
56. Fukao T, Tanabe M, Terauchi Y, et al. PI3K-mediated negative feedback regulation of IL-12 production in DCs. Nat Immunol. 2002; 3:875–881. [PubMed: 12154357]
57. La Flamme AC, MacDonald AS, Pearce EJ. Role of IL-6 in directing the initial immune response to schistosome eggs. J Immunol. 2000; 164:2419–2426. [PubMed: 10679078]
58. Dienz O, Rincon M. The effects of IL-6 on CD4 T cell responses. Clin Immunol. 2009; 130:27–33. [PubMed: 18845487]
59. Hambardzumyan D, Becher OJ, Holland EC. Cancer stem cells and survival pathways. Cell Cycle. 2008; 7:1371–1378. [PubMed: 18421251]
60. Schaller MA, Neupane R, Rudd BD, et al. Notch ligand Delta-like 4 regulates disease pathogenesis during respiratory viral infections by modulating Th2 cytokines. J Exp Med. 2007; 204:2925–2934. [PubMed: 17998388]

61. Schulz O, Edwards AD, Schito M, et al. CD40 triggering of heterodimeric IL-12 p70 production by dendritic cells in vivo requires a microbial priming signal. Immunity. 2000; 13:453–462. [PubMed: 11070164]
62. Patton DT, Garden OA, Pearce WP, et al. Cutting edge: the phosphoinositide 3-kinase p110 delta is critical for the function of $CD4^+CD25^+Foxp3^+$ regulatory T cells. J Immunol. 2006; 177:6598–6602. [PubMed: 17082571]
63. Okkenhaug K, Bilancio A, Farjot G, et al. Impaired B and T cell antigen receptor signaling in p110delta PI 3-kinase mutant mice. Science. 2002; 297:1031–1034. [PubMed: 12130661]
64. Ganesan LP, Joshi T, Fang H, et al. FcgammaR-induced production of superoxide and inflammatory cytokines is differentially regulated by SHIP through its influence on PI3K and/or Ras/Erk pathways. Blood. 2006; 108:718–725. [PubMed: 16543474]
65. Zhang J, Li Y, Shen B. PI3-K/Akt pathway contributes to IL-6-dependent growth of 7TD1 cells. Cancer Cell Int. 2003; 3:1. [PubMed: 12633505]
66. Ronnstrand L. Signal transduction via the stem cell factor receptor/c-Kit. Cell Mol Life Sci. 2004; 61:2535–2548. [PubMed: 15526160]
67. Berlin AA, Lincoln P, Tomkinson A, et al. Inhibition of stem cell factor reduces pulmonary cytokine levels during allergic airway responses. Clin Exp Immunol. 2004; 136:15–20. [See comment]. [PubMed: 15030509]
68. Berlin AA, Hogaboam CM, Lukacs NW. Inhibition of SCF attenuates peribronchial remodeling in chronic cockroach allergen-induced asthma. Lab Invest. 2006; 86:557–565. [PubMed: 16607380]
69. Campbell E, Hogaboam C, Lincoln P, et al. Stem cell factor-induced airway hyperreactivity in allergic and normal mice. Am J Pathol. 1999; 154:1259–1265. [PubMed: 10233863]
70. Lukacs NW, Kunkel SL, Strieter RM, et al. The role of stem cell factor (c-kit ligand) and inflammatory cytokines in pulmonary mast cell activation. Blood. 1996; 87:2262–2268. [PubMed: 8630386]
71. Lukacs NW, Strieter RM, Lincoln PM, et al. Stem cell factor (c-kit ligand) influences eosinophil recruitment and histamine levels in allergic airway inflammation. J Immunol. 1996; 156:3945–3951. [PubMed: 8621935]
72. Oliveira SH, Lukacs NW. Stem cell factor: a hemopoietic cytokine with important targets in asthma. Curr Drug Targets Inflamm Allergy. 2003; 2:313–318. [PubMed: 14561150]
73. Givi ME, Blokhuis BR, Da Silva CA, et al. Cigarette smoke suppresses the surface expression of c-kit and FcepsilonRI on mast cells. Mediators Inflamm. 2013; 2013:813091. [PubMed: 23476107]

■■. This study shows that cigarette smoke decreases c-kit expression on mast cells and inhibits homing of $c\text{-}kit^+$ progenitors to the lung as well as their subsequent maturation. Whereas dendritic cells were not specifically examined, it is possible that their development and function may be affected as well. Lack of $c\text{-}kit^+$ dendritic cells might help clarify the unexplained association observed between cigarette smoke exposure and decreased atopy in children and teens.

74. Steinman RM. Dendritic cells in vivo: a key target for a new vaccine science. Immunity. 2008; 29:319–324. [PubMed: 18799140]

KEY POINTS

- The c-kit/SCF axis has long been known to be important for the differentiation of hematopoietic stem cells into mature cells of the immune system, but in the periphery it historically has been considered to be most important for mast cell biology.
- Our recent work described a novel role for c-kit upregulation and activation of dendritic cells, leading to the promotion of Th2 and Th17 differentiation impacting airway allergic disease.
- Regulation of c-kit and its ligand, stem cell factor, hold potential for the development of new immunologically based therapeutic strategies to treat allergic conditions as well as some cancers.