Functional Deregulation of KIT

Link to Mast Cell Proliferative Diseases and Other Neoplasms

Glenn Cruse, PhD, Dean D. Metcalfe, MD, Ana Olivera, PhD*

KEYWORDS

• Mastocytosis • KIT mutations • KIT signaling • KIT trafficking • KIT inhibitors

KEY POINTS

- KIT, the tyrosine kinase receptor for stem cell factor, is critical for the proliferation, survival, differentiation, and homing of hematopoietic bone marrow stem cells, particularly mast cells, which retain KIT expression and are dependent on KIT activity during their lifespan.
- Gain-of-function mutations in c-Kit resulting in ligand-independent receptor activity associate with hyperproliferative diseases, especially mast cell proliferation disorders (mastocytosis), gastrointestinal stromal tumors (GISTs) and other hematological neoplasms.
- Despite the large number of individual somatic oncogenic mutations identified, most are grouped within mutational hotspots in exon 11 (more frequent in GISTs), encoding for the regulatory juxtamembrane domain, and exon 17 (more frequent in mastocytosis and other germ line malignancies), encoding for the catalytic kinase domain of KIT.
- Structural changes in the receptor induced by these mutations affect the intracellular trafficking of KIT and quantitatively and qualitatively alter normal KIT signaling leading to enhanced proliferation.
- Challenges in the treatment of these diseases include the differential sensitivity to known KIT inhibitors depending on the type of mutation and their relatively low selectivity to KIT, the development of drug resistance, and the presence of other complementing co-oncogenic events or epigenetic modifications contributing to the pathology.

INTRODUCTION

The c-Kit proto-oncogene is the cellular, untruncated counterpart of the gene in the Hardy-Zuckerman feline sarcoma virus genome (v-Kit) responsible for its transforming activity.[1] Gain-of-function mutations in c-Kit promoting tumor formation and

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Mast Cell Biology Section, Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health, 10 Center Drive, Building 10, Room 11C207, MSC 1881, Bethesda, MD 20892, USA
* Corresponding author.
E-mail address: Ana.Olivera@nih.gov

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progression have been identified in certain human cancers, a knowledge that has boosted an interest in targeting the activity of this receptor.

c-Kit encodes for a protein, KIT (CD117), belonging to a family of transmembrane growth factor receptors with intrinsic tyrosine kinase activity.[2] Its specific ligand is stem cell factor (SCF), also known as KIT ligand, mast cell growth factor, or steel factor.[3,4] SCF is primarily, but not exclusively, produced by stromal cells, such as fibroblasts, in 2 major forms, a soluble form and a membrane-bound form, which are present at varying ratios in different tissues.[3,5,6] Both forms activate KIT but may mediate qualitatively and quantitatively different types of responses,[7,8] although the specific mechanisms remain largely unknown.

KIT is highly expressed in hematopoietic stem cells from the bone marrow, and its activity is critical for constitutive hematopoiesis and for the proliferation, survival, differentiation, and homing of these cells.[8–10] Expression of KIT is generally lost during the differentiation process of most hematopoietic cells, with the exception of mast cells, which retain KIT through their lifespan. KIT, thus, plays an important role in mast cell proliferation, survival, and function.[11–15] KIT expression can be upregulated during an immune response in eosinophils[16] and dendritic cells,[17] whereas in both human basophils and eosinophils, KIT expression is generally found at low levels.[18,19] The expression of KIT is, however, not restricted to hematopoietic cells: it is expressed in melanocytes, interstitial cells of Cajal in the gastrointestinal tract,[20] and other cell types.[21–24] Accumulated evidence in rodent models with KIT alterations has provided insights on the cell populations that are most critically KIT dependent. Thus, mice carrying mutations that impair KIT structure or expression (such as $WBB6F_1$- $Kit^{W/W-v}$ and C57BL/6-$Kit^{W-sh/W-sh}$ mice) exhibit specific phenotypic abnormalities in their adulthood, including profound mast cell and melanocyte deficiency, macrocytic anemia, reduced fertility, and a lack of gut interstitial cells of Cajal resulting in reduced pacemaker activity in the small intestine.[4,20,24] The absence of KIT or its ligand in mice is embryonically or perinatally lethal, suggesting a critical, broader biologic role of SCF/KIT signaling during embryogenesis.[4] In humans, loss-of-function mutations in c-Kit associate with piebaldism, a rare, autosomal dominant disorder characterized by congenital white patches in the skin and hair caused by improper migration of melanoblasts in the embryo,[25] whereas acquired gain-of-function mutations in c-Kit result in particular neoplastic diseases.

In this review, the authors provide a general overview of the consequences of gain-of-function mutations in c-Kit, the structure and molecular mechanisms governing KIT signaling, and describe how gain-of-function mutations in c-Kit result in its overactive function and lead to cellular transformation, with particular focus on mast cells and disorders of pathologic mast cell proliferation.

C-KIT MUTATIONS AND LINK TO MALIGNANCIES

Human malignancies associated with activating c-Kit mutations include mast cell proliferative disorders; gastrointestinal stromal tumors (GISTs); and, less commonly, melanoma and acute myeloid leukemia. Increased expression of normal c-Kit may also contribute to tumorigenesis in solid lung cancers from small lung cells that do not normally express KIT and are exposed to environments rich in SCF. Activating mutations in small lung cancer cells, nonetheless, have rarely been found; their involvement in tumor progression is still unclear.[26–28] Dysregulation of KIT activity plays a central role, however, in the pathogenesis of those malignancies originated from cells dependent on SCF for differentiation/survival, such as mast cells and interstitial cells of Cajal.[29–33] GISTs are thought to derive from interstitial cells of Cajal; in up to 80% of