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Emerging functions of c-kit and its ligand stem cell factor in dendritic cells:

Regulators of T cell differentiation

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Abstract

The receptor tyrosine kinase, c-kit, and its ligand, stem cell factor (SCF), function in a diverse range of biological functions. The role of c-kit in the maintenance and survival of hematopoietic stem cells and of mast cells is well recognized. c-kit also plays an important role in melanogenesis, erythropoiesis and spermatogenesis. Recent work from our laboratory highlights an important role of c-kit in the regulation of expression of two molecules in dendritic cells (DCs), interleukin-6 (IL-6) and Jagged-2 (a ligand of Notch), which are known to regulate T helper cell differentiation. Our study shows that induction of c-kit expression and its signaling in DCs promotes Th2 and Th17 responses but not Th1 response. c-kit inhibition by imatinib mesylate (Gleevec) in DCs was previously shown to promote natural killer cell activation which may be due to dampening of IL-6 production by the DCs. Since dysregulation of c-kit function has been associated with various disease states including cancer, in this perspective we have focused on known and novel functions of c-kit to include molecules such as IL-6 and Notch that were not previously recognized to be within the purview of c-kit biology. We have also reviewed the differential expression pattern of SCF and c-kit on various cell types and its variation during development or pathology. The recognition of previously unappreciated roles for c-kit will provide better insights into its function within and beyond the immune system and pave the way for developing better therapeutic strategies.

Keywords

c-kit; SCF; interleukin-6; jagged-2; dendritic cells; T cells; differentiation

c-kit and Stem Cell Factor

c-kit is a type III tyrosine kinase receptor that was cloned soon after the identification of the v-kit oncogene as the transforming gene in the Hardy-Zuckerman 4 feline virus.[1–3] It shares strong homology and function to platelet-derived growth factor receptor, and macrophage colony stimulating factor receptor.[4] All type III receptors are characterized by the five immunogloblulin-like domains in the extracellular region, followed by a 70–100 amino acids long intracellular kinase domain. Similar to most tyrosine kinase receptors, the extracellular domain facilitates the binding of the ligand and the cytoplasmic domain serves to transduce the signal.[2,3,5,6] Alternate splicing of murine c-kit mRNA results in two

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isoforms characterized by the presence or absence of a GNNK (glycine-asparagine-asparagine-lysine; residues 510–513) tetrapeptide in the juxtamembrane region of the extracellular domain.[7,8] In humans, the expression of similar splice variants has also been documented. These isoforms of c-kit are expressed in different ratios in various cell types and also differ in their signaling capabilities.[9,10]

Stem Cell Factor, the ligand of c-kit is encoded by the Steel (Sl) locus on chromosome 12 in humans and chromosome 10 in mice.[11,12] Like c-kit, SCF also exhibits two distinct isoforms that arise from alternative splicing of exon 6 of the mRNA.[13,14] The primary translation product of 248 amino acids contains a proteolytic cleavage site encoded by exon 6 and post-translational processing at this site results in the soluble form of SCF comprising 165 amino acid residues.[13–15] In contrast, the membrane-bound SCF, which is 220 amino acid residues long, results from an alternatively spliced mRNA that lacks the proteolytic cleavage site encoded by exon 6, resulting in anchoring of the protein to the membrane. The membrane-bound form may also produce a soluble form by proteolytic cleavage.[16,17] Membrane-bound SCF has signaling properties, distinct from that of the soluble form and this results in varied biological functions mediated by the two isoforms.[18,19]

The binding of SCF induces the homodimerization of the c-kit receptor resulting in the phosphorylation of selective tyrosine residues in c-kit, thereby unmasking docking sites for the Src-homology2 (SH2)-containing signal transducers.[20] Site-specific mutagenesis studies have revealed a hierarchical importance in the phosphorylation of tyrosine residues. Some mutations can completely abrogate c-kit signaling, while others only significantly dampen the overall signaling.[21,22]

The discovery of the c-kit proto-oncogene marked an important milestone in understanding the biology of this receptor that is widely expressed in hematopoietic stem cells (HSC), myeloid progenitor cells, dendritic cells (DCs), mast cell and pro-B and pro-T cells.[2,3] In many cell types, like the B and T cells, the expression of c-kit is lost upon cell differentiation. However, mast cells, natural killer (NK) cells and DCs of the immune system retain their expression of c-kit suggesting an important role for this molecule in these cell types.[11,23] c-kit plays a crucial role in mast cell development, survival and function through interactions with its ligand, SCF.[24–26] Other cell types that express c-kit include melanocytes, germ cells, and interstitial cells of Cajal.[27]

Certain lineages of cells that express c-kit also produce its ligand, SCF, indicating a self-regulated[23] feedback to enhance receptor expression. c-kit signaling has profound effects in various biological functions such as spermatogenesis, melanin formation and erythropoiesis.[23,28] Mutations in c-kit results in the development of various tumors due to aberrant signaling of the receptor, which necessitates a complete understanding of c-kit structure, the initiation of signaling events[2,28] as well as characterization of downstream targets of the receptor.[2,29]

c-kit Signaling Pathway

The involvement of PI3-kinase in c-kit signaling has been extensively characterized. A combination of molecular mutagenesis studies and biochemical analyses has shed light on the relationship between c-kit and PI3-kinase. The p85 regulatory subunit of PI3-kinase specifically associates with phoshorylated tyrosine residue 719 of c-kit, resulting in the recruitment and phosphorylation of protein kinase B (AKT).[30] Transgenic mice harboring a point mutation in the tyrosine residue have revealed the physiological importance of this residue.[31] Substitution of tyrosine with phenyalanine resulted in both reduced spermatogenesis and impaired follicular development. Phosphorylated-AKT enhances the survival and proliferation of the primordial cells and specifically mediates several

downstream functions through NFκB signaling as well as phosphorylation of the pro-apoptotic molecule BAD.[20] Phosphorylation of BAD inhibits the pro-apoptotic function of the molecule, which is one of the reasons why impaired c-kit signaling results in reduced proliferation and survival of several cell types. The c-kit gene maps to the dominant white spotting (W) locus in mice.[32] Mutations in the W locus cause deficiency in melanocytes[25,29,31,33,34] as well as reduced PI3-kinase activity.[35] It is interesting to note that extracellular c-kit mutations result in hyperactivation of c-kit, marked by prolonged PI3-kinase activation and enhanced cell survival and proliferation.[34] In addition to PI3-kinase activation, binding of SCF has been shown to induce activation of multiple additional pathways, including phospholipase C (PLC)-gamma, Src kinase, Janus kinase (JAK)/Signal Transducers and Activators of Transcription (STAT) and mitogen activated protein (MAP) kinase pathways.[23] In a recent study, distinct roles of the Src kinase and the PI3-kinase pathways were noted in regards to c-kit function. Mutation in the Src kinase docking site blocked pro B and pro T cell development while that in the PI3-kinase binding site affected spermatogenesis.[36]

There are mechanisms in place in cells that downregulate c-kit signaling to prevent chronic activation of the receptor, which can promote cancer. Protein kinase C, a known negative regulator of PI3 kinase pathways, phosphorylates residues S741 and S746 and downregulates c-kit signaling.[20,37] This is evident from mutational studies, where substitution of these serine residues to alanine resulted in prolonged c-kit signaling. SOCS1, SOCS6 and SOCS8 bind to c-kit and dampen downstream signaling of the receptor.[33,38,39] Additional negative regulators of c-kit signaling include SHIP[40,41] and the GTPase activating protein neurofibromin-1 (NF-1).[42] Furthermore, ubiquitination of c-kit via Cbl, a ubiquitin ligase, and subsequent proteasomal degradation may be also involved in c-kit downregulation.[43] While chronic activation of c-kit may promote tumorigenesis, loss of function of c-kit can be also deleterious since studies suggest that loss of kit may allow melanoma cells to escape SCF-mediated apoptosis thus allowing tumor growth and metastasis.[44] Thus, deregulation of activation or inhibitory pathways of c-kit has adverse effects, often resulting in tumor formation.

Differential Expression of c-kit and SCF Regulates Biological Functions

The regulation of c-kit signaling is also fine-tuned by whether SCF is expressed in membrane-bound or soluble form. Association of c-kit with soluble SCF results in transient activation of the receptor whereas membrane-bound SCF prevents the internalization of the receptor and promotes sustained downstream activation.[45,46] The expression of membrane-bound form of SCF brings into play cell-cell interactions that underlie many of the biological functions of c-kit. For example, the expression of c-kit but not SCF is found on a significant population of HSCs and the renewal of these cells is promoted by fibroblasts, which express SCF but not the receptor.[47–49] Additionally, the fact that the expression of both ligand and receptor is altered during injury, infection and inflammation reinforces the concept that selective expression of the ligand or the receptor is key in maintaining homeostasis. The brain produces high levels of soluble SCF.[15] However, during brain injury, the level of membrane-bound SCF is elevated which has been shown to be important not only for recruiting neural stem cells to the site of injury, but for also activating c-kit expressed on the stem cells which contributes to the repair process.[50] Our recent study has shown that the expression of c-kit on lung DCs from naïve mice is low, but the expression of both the membrane-bound ligand and receptor is significantly elevated in response to certain allergens causing persistent signaling downstream of c-kit due to cell-cell interactions.[51] Given that both receptor and ligand can be expressed by the same cell type under specific conditions, it is critical that such expression patterns are prevented under homeostatic conditions to minimize inadvertent activation of the receptor. 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. In the setting of cancers, alteration of c-kit function and signaling has been studied extensively in association with gastrointestinal stromal tumors (GIST).[52] In GIST, the gain-of function mutation in exon 11 leads to constitutive activation of the receptor even in the absence of SCF.[52] However, recent studies have demonstrated increased tyrosine phosphorylation of the receptor even in the absence of gain-of function mutations in c-kit in GIST patients, which has also been associated with the presence of membrane-bound SCF expressed by tumor cells.[53] Several other cancers have also shown altered or increased expression of the receptor and ligand suggesting a paracrine or autocrine mechanism that induces an oncogenic signaling cascade in cells.[54]

Recent studies have demonstrated a role for the intracellular second messenger, cyclic AMP (cAMP), in the expression of both c-kit and SCF in different cell types. In several cancer cell lines, an elevated level of cAMP induced by agents such as forskolin has been associated with increased expression of c-kit.[55–58] However, the elevation in c-kit expression mediated by cAMP is not solely restricted to tumor cells as was revealed in our study of allergen-induced c-kit expression in DCs. In DCs, the increase in c-kit expression in response to both mucosal adjuvant cholera toxin (CT) and the allergen house dust mite (HDM) was inhibited by a cAMP antagonist.[51] Similarly, treatment with forskolin or CT promoted c-kit expression in human ovarian carcinoma cell lines, which constitutively express SCF.[58] In keeping with the antiproliferative effects of cAMP, the increase in intracellular cAMP level in these cells inhibited cell proliferation, which was not dependent on c-kit expression. Interestingly, cAMP has been also shown to directly activate the SCF promoter in Sertoli cells. An unidentified cAMP-induced factor has been shown to bind SCF promoter resulting in increased expression of the gene.[59] Since 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 and IL-6

c-kit regulates various biological functions and studies including our own show that c-kit is an important regulator of interleukin-6 (IL-6) production.[51,60,61] This suggests that the biological effects attributed to c-kit may be partly mediated by the pleiotropic cytokine IL-6 that possesses diverse pro- and anti-inflammatory properties.[62] Studies involving mast cells have defined a role for c-kit in regulating IL-6 production. Bone marrow mast cells from c-kit mutant mice displayed reduced IL-6 levels and conversely mice lacking RabGEF1, a negative regulator of c-kit signaling, showed enhanced IL-6 production and sustained phosphorylation of AKT and ERK in mast cells.[60,61] Recently, we have shown that co-expression of c-kit and membrane-bound SCF promotes IL-6 production in dendritic cells (DCs) mediated by the PI3-kinase pathway.[51] Impaired c-kit signaling or AKT activation resulted in a decrease in IL-6 production in DCs in response to allergen or the mucosal adjuvant cholera toxin (CT). When stimulated with CT, DCs from mice expressing a catalytically inactive form of the p110δ subunit of PI3-kinase were substantially impaired in IL-6 production.[51] The residual IL-6 production in these DCs was probably due to functional MAP kinase pathway, which can also activate NFκB resulting in IL-6 production.[63]

A well-documented role for IL-6 is its ability to inhibit IL-12 production.[64–66] Several lines of studies have now established that IL-12$^{-/-}$ mice are prone to formation of several tumors and administration of IL-12 mitigates tumor growth.[67,68] Hence, the ratio of the signaling molecules downstream of IL-6 and IL-12, STAT-3 and STAT-4 respectively, in tumor cells during their genesis can influence tumor progression.[69] It is also interesting to note that

while the PI3 kinase pathway promotes IL-6 production, it negatively regulates IL-12 gene expression.[70] In summary, dysregulated c-kit signaling in tumors resulting in continuous activation of the AKT or MAP kinase pathway could contribute to the high levels of IL-6 observed in these cancers. Also, IL-6, via prolonged activation of STAT-3 and concomitant suppression of IL-12, could further accelerate tumor growth.

Several adapter proteins have been associated with PI3-kinase signaling and a significant body of research has focused on adapter molecule, Gab2. Gab2 is an important activator of PI3-kinase and Gab2-deficient mice show reduced airway inflammation, decreased IL-6 production and a reduction in mast cells.[71] This study highlighted the role of c-kit-mediated signaling via PI3-kinase and Gab-2 in IL-6 production. Gab-2 is also a limiting signaling component in the MAP kinase pathway[72] underscoring the importance of this molecule in the fine-tuning of IL-6 gene expression.

In the area of stem cells, a relationship between c-kit and IL-6 has not been adequately explored, even though pivotal roles for these two molecules in regulating stem cell renewal has been documented in several studies. In a model of myocardial infarction, c-kit$^+$ stem cells from the bone marrow were recruited to the heart to repair myocardial injury.[73] In addition, c-kit receptor mutant mice were found to be less efficient in the mobilization of these stem cells.[73] Similarly, IL-6 also acts as a trigger in recruiting myocardial stem cells to the heart, and a recent study profiling early gene activation following myocardial infarction showed a 420-fold increase in IL-6 expression that was maintained for 28 days following the procedure. This strengthens the role of IL-6 as a cytokine involved in stem cell renewal and proliferation, but not necessarily as an inflammatory cytokine.[74] Although STAT-3 is activated by IL-6, the transcription factor, hypoxia inducible factor-1α (HIF-1α), can be also activated via IL-6.[75] Studies have documented HIF-1α to be responsible for the recruitment and stabilization of neural stem cells.[76] It is tempting to speculate that the deficient mobilization of neural and myocardial stem cells to the site of injury in c-kit mutant mice is a result of impaired IL-6 production and, in turn, reduced HIF-1α activation. Intriguingly, a recent study has suggested that HIF-1α can activate the SCF promoter and SCF production in breast cancer cells was found to increase significantly upon overexpression of HIF-1α.[77] Collectively, these studies suggest that the convergence of signaling events triggered upon c-kit activation influences the balance between cell division and cell death.

c-kit and Notch in Hematopoietic Stem Cells and Progenitors

Kit-mediated signal transduction is critical for the normal development and survival of haematopoietic progenitor cells.[78,79] However, expression of c-kit is generally lost during hematopoietic cell differentiation.[24] Similar to c-kit, the protein Notch is also expressed by HSCs.[80,81] Notch is a transmembrane protein and has 4 members, Notch 1–4 that interact with the ligands, Jagged-1, Jagged-2, Delta-like 1, 3 and 4 that are also expressed on the cell surface.[80,81] Thus, cell-cell interaction is also involved in Notch activation, which leads to a stepwise proteolytic processing of Notch to Notch intracellular domain (NICD).[80,81] NICD then translocates to the nucleus where it interacts with the DNA-binding protein RBP-Jk to induce target gene transcription via recruitment of histone acetylases and transcriptional coactivators such as Mastermind.[80,81] During fetal and adult development, expression of Notch continues in the proliferative layers of several mature tissues. There is considerable interest in the events that trigger Notch-Notch ligand interactions but relative concentrations appear to play an important role in deciding whether interactions occur inter- or intracellularly.[80,81] More importantly, Notch ligands have been associated with both activation and inhibition of Notch signaling. Notch is involved in cell fate decisions. Somite formation in vertebrates provides an excellent example of Notch behaving as a

transcriptional oscillator.[82,83] Thus, repetitive cycles of Notch activation and inactivation cause specific pattern formation and segmental boundary in the presomitic mesoderm. High levels of ligand have been shown to inhibit Notch signaling while lower levels promote Notch activation. This mechanism was initially appreciated in Drosophila during wing development.[84,85] In higher eukaryotes, Delta-like 3 in the Xenopus appears to only exert inhibitory activity.[86] In humans, it has been suggested that high levels of Delta expression during keratinocyte differentiation could act as an inhibitory mechanism of Notch signaling to maintain stem cell population.[87] The detailed mechanisms responsible for the inhibitory effects are unclear although intercellular ligand-ligand interactions as well as intracellular receptor titration by ligand have been proposed.[88]

Recent studies suggest functional interaction between c-kit and Notch pathways. Using a Pax-5-deficient pro-B cell line blocked in its B cell potential, as well as a bone-marrow-derived lymphoid and myeloid progenitor, it was shown that Notch signaling rapidly upregulates c-kit expression which was required for T cell development.[89] However, the development of non-T cells (NK or myeloid) was found to be c-kit-independent.[89] In tissue culture, Lin-Sca-1^{+}c-kit^{+} murine HSCs stimulated by Flt3 ligand, interleukin-7 and Delta-like 1-expressing OP-9 fibroblasts undergo de novo T cell development.[90] In subsequent studies, however, conditional deletion of Delta-like 1 was found to block the development of marginal zone B cells but did not impair T cell development.[91] In the developing nervous system, c-kit signaling is involved in survival, migration, proliferation and differentiation of neural crest precursors.[92,93] In the ciliary epithelium, which is derived from the central nervous system (CNS), c-kit signaling upregulated Notch expression and cooperation between c-kit and Notch was required for the maintenance of neural stem cells.[94]

c-kit and Notch Connection Beyond Hematopoietic Stem Cells

It is clear that the role of c-kit in the regulation of the immune system extends beyond its well-established function in mast cells.[26] A role for c-kit in the function of DCs, the key antigen-presenting cells of the immune system, was largely unappreciated prior to our study investigating mechanisms underlying production of IL-6, a cytokine that promotes Th17 and Th2 development.[51] The HDM and the mucosal adjuvant CT, both of which promote Th2 and Th17 responses, upregulated c-kit expression in DCs causing increased IL-6 production by the cells.[51] In another study, c-kit signaling in DCs was shown to inhibit NK cell activation, which was alleviated by Gleevec resulting in antitumor effects.[95] Gleevec (imatinib mesylate/STI571) is an allosteric inhibitor of c-kit, which is being effectively used in the treatment of different cancers like GIST and chronic myeloid leukemia. Gleevec's mode of action involves inhibition of tyrosine kinase activity of specific receptors including that of c-kit.[96] Although the NK-activating effect of Gleevec mediated by DCs was found to be independent of IL-12,[95] it is possible that inhibition of c-kit by Gleevec resulting in downmodulation of IL-6 production contributed to NK activation since IL-6 has been shown to cause anergy and NK cell dysfunction.[97] In our study linking c-kit to increased IL-6 production, basal Jagged-2 expression was blunted in DCs isolated from c-kit mutant mice which, unlike in DCs isolated from wild-type mice, could not be upregulated by CT.[51] Unlike CT, the Th1-promoting adjuvant, CpG oligodeoxy-nucleotide, inhibited Jagged-2 expression but promoted expression of Delta-like 4, which inhibits Th2 and promotes Th1 development. The expression of Delta-like 4 or Jagged-1 was not affected by lack of functional c-kit in the DCs. This study showed that both basal and induced Jagged-2 expression is dependent on c-kit in DCs. In additional studies, Jagged-2 expression has been shown to be upregulated under Th2-inducing conditions.[98,99]

The relationship between c-kit and Jagged-2 and increased IL-6 production revealed in our study was similar to observations of Jagged-2-promoted IL-6 secretion from malignant

plasma cells from multiple myeloma (MM) patients that may involve paracrine or autocrine mechanisms.[100,101] MM is a plasma cell malignancy associated with increased accumulation of monoclonal plasma cells in the bone marrow. Interestingly, while MM is characterized by increased IL-6 secretion which functions as an autocrine growth factor for these cells, ~30% of MM patients also express c-kit. c-kit is not expressed by plasma cells present in healthy individuals. Although expression of c-kit was associated with better prognosis in MM in one study,[102] a different study has shown that MM cells with expression of the c-kit isoform lacking the GNNK tetrapeptide in its juxtamembrane domain are more resistant to the anti-myeloma drugs, bortezomin and melphalan.[103] In both $GNNK^+$ and $GNNK^-$ MM cells, SCF promoted Akt phosphorylation although the kinetics and duration of phosphorylation were different between cells expressing the 2 isoforms.[103] Activation of ERK1/2 was low in response to SCF in both types of cells and explained the weak mitogenic effect of SCF on MM cells in general.[103] Another Phase II clinical trial with Gleevec found limited therapeutic effect of this drug in MM.[104] These studies suggest that the function of c-kit in different cell types may depend on the specific isoform of c-kit expressed by the cell. It will be interesting to determine whether $c\text{-}kit^+$ plasma cells in MM patients exhibit increased Jagged-2 expression and also whether Jagged-2 expression is related to a specific isoform of c-kit. Thus, the success of therapies targeting c-kit in specific malignancies may depend on which isoform of c-kit is expressed in an individual. In GIST, where Gleevec has met with better success, the GNNK form of c-kit may be more prevalent.

While a role for c-kit in Jagged-2 expression was not recognized until recently, co-expression of c-kit and Jagged-2 was noted in other contexts in previous studies. For example, hematopoietic progenitors were shown to express c-kit and Jagged-2,[105] and the latter promoted survival and proliferation of the progenitors and their development into NK cells.[106] It is interesting that c-kit can promote both development and activation of NK cells. Jagged-2 is expressed in multiple tissues in adult mice and homozygous Jagged-2 mutant mice display limb and craniofacial deformities along with altered T cell receptor (TCR) αβ/γδ ratios.[107] Jagged-2-expressing mobilized $Lin\text{-}Sca\text{-}1^+c\text{-}kit^+$ hematopoietic progenitor cells, unlike HSCs, can directly promote expansion of $CD4^+CD25^+Foxp3^+$ T regulatory (Treg) cells and this was found to be associated with Notch signaling.[108] In an earlier study, Jagged-1 overexpressing antigen-presenting cells when adoptively transferred into mice induced tolerance in the recipients.[109] Collectively, these reports beg the question as to why c-kit and Jagged-2 in one context promotes Th2/Th17 but induces Tregs/immunesuppression in another. Although the reason is unclear at the present time, based on prior literature it may be speculated that the level of Jagged-2 expression in a DC or hematopoietic progenitor cell dictates immune activation versus suppression. It will be also important to determine why c-kit specifically influences Jagged-2 expression. One possible reason is to utilize Jagged-2 in cell survival and maintenance of a specific phenotype based on recent findings.[103,106]

Perspective

Among tyrosine kinase receptors, c-kit ranks high as a regulator of a broad spectrum of biological functions. Recent discoveries involving c-kit continue to provide insights into the diverse roles of this receptor.[51,95] The cardinal rule for tyrosine kinase receptor activation is that phosphorylation and dephosphorylation should be stringently regulated. Dysregulation in either of these key events leads to altered function of the receptor. While c-kit function has been best studied in the context of mast cell biology, recent studies including our own highlight additional functions of this receptor in the immune system particularly in DC function.[51,95] Harnessing the potential of these DCs in immunotherapy could lead to treatments for many tumors as well as to combat viral infections, both of which require significantly high levels of IFNγ to activate the cytolytic CD8 T cells. In future studies, it

will be also important to evaluate the proliferative and differentiation potential of HSCs under conditions of constitutive c-kit expression. Stem cells isolated from patients with persistent c-kit signaling may have high self-renewal potential given that mice with specific c-kit mutations resulting in reduced c-kit activation have been shown to be fertile and viable, but with significantly reduced numbers of HSCs.[110] Stem cells endowed with increased self-renewal capacity arising from specific c-kit mutations could be identified, selected and potentially utilized in the treatment of neurodegenerative diseases like Alzheimer's and Parkinson's. One of the areas in c-kit biology that has not been adequately explored is the function of the different splice forms of c-kit and SCF in different biological contexts. Broadening our understanding of the generation of these splice forms and their signaling abilities will provide better insights into c-kit function and aid in the design of more efficient therapeutic targets.

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Abbreviations

SCF	stem cell factor
DC	dendritic cells
HSC	hematopoietic stem cells
CT	cholera toxin
MM	multiple myeloma

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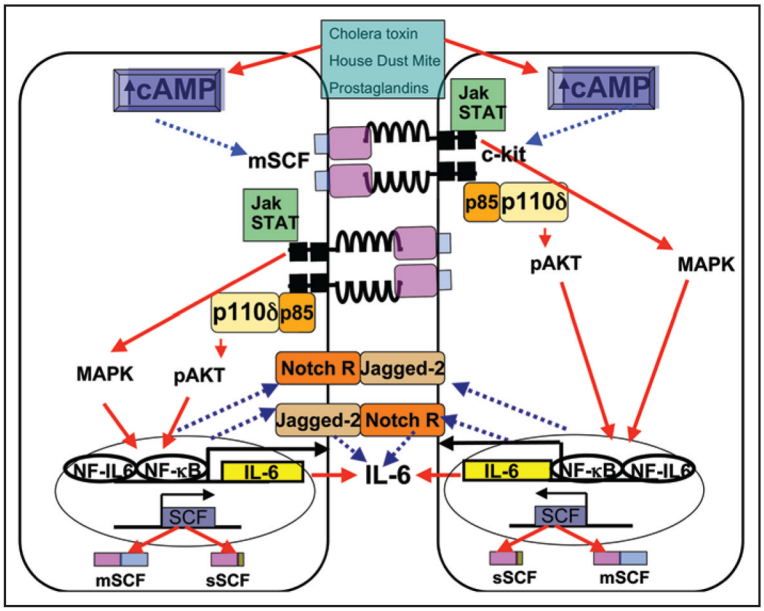

Figure 1.

Dual upregulation of c-kit and membrane-bound SCF (mSCF) on dendritic cells by allergens and allergy-inducing adjuvants promotes IL-6 and Jagged-2 expression. Dendritic cells stimulated with CT, house dust mite or prostaglandins upregulate c-kit and mSCF expression that is mediated by cAMP.[51] c-kit activation by mSCF via cell-cell interactions, triggers sustained downstream activation of the PI3 kinase/AKT pathway[51] and possibly MAPK and JAK-STAT pathways[23] resulting in increased production of IL-6, whose transcription is known to be dependent on NFκB and NF-IL6,[111] and may also involve Notch/Notch ligand. Activation of c-kit also upregulates expression of Jagged-2,[51] and Notch receptors (NotchR).[94] The red arrows show known mechanisms of activation while the broken blue arrows indicate activation pathways for which the mechanisms have yet to be determined.