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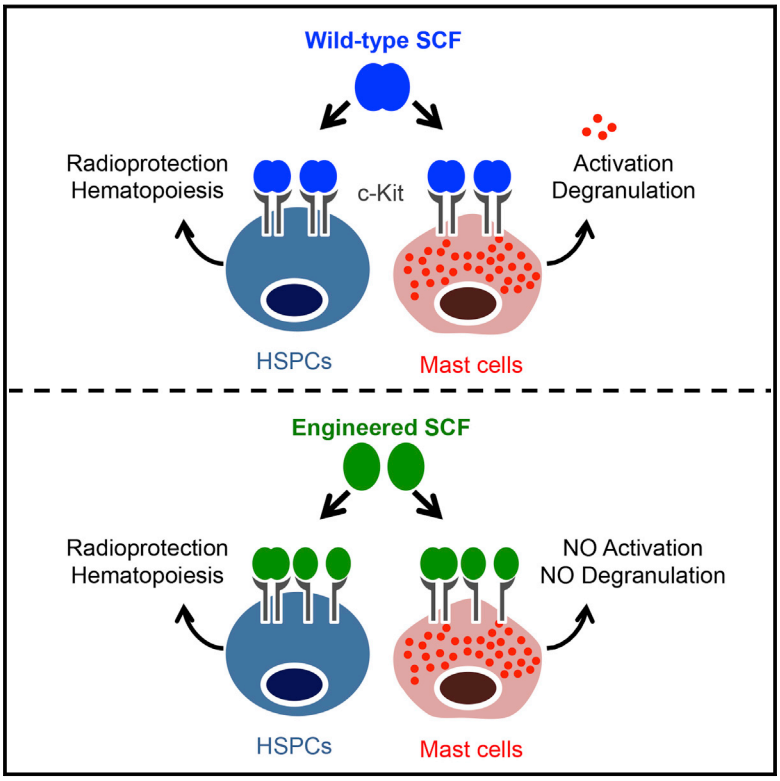
Decoupling the Functional Pleiotropy of Stem Cell Factor by Tuning c-Kit Signaling

Graphical Abstract



Highlights

- An engineered variant of stem cell factor acts as partial agonist of c-Kit
- SCF partial agonist exhibits biased activation of HSPCs versus mast cells
- Partial agonist of c-Kit retains therapeutic efficacy but mitigates toxicity in vivo

Authors

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In Brief

A ligand engineering strategy is used to amplify hematopoietic stem cells but avoid unwanted off-target effects mediated by mast cells.

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Decoupling the Functional Pleiotropy of Stem Cell Factor by Tuning c-Kit Signaling

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SUMMARY

Most secreted growth factors and cytokines are functionally pleiotropic because their receptors are expressed on diverse cell types. While important for normal mammalian physiology, pleiotropy limits the efficacy of cytokines and growth factors as therapeutics. Stem cell factor (SCF) is a growth factor that acts through the c-Kit receptor tyrosine kinase to elicit hematopoietic progenitor expansion but can be toxic when administered in vivo because it concurrently activates mast cells. We engineered a mechanism-based SCF partial agonist that impaired c-Kit dimerization, truncating downstream signaling amplitude. This SCF variant elicited biased activation of hematopoietic progenitors over mast cells in vitro and in vivo. Mouse models of SCF-mediated anaphylaxis, radioprotection, and hematopoietic expansion revealed that this SCF partial agonist retained therapeutic efficacy while exhibiting virtually no anaphylactic off-target effects. The approach of biasing cell activation by tuning signaling thresholds and outputs has applications to many dimeric receptor-ligand systems.

INTRODUCTION

The majority of secreted growth factors (GFs) and cytokines exert their effects through homo- or hetero-dimeric cell surface receptor complexes to initiate intracellular kinase-mediated signal transduction (Atanasova and Whitty, 2012; Klemm et al., 1998; Schlessinger and Ullrich, 1992; Stroud and Wells, 2004; Wang et al., 2009). Collectively, cytokines (e.g., interleukins, interferons, etc.) and GFs (e.g., EGF, NGF, TGF, etc.) that act through dimeric receptors hold great promise as therapeutics for a wide range of diseases. However, while antagonism of these molecules has been clinically successful, principally for immune diseases and cancer (Nepom et al., 2013), effective therapeutic exploitation of their agonistic properties has been limited to relatively few cases largely due to the difficulty of controlling agonism in vivo (Bendall and Bradstock, 2014; Floros and Tarhini, 2015).

Because GFs and cytokines act on multiple different cell types that express their receptors, they tend to exhibit pleiotropic activities, which has limited their clinical utility as agonists (Moraga et al., 2014; Nicola, 1994; Thomas et al., 2004; Yea et al., 2015). Pleiotropic actions can induce counterbalancing cellular activities, resulting in blunted therapeutic efficacy (Hart et al., 2014; Lin et al., 1995). Furthermore, pleiotropy exacerbates off-target toxicities through activation of undesired cell types (Baldo, 2014; Krieg et al., 2010). Previous studies have shown that natural and engineered ligands, which modulate receptor dimerization by altering receptor-ligand complex stability, affinity, and/or geometry, have the capacity to modulate downstream signaling outputs and target cell selectivity (Levin et al., 2014; Macdonald-Obermann and Pike, 2014; Mitra et al., 2015; Moraga et al., 2015a, 2015b; Riese, 2011; Yea et al., 2015). Engineered cytokine ligands that differentially engage their heterodimeric receptors can induce partial receptor activation and exhibit biased