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

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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

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Conflicts of interest

The authors declare no conflicts of interest.

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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, therefore, 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.

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■ of special interest

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- . This study shows that cigarette smoke decreases c-kit expression on mast cells and inhibits homing of c-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-kit⁺ dendritic cells might help clarify the unexplained association observed between cigarette smoke exposure and decreased atopy in children and teens.
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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.