



HHS Public Access

Author manuscript

J Allergy Clin Immunol. Author manuscript; available in PMC 2023 June 01.

Published in final edited form as:

J Allergy Clin Immunol. 2022 June ; 149(6): 1845–1854. doi:10.1016/j.jaci.2022.04.012.

KIT as a master regulator of the mast cell lineage

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Abstract

The discovery in 1987/1988 and 1990 of the cell-surface receptor KIT and its ligand, stem cell factor (SCF), were critical achievements in efforts to understand the development and function of multiple distinct cell lineages. These include hematopoietic progenitors, melanocytes, germ cells, and mast cells, which all are significantly affected by loss-of-function mutations of *KIT* or *SCF*. Such mutations also influence the development and/or function of additional cells, including those in parts of the CNS and the interstitial cells of Cajal (that control gut motility). Many other cells can express KIT constitutively or during immune responses, including dendritic cells, eosinophils, ILC2 cells, and taste cells. Yet the biological importance of KIT in many of these cell types largely remains to be determined. We here review the history of work investigating mice with mutations affecting the *W* locus (that encodes KIT) or the *S* locus (that encodes SCF), focusing especially on the influence of such mutations on mast cells. We also briefly review efforts to target the KIT/SCF pathway with anti-SCF or anti-KIT antibodies in mouse models of allergic disorders, parasite immunity, or fibrosis in which MCs are thought to play significant roles.

Keywords

Allergic disorders; KIT; mast cells; parasite immunity; stem cell factor (SCF)

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Disclosure Statement: Peter Valent: Consultancy (honoraria): Blueprint, Novartis, Deciphera, Celgene, Incyte; Research Grant: Celgene, Pfizer. The rest of the authors declare that they have no relevant conflicts of interest.

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Introduction

The importance of mutations at both the *W* (white spotting) locus and *Sl* (the steel) locus have interested mouse geneticists for many years¹. Russell is credited with proposing that the *W* locus encoded a receptor for a growth factor needed by melanocytes, germ cells, and hematopoietic cells whereas *Sl* encoded the ligand for that receptor¹. This idea was proposed based in part on the observations that the hematopoietic defects in mice with two mutations at *W*, but not those in mice with two mutations at *Sl* (which also exhibited defects in hematopoiesis), could be repaired by the adoptive transfer of bone marrow cells of the wild type mice¹. By contrast, the transfer of hematopoietic cells from mice with two mutations at *Sl* could repair the defective hematopoiesis expressed in *W* mutant mice¹. Yukihiro Kitamura and colleagues then made the important observations that mice with two loss-of-function mutations at either *W* (i.e., WBB6F1-*W/W^v* mice) or *Sl* (i.e., WCB6F1-*Sl/Sl^d* mice) also were profoundly mast cell (MC) deficient, and that the *W* mutant mice, but not the *Sl* mutant mice, could be cured of their MC deficiency by adoptive transfer of normal hematopoietic stem cells^{2, 3}.

In 1988, the exciting discovery that the receptor Kit⁴ was encoded at *W^{5, 6}* stimulated the efforts of several groups to identify the gene for that receptor's ligand. In 1990, 4 different groups simultaneously reported evidence that the ligand for Kit was encoded by the *Sl* locus⁷⁻¹⁴. Once Kit and its ligand, now known primarily as stem cell factor (SCF), but called Kitl in the mouse, were discovered, many studies ensued probing the mechanism of interactions between Kit and SCF and the effects of SCF on various Kit+ cells. It soon became clear that some cells expressed Kit transiently (such as hematopoietic progenitors, which generally lost Kit expression as the cells matured into various hematopoietic lineages^{15, 16}) whereas other cells, such as MCs, expressed Kit constitutively¹⁵⁻²⁰.

It is now clear that KIT and its ligand participate in the development and function of multiple distinct cell lineages, including hematopoietic progenitors, melanocytes, germ cells, and MCs. Mutations in *Kit* or *SCF (Kitl)* also influence the development and/or function of additional cells, including melanoblasts, some cells in the central nervous system (CNS), and the interstitial cells of Cajal, that control gut motility. We here review the history of work investigating mice with mutations affecting the *W* locus that encodes KIT or the *Sl* locus that encodes SCF, focusing especially on the influence of such mutations on MCs. We also briefly review efforts to target the KIT/SCF pathway with anti-SCF or anti-KIT antibodies in mouse models of allergic disorders, parasite immunity, or fibrosis in which MCs are thought to play major roles.

Mast cell-deficiency in *W* and *Sl* mice

MC-deficient mice were first described in the late 1970s by Yukihiro Kitamura and his colleagues. These studies took advantage of WBB6F1-*W/W^v* mice², that had one *W* allele (on the C57BL/6 background, homozygous *W* mutations were known to be lethal) and one *W^v* allele, which impaired but did not fully eliminate the function of Kit (now known to be the *W* product). They reported that MC numbers in adult WBB6F1-*Kit^{W/W^v}* (*W/W^v*)² and WCB6F1/J-*Kit^{Sl/Sl^d}* (*Sl/Sl^d*)³ mice were <1% of the wild type levels and that the

MC-deficiency in W/W^v mice can be repaired by adoptive transfer of bone marrow cells from wild type² or Sl/Sl^{d3} mice; by contrast, the transfer of wild type bone marrow cells to Sl/Sl^d mice did not restore MCs in these mice. They also found that MCs appeared in the skin of MC-deficient W/W^v mice when it was engrafted onto Sl/Sl^d mice, but not in Sl/Sl^d skin that had been engrafted onto W/W^v mice³.

Findings from these bone marrow transplantation and skin engraftment experiments confirmed the hematopoietic origin of the MC lineage. They also supported Kitamura's hypothesis that the MC-deficiency in W/W^v mice was caused by an intrinsic defect of their MC precursors in the bone marrow, whereas the tissue microenvironment required for proper MC development and differentiation was impaired in Sl/Sl^d mice. In addition to their MC deficiency, W/W^v and Sl/Sl^d mice exhibited remarkably similar phenotypic abnormalities in fertility, pigmentation and hematopoiesis, despite carrying distinct mutations in W and Sl alleles. These observations suggested interactions between gene products of W and Sl alleles, and that such interactions were critically important for the development of germ cells, melanocytes, and hematopoietic cell lineages, including MCs^{1, 21}.

KIT receptor and its ligand SCF

The molecular mechanisms accounting for the abnormal phenotypes of W and Sl mice became clear when their gene products were identified and characterized to have a receptor-ligand relationship. The search for a functional link between W and Sl gene products started with the localization of KIT (CD117) to the W (*Dominant white spotting*) locus in mice by genetic mapping^{5, 6}. KIT is a type III cell surface tyrosine kinase receptor, consisting of 5 immunoglobulin-like extracellular domains, a transmembrane region, and an intracellular tail with tyrosine phosphorylation sites and kinase activity (Fig. 1). KIT is expressed primarily on the progenitors of the reproductive, hematopoietic, and melanogenesis systems (Table 1). While most of the terminally differentiated cells of hematopoietic origin essentially lose KIT expression on their surface, KIT expression remains high on MCs throughout their developmental history^{22, 23}. Nevertheless, some KIT has been detected on the surface of other differentiated cells, including dendritic cells²⁴, eosinophils²⁵, ILC2 cells²⁶ and taste cells²⁷, either constitutively or during immune reactions (Table 1). KIT is also highly expressed in parts of the CNS^{28, 29} and in the interstitial cells of Cajal that control gut motility³⁰ (Table 1).

In just 2 years after the localization of KIT to the W locus, several groups independently identified Sl (*Steel*) encoded SCF as the ligand for KIT⁷⁻¹⁴. SCF is a potent hematopoietic growth factor with strong activities in promoting MC growth⁷⁻¹⁴. SCF is expressed mainly by keratinocytes, fibroblasts, smooth muscle cells and endothelial cells (Table 2). This growth factor supports proliferation, migration, survival, and differentiation of germ cells, melanocytes and hematopoietic cells. SCF maps to chromosome 12 in humans and chromosome 10 in mice and is encoded by 9 exons in both mouse and human. SCF is produced in two main isoforms, SCF²²⁰ and SCF²⁴⁸, by alternative splicing³¹ (Fig. 2). Both SCF²²⁰ and SCF²⁴⁸ isoforms encode membrane-bound SCF, which consists of intracellular, transmembrane and extracellular domains. SCF²⁴⁸ has an additional protease cleavage site that is encoded by exon 6 and that can be cleaved by chymase, metalloprotease 9, and

proteases of the ADAMs family to generate 165 amino acid soluble SCF¹⁶ (Fig. 2). Soluble SCF can also be generated, with less efficiency, from SCF²²⁰ by the cleavage of exon 7 (Fig. 2).

The active form of SCF is a noncovalently associated homodimer which binds to the first 3 extracellular Ig domains of the KIT receptor¹⁶. The 4th and 5th extracellular Ig domains of the KIT help stabilize the homo-dimeric state of the receptors upon ligand binding¹⁶. Similar to other tyrosine kinase receptors, dimerization or oligomerization is required for the activation of the intrinsic tyrosine kinase and transphosphorylation of the KIT receptors¹⁶. Soluble SCF in circulation exists mostly in a monomeric form that does not activate KIT³². The expression of SCF²²⁰ and SCF²⁴⁸ is tissue-specific¹⁵ (Table 2). Membrane and soluble SCF homodimers can each activate KIT, but have different biological functions in hematopoiesis with a more critical role for SCF²⁴⁸ in MC development and survival^{33, 34}. Hence, blocking soluble SCF specifically by anti-SCF²⁴⁸ antibody has been used to probe the importance of SCF/KIT interactions in regulating MC functions in animal models of asthma²⁶, pulmonary fibrosis³⁵, and food allergy³⁶.

Mast cell-deficient mice with KIT mutations and newer models of mast cell deficiency

Because the MC-deficiency in *W* mutant mice can be “repaired” by systemic or local engraftment of MC precursors or differentiated MC populations, these mice have been widely used to investigate MC biology^{37, 38}. Such studies have been used to advance knowledge about MC functions (either beneficial or detrimental) and the regulation of MC developmental pathways. Most work with MC-deficient mice was conducted in WBB6F₁-*Kit*^{W/W^{-v}} or C57BL/6-*Kit*^{W-sh/W-sh} mice carrying mutations that affect the structure or expression of KIT. However, because these mutant mice also express many other non-MC abnormalities due to their *Kit* mutations, we have recommended that *in vitro*-derived MCs be adoptively transferred into WBB6F₁-*Kit*^{W/W^{-v}} or C57BL/6-*Kit*^{W-sh/W-sh} mice to produce “MC knock-in” mice^{37, 38}. This approach permits comparison of results in three groups of mice: *Kit* mutant MC-deficient mice, the corresponding wild type mice, and *Kit* mutant mice engrafted with populations of wild type or genetically-altered MCs. If any difference in expression of a biological response in *Kit* mutant MC-deficient mice and wild type mice is normalized by the engraftment of MCs into the *Kit* mutant mouse (particularly if similar results are obtained with both WBB6F₁-*Kit*^{W/W^{-v}} and C57BL/6-*Kit*^{W-sh/W-sh} mice), this can be interpreted as evidence favoring an important contribution of MCs in the biological response under investigation^{37, 38}.

However, when interpreting findings using this “MC knock-in” approach, one must keep in mind that the numbers, anatomical location and phenotype of the transferred MCs may not be identical to those in the corresponding wild type mice^{37, 38}. Prompted by these concerns, and considering the many phenotypic abnormalities unrelated to MCs in *Kit* mutant mice, alternative mouse models with inducible or constitutive MC-deficiencies that are independent of *Kit* mutations were generated by several groups³⁷⁻⁴¹. These newer models, which have been reviewed in detail^{37, 39-41}, employ a variety of approaches for

achieving more selective depletion of mast cells than occurs in the various *Kit* mutant animals. Some of these mice (e.g., *Cpa3cre* mice) are now available on inbred C57BL/6 or BALB/c genetic backgrounds⁴² and offer several advantages over *Kit* mutant mice, in that they are more selective in depleting mast cells while sparing other cell types that express Kit. They are particularly useful for investigations of the MCs' roles in tissue sites, e.g., the gastrointestinal tract and central nervous system, which are difficult to repair of their MC-deficiency by MC engraftment. However, these *Kit*-independent MC-deficient mice may also have functionally significant defects in other cell lineages, such as basophils^{37, 39–41}.

Regulation of KIT expression and signaling in mast cells

Several intrinsic and extrinsic mechanisms are known to modulate KIT expression in MCs. MITF (microphthalmia [*mi*] associated transcription factor) encoded by the *mi* locus is a basic helix-loop-helix leucine zipper transcription factor critical for KIT expression and development of MCs^{43, 44}. Also, KIT signaling controls MITF expression in MCs at posttranscriptional levels, with the involvement of miR-539 and miR-381⁴⁵. GATA2 is another transcription factor implicated in KIT expression in MCs, and it has been reported that MCs from GATA-2-deficient people express reduced levels of KIT and FcεRI and exhibit lower IgE-mediated degranulation⁴⁶. 3BP2 (SH3-binding protein 2) is a cytoplasmic adaptor protein that positively regulates FcεRI signaling and degranulation in MCs⁴⁷. Silencing of 3BP2 in HMC-1 cells (an immature human MC leukemia cell line with activating mutations in KIT), LAD2 cells (another human MC line, but with WT KIT), and CD34⁺ progenitor-derived human MCs impairs KIT signaling and affects PI3-kinase and MAPK pathways⁴⁸. Inhibition of 3BP2 also reduces expression of KIT as well as MITF, leading to more apoptosis in these MCs⁴⁸. Thus, 3BP2 is important for human MC survival by directly controlling KIT expression and KIT-mediated signal transduction⁴⁸.

KIT levels in MCs are modulated by extrinsic factors such as cytokines, growth factors and environmental pollutants. IL-4 and IL-10 can suppress KIT expression in mouse bone marrow-derived cultured MCs⁴⁹ and in HMC-1⁵⁰. Addition of IL-4 to fetal liver cells grown in SCF-containing medium markedly down-regulates surface KIT and interferes with MC growth and development⁵¹. In mouse bone marrow-derived cultured MCs, TGF-β down-regulates KIT via the transcription factor Ehf⁵². Exposure of mouse bone marrow-derived MCs to cigarette smoke-conditioned medium reduces KIT and FcεRI expression, granularity and IgE/antigen-mediated degranulation and cytokine production in these cells⁵³. Cigarette smoke contains over 4,700 chemical compounds, but the compound(s) responsible for KIT suppression was not identified in that study⁵³.

SCF binding of KIT downregulates KIT and triggers several complex membrane and intracellular signaling events in MCs^{16, 54, 55}. Like other tyrosine kinase receptors, crosslinking of KIT by SCF leads to receptor dimerization and conformational changes that facilitate trans-phosphorylation/auto-phosphorylation of the receptors by KIT's intrinsic tyrosine kinase activity^{16, 55}. These phosphorylated tyrosine residues then serve as docking sites for intracellular signaling molecules, such as Src family kinases (LYN, FYN), and Src homology 2 (SH2) domain-containing intracellular proteins (p85 subunit of PI3K, SHC, GRB2, GAB2, PLCγ, SHP2, etc). The recruitment and activation of

these intracellular proteins propagates subsequent downstream signaling cascades, leading to activation of RAS/RAF/MEK/MAPK, JAK-STAT, PI3K/AKT/RPS6K, and PLC/PKC pathways. The KIT signaling circuits are remarkably similar to signaling pathways elicited by FcεRI crosslinking, except that the recruitment and phosphorylation SYK and adaptor protein LAT are associated with the activation of FcεRI but not KIT⁵⁵. Phosphorylation of the transmembrane adaptor protein, NTAL, is a prerequisite for MC degranulation following FcεRI aggregation and is involved in SCF potentiation of antigen/IgE-induced degranulation⁵⁶. However, KIT and FcεRI appear to utilize different mechanisms to induce NTAL phosphorylation: FcεRI utilizes LYN and SYK for NTAL phosphorylation whereas KIT can phosphorylate NTAL directly⁵⁶.

KIT expression and activation have to be tightly regulated in order to maintain MC homeostasis. There are several mechanisms by which KIT signaling can be downregulated. Upon SCF binding, KIT is rapidly internalized and degraded via CBL (an E3 ubiquitin ligase) in an ubiquitin-dependent mechanism¹⁶. Inactivation can also be achieved by a negative feedback loop where activation of protein kinase C results in serine phosphorylation and inactivation of KIT¹⁶. Dephosphorylation of KIT by intracellular tyrosine phosphatases, e.g. SHP1, can also inactivate KIT¹⁶. ALDH2 (Mitochondrial aldehyde dehydrogenase)-deficient MCs have reduced SHP1 activities. These cells overreact to SCF stimulation of proliferation and IL-6 production with enhanced KIT phosphorylation and signaling⁵⁷. On the other hand, the tyrosine phosphatase, SHP2, can enhance KIT signaling in MCs, by upregulation of ERK and downregulation of Bim⁵⁸, and SHP2 can promote survival and chemotaxis toward SCF⁵⁹. Finally, RABGEF1 is a guanine nucleotide exchange factor (GEF) for RAB5 and forms a complex with rabaptin-5 that is critical for endocytic membrane fusion. RABGEF1-deficient MCs exhibit enhanced SCF/KIT signal transduction and cellular responses⁶⁰.

Regulation of mast cell homeostasis by KIT-SCF interactions

MCs retain high levels of KIT throughout all stages of their development. Interactions of SCF and KIT therefore influence multiple aspects of MC cellular responses (Fig. 3) and dysregulation of SCF/KIT activation will significantly perturb MC homeostasis. As described above, loss of function mutations in SCF/*Sl* or KIT/*W* result in MC deficiency; by contrast, gain of function mutations in KIT lead to MC hyperplasia and activation, as seen in mastocytosis and MC activation syndromes^{61–63}.

Although immortal human MC lines arising from cells with constitutively active KIT are available for *in vitro* experiments, the discovery of SCF as a key MC growth factor has helped establish culture methods for the generation of MCs carrying normal KIT function. These can be used for biochemical analyses and functional studies that otherwise would be difficult to perform with the limited numbers of MCs that can be obtained from tissues. These *in vitro* cultured human MCs have been generated from progenitors in cord blood^{64–66}, bone marrow^{18, 67, 68}, peripheral blood^{18, 66, 68, 69}, embryonic stem (ES) cells⁷⁰, and fetal liver⁵¹ in SCF-containing medium. Collectively, these reports have demonstrated that the growth and development of human MCs *in vitro* depends on SCF, although development of human MC progenitors from peripheral blood in IL-3 and IL-6, but

in the absence of SCF, has been reported⁷¹. Although mouse MC development in culture can be supported by IL-3 alone without added SCF, the addition of SCF markedly potentiates the growth of mouse MCs *in vitro*. Thus, mouse MCs can be generated from fetal skin⁷², fetal liver⁷³, bone marrow⁷⁴, peritoneal cells⁷⁵ or ES cells⁷⁶ in SCF or SCF plus IL-3.

In murine rodents and humans, the phenotype, numbers and functions of MCs generated in SCF can be profoundly influenced by the presence of other cytokines, such as IL-3, IL-4, IL-6, IL-9, IL-10, etc^{77, 78}. Mouse bone marrow-derived cultured MCs developed in IL-3 alone or in IL-3+SCF remain phenotypically immature. These MCs are negative with safranin and berberine staining, produce almost no heparin or the chymases, MMCP-4 and α -2⁷⁸⁻⁸⁰. On the other hand, fetal skin- and ES cell-derived cultured MCs generated in SCF+IL-3 exhibit phenotypic characteristics that more closely mimic a “mature phenotype” like that of connective tissue type MCs (CTMCs), including positive staining for safranin and berberine sulfate, and degranulation in response to substance P and compound 48/80^{72, 76}. MCs with a more mature phenotype also can be generated *in vitro* by culturing mouse bone marrow cells in SCF alone or sequentially in IL-3 followed by SCF⁷⁹⁻⁸¹.

A recent report has identified in mouse lung two distinct MC populations based on β 7 integrin expression⁸². MCs with constitutive β 7^{Low} expression are heavily granulated, express CTMC signature genes, and remain static in numbers during inflammation. On the other hand, β 7^{High} MCs are hypo-granulated, enriched for gene transcripts associated with MMCs, and contribute to allergic airway inflammation. These inducible β 7^{High} MCs increase in numbers and exhibit transcriptional changes following type 2 inflammatory stimulation. While multiple mediators and cytokines are likely to induce development and activation of β 7^{High} MCs, SCF/KIT-dependent TGF- β stimulation of IL-3-derived BMCMCs was shown to be an important signal that can induce recapitulation of certain aspects of the inflammatory phenotype of β 7^{High} MCs *in vivo*⁸².

Transcriptome analysis shows that the sequential culture in IL-3 followed by SCF partially programs immature bone marrow-derived MCs toward having a CTMC phenotype through transcriptional upregulation of heparin sulfate biosynthesis enzymes, certain MC-specific proteases, MRGPR family members, and transcription factors required for MC lineage determination⁸¹. Exposure of IL-3-derived MCs to SCF and IL-4 greatly enhances their expression of neurokinin 1 receptors and increases sensitivity to substance P stimulation^{83, 84}. In addition to supporting the development of MCs from precursors, SCF can induce proliferation of fully differentiated MCs *in vivo*⁸⁵ and *in vitro*⁷⁹, sustain MC survival by suppressing apoptosis^{86, 87}, act as a chemotactic factor to induce MC migration⁸⁸⁻⁹⁰, and promote MC adhesion to fibronectin⁹¹.

The *in vivo* effects of SCF on MCs have been demonstrated in murine rodents and humans. SCF injections induce MC development in SCF-deficient *Sl/Sl^d* mice¹⁴, as well as expansion of MC populations in wild type mice^{79, 85, 92}, rats⁸⁵, cynomolgus monkeys⁹³ and human subjects^{94, 95} through the recruitment and/or local expansion of MC progenitors. However, continuous SCF administration is required to maintain high numbers of MCs, as such SCF-induced MCs are eliminated by apoptosis and MC numbers decline rapidly to nearly baseline levels after cessation of SCF treatments^{92, 93}.

In addition to growth and development, MCs are activated by SCF to express functional responses. SCF can induce MCs to secrete cytokines and mediators *in vitro*^{96–100} and activate MCs to degranulate and express cellular function *in vivo*^{94, 95, 97, 101}. However, MC mediator release induced by SCF can result in undesirable side effects that limit the therapeutic value of this growth factor in promoting hematopoiesis and other applications. To mitigate MC side effects, Ho et al. engineered an SCF variant that selectively stimulates hematopoietic progenitors over MCs¹⁰². This SCF partial agonist was shown to support hematopoietic expansion but not SCF/MC-mediated anaphylaxis in mice¹⁰².

In MCs, SCF/KIT interactions synergize with the activation of other receptors, such as FcεRI^{96, 103–107}, IL-33/ST2¹⁰⁸ and TLR¹⁰⁹. *In vivo*, short-term treatment with SCF can potentiate IgE-mediated mediator release by MCs whereas chronic SCF exposure increases MC numbers but reduces certain aspects of IgE-dependent anaphylaxis¹¹⁰. *In vitro*, prolonged incubation of mouse bone marrow-derived MCs with SCF reduces IgE-dependent degranulation and cytokine production, and is associated with ineffective cytoskeletal reorganization and down-regulation of expression of the Src kinase Hck¹¹¹.

Targeting the KIT/SCF pathway in mast cell-associated diseases

The use of tyrosine kinase inhibitors (TKIs) for treatment of mastocytosis and mast cell activation disorders in humans is covered in other contributions in this series^{112–116} and elsewhere¹¹⁷. Briefly, the clinical value of both agents that act on WT KIT (e.g., imatinib) and those that act on the KIT D816V mutant (e.g., midostaurin and avaprotinib) has been demonstrated in the treatment of appropriate advanced systemic mastocytosis patients^{112–117}. By contrast, the clinical utility of KIT/SCF blocking antibodies in mast cell-associated disorders awaits definitive demonstration. We therefore will focus here mainly on experimental studies that have targeted the KIT/SCF pathway with anti-SCF or anti-KIT antibodies in mouse models of allergic disorders, parasite immunity, or fibrosis in which MCs are thought to play a major role. We will also briefly mention promising ongoing studies of a humanized anti-KIT monoclonal antibody in chronic inducible or chronic spontaneous urticaria.

Given the adverse effects of MCs in allergic diseases, inhibition of KIT/SCF-induced MC proliferation and activation would seem to be a plausible approach for the prevention or treatment of some of these disorders. However, there are many other approaches that are now used (or in development) to treat diseases in which MCs and IgE are importantly involved. These include existing agents that neutralize MC-derived mediators (e.g., anti-histamines, anti-leukotrienes) or reduce expression and activation of FcεRI (using anti-IgE antibodies such as Omalizumab or Ligelizumab), drugs such as gluco-corticosteroids (that, among other effects, stabilize MCs), and agents in development that suppress key signaling molecules (e.g., BTK, SYK) downstream of MC receptor activation (using small molecule inhibitors) or enhance relevant inhibitory mechanisms (e.g., Siglec 8; CD200R; CD300a; FcγRIIb)^{118, 119}.

Nevertheless, blocking the KIT/SCF pathway with anti-KIT/anti-SCF antibodies has been explored in models of mastocytosis¹²⁰, allergy^{26, 36, 121, 122}, and other settings involving

MCs^{35, 123, 124}. Another approach to block KIT signaling and activation in MCs employs a bispecific antibody linking KIT with the inhibitory receptor CD300a¹²⁵. This bispecific antibody can inhibit SCF-induced human MC differentiation, activation and survival, abrogate constitutive KIT activation in HMC-1 cells, and block skin reactions induced by SCF injections in mice¹²⁵. However, it remains to be determined whether, and in which settings, targeting of the KIT/SCF pathway may have advantages over other treatment approaches now being used or in development.

Allergic disorders

Work in MC-deficient *Kit*^{W-sh/W-sh} and/or *Kit*^{W/W-v} mice has supported the contribution of MCs in the development of multiple features of chronic asthma^{26, 126, 127}. While the detrimental effects of MCs are primarily mediated through IgE/FcεRI aggregation, FcRγ-independent mechanisms of MC activation can also significantly contribute to elevations of serum histamine and increased numbers of airway goblet cells associated with chronic allergic airway inflammation in mice¹²⁶. The development of many FcRγ-dependent and some FcRγ-independent features of allergic airway disease also depends on MC expression of IFN-γR¹²⁷. In addition to FcRγ- and IFN-γR-mediated activation, MCs' responses to SCF can contribute to the severity of allergic airway inflammation, hyper-responsiveness and remodeling^{26, 54}. As fibroblasts in asthmatic lungs overexpress predominately the SCF²⁴⁸ isoform, anti-SCF²⁴⁸ antibody that specifically targets exon 6 of the SCF²⁴⁸ was generated to explore the importance of soluble SCF in allergic asthma. In a mouse model of chronic asthma elicited by cockroach antigen, anti-SCF²⁴⁸ antibody attenuates airway inflammation, airway hyper-responsiveness, Th2 cytokine levels, mucus deposition, and numbers of MCs and other KIT+ cells, ILC2 and eosinophils, in the lungs²⁶. Targeted deletion of SCF specifically in fibroblasts has similar effects as those observed with anti-SCF²⁴⁸ antibody in this chronic asthma model²⁶. This study demonstrated that fibroblast-derived SCF, mainly SCF²⁴⁸, can regulate effector function of MCs as well as KIT+ ILC2 in allergic airway inflammation and remodeling²⁶.

Intestinal MC hyperplasia and activation is a hallmark of food allergy¹²⁸. Brandt et al. used an anti-KIT blocking antibody (ACK2) to deplete intestinal MCs and plasma MMCP1¹²¹. Such anti-KIT treatment also blocked augmented intestinal permeability and diminished oral allergen-induced diarrhea in mice¹²¹. In another study, anti-SCF²⁴⁸ antibody treatment attenuated intestinal anaphylaxis (i.e., reduced diarrhea and hypothermia) with reductions in Th2 cytokines, ILC2, eosinophils and intestinal MCs in a mouse model of food allergy elicited by ovalbumin sensitization and intragastric challenges³⁶.

CDX-0519 (Celldex Therapeutics) is a humanized anti-KIT monoclonal antibody that inhibits SCF-mediated activation by binding to the extracellular dimerization domain of KIT^{129, 130}. This antibody is currently being evaluated for safety and efficacy in chronic spontaneous urticaria (CSU) (<https://clinicaltrials.gov/ct2/show/NCT04538794>) and chronic inducible urticaria (CIndU) (<https://clinicaltrials.gov/ct2/show/NCT04548869>). Terhorst-Molawi et al. recently reported that a single dose of CDX-0159 resulted in sustained control of urticaria and reductions of cutaneous MC numbers and circulating tryptase and SCF in antihistamine refractory CIndU¹²².

Parasite immunity

Anti-SCF and anti-KIT blocking antibodies have been used to investigate the contribution of MCs in parasite immunity. These blocking antibodies abrogate MC hyperplasia induced by the parasite *Trichinella (T.) spiralis* and result in delayed worm expulsion¹²³. By contrast, while anti-SCF antibody treatment diminish intestinal MC hyperplasia in rats infected with *Nippostrongylus brasiliensis* (or *T. spiralis*), such treatment decreased parasite egg production during *N. brasiliensis* infection¹²⁴. These findings indicate that while activation of SCF/KIT and MCs is protective for certain parasite infection, the effects of SCF and/or MCs may actually favor parasite fecundity in some settings.

Fibrosis

The SCF/KIT pathway also has been implicated in pulmonary fibrosis and remodeling. Lung fibroblasts from idiopathic pulmonary fibrosis (IPF) patients and from mice treated with bleomycin preferentially express the SCF²⁴⁸ isoform³⁵. In fibroblast-MC (LAD2) coculture, anti-SCF²⁴⁸ antibody decreased the expression of *COL1A1*, *COL3A1*, and *FNI* transcripts in IPF, but not normal, lung-derived fibroblasts. Administration of anti-SCF²⁴⁸ after bleomycin instillation in mice significantly reduced KIT⁺ MCs, eosinophils, and ILC2 cells and expression of profibrotic genes (*coll1a1*, *fn1*, *acta2*, *tgfb*, and *ccl2* transcripts)³⁵.

However, like tyrosine kinase inhibitors, the effects of anti-SCF and anti-KIT blocking antibodies do not necessarily reflect solely their actions on MCs. For example, SCF can activate ILC2 cells to produce key allergic cytokines and the effects of anti-SCF antibody in chronic allergic inflammation could be attributable, at least in part, to ILC2 inhibition²⁶. Also, anti-KIT antibody could potentially trigger MC degranulation. In a phase 1 clinical study that examined the anti-KIT antibody drug conjugate for the treatment of gastrointestinal stromal tumors (GIST), some participants developed rapid hypersensitivity reactions with elevated serum tryptase after infusion¹³¹. This anti-KIT antibody drug conjugate was shown to induce degranulation of peripheral blood derived MCs by coligation of Fc γ R and KIT¹³¹.

Conclusions

The identification of the receptor Kit as the product of the *W* (white spotting) locus in the mouse and SCF (Kitl), the Kit ligand, as the product of the mouse *Sl* (steel) locus were significant achievements. These discoveries have helped to explain many of the phenotypic abnormalities of the mutant mice that have been most central to our understanding of the origin and development of the MC lineage: WBB6F1-*W/W^v* mice (now known as WBB6F1-*Kit^{W/W^v}* mice) and WCB6F1-*Sl/Sl^d* mice (now known as WCB6F1/J-*Kit^{Sl/Sl^d}* mice). And while Kit and its ligand are most strongly involved in the development of hematopoietic precursors, germ cells, melanocytes and MCs, MCs represent an example (perhaps the most striking example) of a hematopoietic cell lineage that retains high levels of expression of Kit on the surface both throughout its development and as “mature” cells residing in the tissues.

However, it has become evident that KIT and its ligand participate in the development and function of multiple distinct cell lineages. These include cells in parts of the CNS, the

interstitial cells of Cajal in the gut, taste cells, and several hematopoietic cells in addition to MCs, including dendritic cells, eosinophils, and ILC2 cells. While the importance of KIT and its ligand in influencing the biology of some of these cell types remains to be fully understood, the potential diversity of the roles of this receptor-ligand interaction in regulating multiple distinct lineages should always be kept in mind when evaluating the effects of attempting to antagonize such interactions therapeutically. Many of the concepts developed in mouse studies now appear also to be relevant in humans, including in various human diseases. On the other hand, one should also always consider the possibility of differences in the biology of interactions between KIT and its ligand in mice versus humans.

Considering all of these caveats, when can targeting KIT and/or its ligand be therapeutically useful? If KIT is mutated and has increased function, as in many variants of human mastocytosis, then using agents that target KIT (albeit not fully specifically) can have clinical benefit^{113–117}. Other settings may be certain forms of severe refractory asthma, in which treatment with imatinib (that targets KIT, and other receptors) can have benefit^{132, 133}, or instances of severe mast cell activation¹¹². Finally, recent studies of a humanized anti-KIT monoclonal antibody that inhibits SCF-mediated activation show promise in sustained control of chronic inducible urticaria¹²². But questions remain as to whether, and in which other conditions, the specific targeting of KIT (or SCF) can be clinically useful - and whether the side effects of such treatment will be tolerable.

Abbreviations:

acta2	actin alpha 2
ADAM	a disintegrin and metalloproteinase
ALDH2	mitochondrial aldehyde dehydrogenase
BMCMC	bone marrow-derived cultured mast cel
3BP2	SH3-binding protein 2
BTK	bruton tyrosine kinase
CBL	casitas B-lineage lymphoma
ccl2	C-C motif chemokine ligand 2
COL1A1	collagen type 1 alpha 1 chain
COL3A1	collagen type 3 alpha 1 chain
CNS	central nervous system
CTMC	connective tissue type mast cell
Ehf	ETS homologous factor
ES	embryonic stem
FcεRI	Fc epsilon receptor type I

FcγR	Fc gamma receptor
FcRγ	Fc receptor gamma chain
FN1	fibronectin 1
GAB2	GRB2-associated-binding protein 2
GRB2	growth-factor receptor-bound protein-2
HMC-1	human mast cell leukemia-1
IFN-γR	interferon gamma receptor
IL	interleukin
ILC2	type 2 innate lymphoid cell
IgE	Immunoglobulin E
IPF	idiopathic pulmonary fibrosis
JAK	Janus kinase
Kitl	KIT ligand
LAD2	laboratory of allergic diseases 2
LAT	linker for activation of T cells
MAPK	mitogen-activated protein kinase
MC	mast cell
MITF	microphthalmia associated transcription factor
MMC	mucosal mast cell
MMCP	mouse mast cell protease
MRGPR	mas-related G protein-coupled receptor
NTAL	non T cell activation linker
PI3K	phosphoinositide 3-kinase
PKC	protein kinase C
PLCγ	phospholipase C gamma
RABGEF1	RAB guanine nucleotide exchange factor 1
RPS6K	ribosomal protein S6 kinase
SCF	stem cell factor
SH2	Src homology 2

SHC	Src homology and collagen
SHP	tyrosine phosphatase
Siglec 8	sialic acid binding Ig like lectin 8
SI	steel
ST2	suppressor of tumorigenicity 2
STAT	signal transducer and activator of transcription
SYK	spleen tyrosine kinase
TGF-β	Transforming growth factor beta
Th2	T helper 2
TKI	tyrosine kinase inhibitor
TLR	toll-like receptor
W	white spotting

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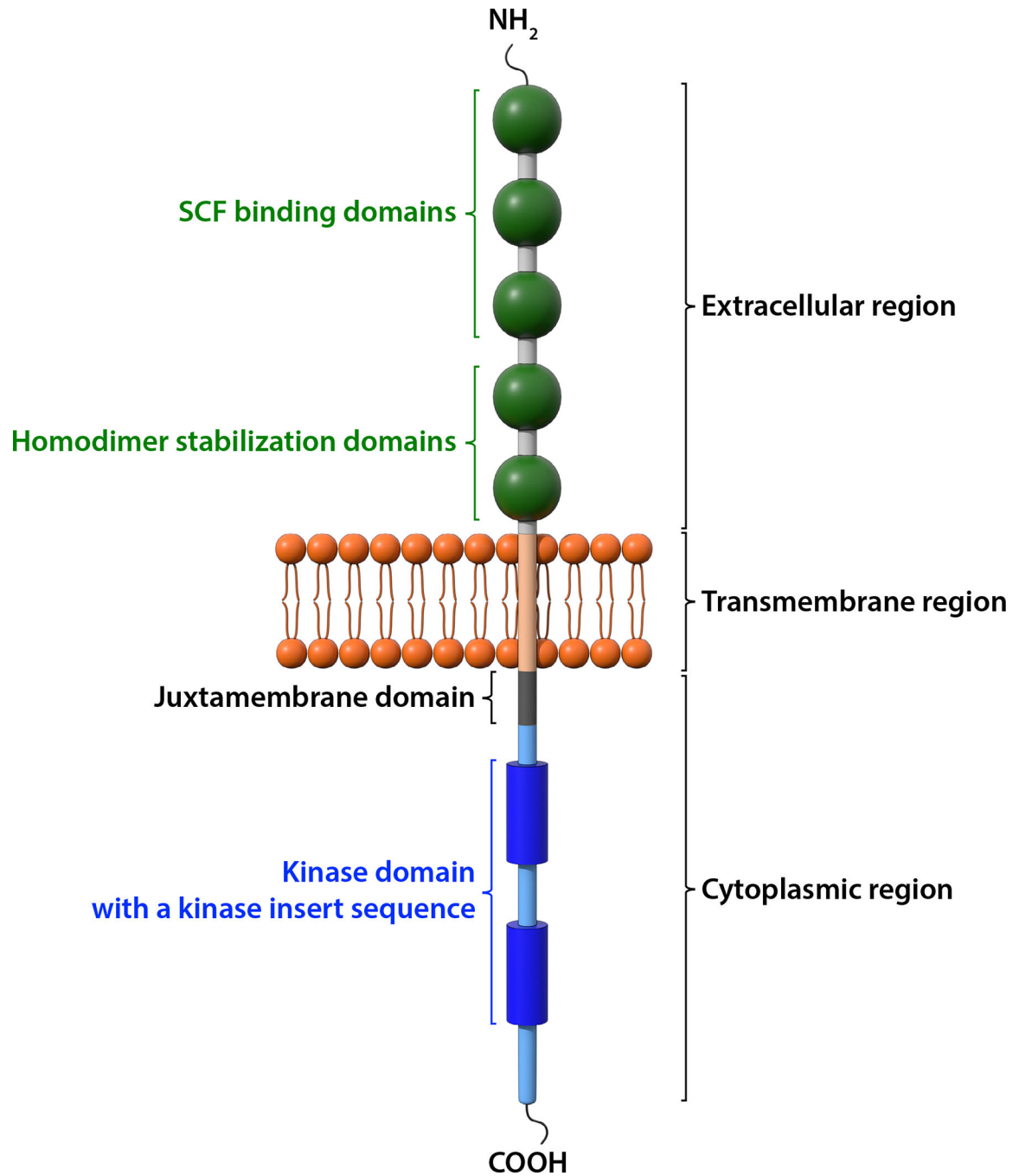


Figure 1. Structure of the KIT receptor.

KIT is a member of the receptor tyrosine kinase III family. It consists of an extracellular region, a transmembrane domain, and a cytoplasmic region. There are five immunoglobulin (Ig)-like domains in the extracellular region. The first three Ig-like domains bind to SCF and the 4th and 5th Ig-like domains facilitate dimerization upon ligand binding. The intracellular tyrosine kinase domain is interrupted by a hydrophilic insert sequence. The juxtamembrane domain, the kinase domain and the carboxyl terminal tail are involved in signal transduction when the KIT receptor is activated.

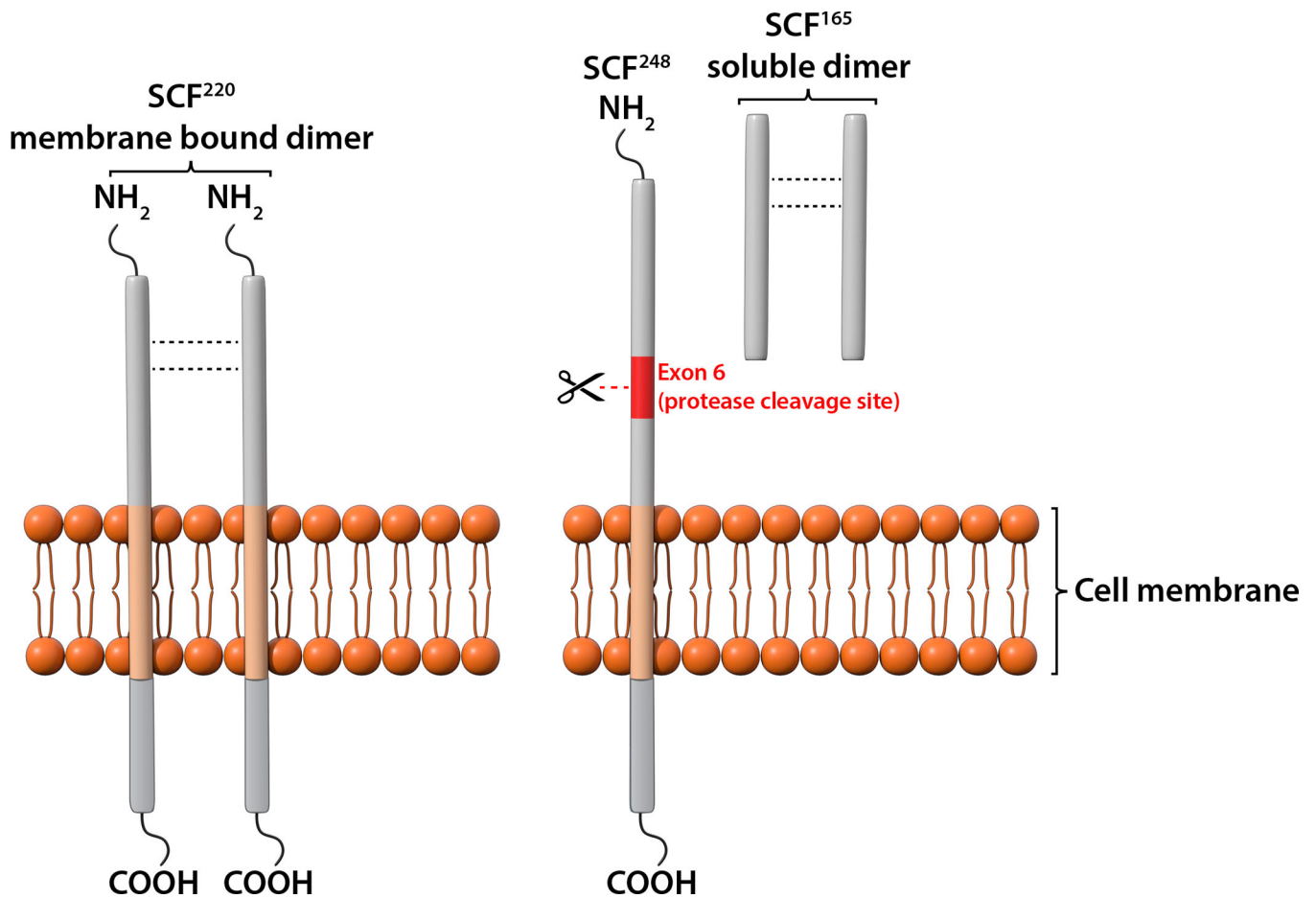


Figure 2. Structure of two SCF isoforms.

Two main SCF isoforms, SCF²²⁰ and SCF²⁴⁸, are produced by alternative splicing. Both SCF²²⁰ and SCF²⁴⁸ consist of an extracellular domain, a transmembrane domain and an intracellular tail. Exon 6 in SCF²⁴⁸ encodes a protease sensitive site that can be cleaved to generate soluble SCF¹⁶⁵. Minor amounts of soluble SCF also can be generated from SCF²²⁰ by an alternative protease cleavage site encoded by exon 7 (not depicted). Biologically active SCF is a non-covalent dimer in either membrane-associated or soluble form.

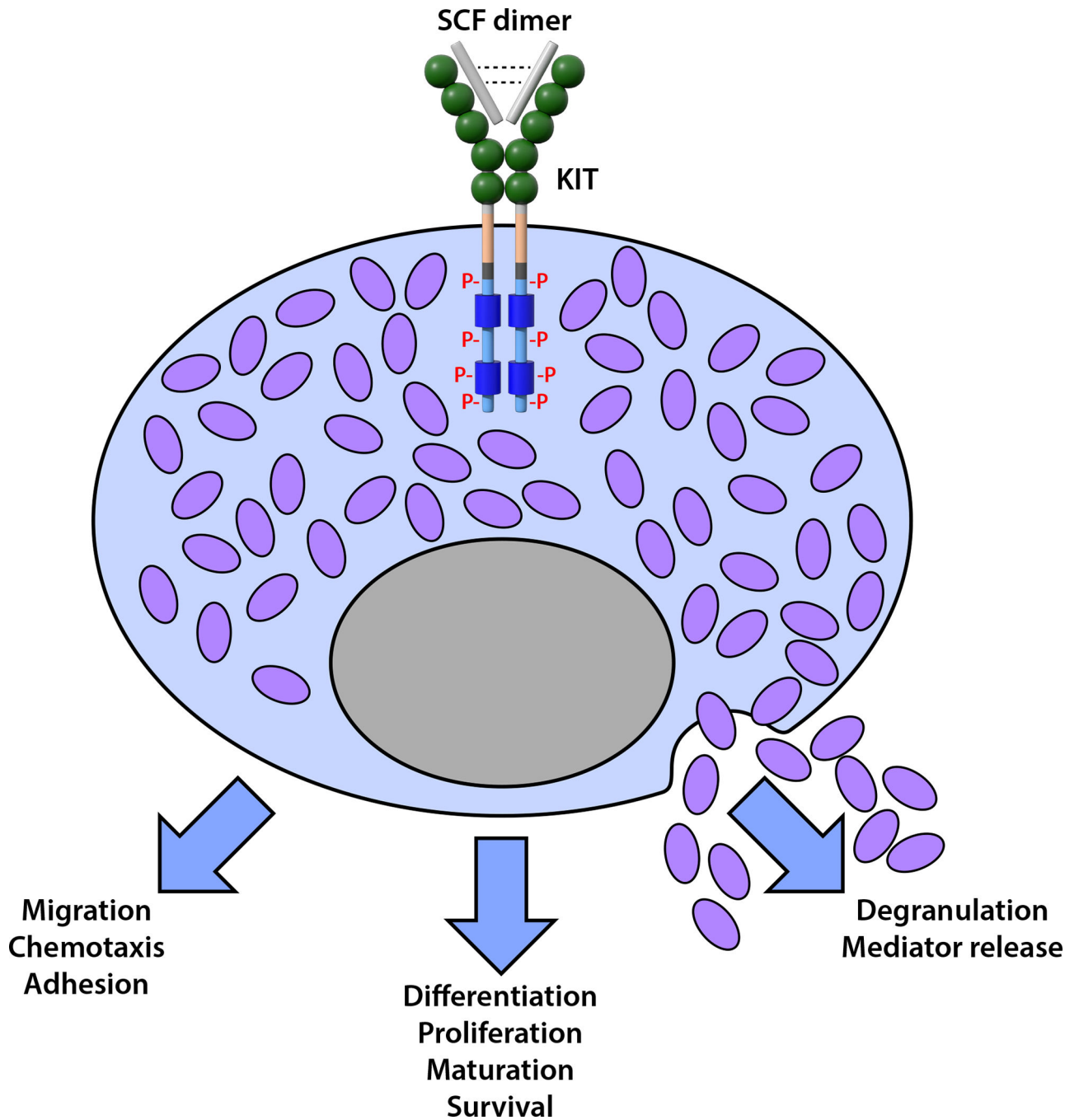


Figure 3. Pleiotropic effects of SCF-KIT interactions on mast cell development and function. The binding of the SCF homodimer induces dimerization and phosphorylation of the KIT receptor, which can promote the differentiation, proliferation, maturation, and/or enhanced survival of cells in the MC lineage. SCF-KIT interactions can also activate MCs to express cellular functions and promote MC migration, chemotaxis, and adhesion, and, at high concentrations, MC degranulation and mediator release. **P**: phosphorylated tyrosine

Table 1.

Cellular expression of KIT*

Activated CD8⁺ T cells
Central Nervous System (mainly in cerebellum)
Certain epithelial cells
Dendritic cells
Eosinophils
Germ cells
Hematopoietic stem cells and early progenitors
ILC2 cells
Interstitial cells of Cajal
Mast cells
Melanocytes
Taste cells

* Listed alphabetically, not based on level of expression.

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Table 2.

Cellular expression of SCF*

Bone marrow stromal cells and macrophages
Endothelial cells
Eosinophils
Fibroblasts
Keratinocytes
Mast cells
Smooth muscle cells

* Listed alphabetically, not based on level of expression.

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