Molecular Defects in Mastocytosis

KIT and Beyond *KIT*

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KEYWORDS

• Systemic mastocytosis • *KIT* • Mutation • Signaling • *TET2* • *ASXL1* • Spliceosome • Targeted therapy

KEY POINTS

- The *KIT* D816V mutation is found in almost all the adult patients presenting with different subvariants of systemic mastocytosis (SM).
- The clinical course and prognosis of the different subvariants vary greatly among patients with SM.
- Additional genetic lesions and aberrant overexpression of signaling pathways are found in aggressive SM and SM with associated hematologic non–mast cell-lineage disease.
- These additional genetic aberrations or overexpression of signaling pathways are associated with progression of the disease and worsen significantly the prognosis of patients with SM.

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INTRODUCTION

Mast cells (MCs) are multifunctional immune cells derived from hematopoietic stem cell (HSC) in the bone marrow (BM). Committed BM MC progenitors (MCPs) are released into the bloodstream, where they have been identified in humans as CD34+/KIT+/CD13+/FcεRI– cells.[1] Human MCPs migrate into the peripheral tissues, where they differentiate terminally into 2 major subtypes: $MC_{tryptase}$ (MC_T) and $MC_{tryptase\text{-}chymase}$ (MC_{TC}). MC_T are found preferentially in mucosal tissues, whereas MC_{TC} are prominent in serosal tissues.[2,3] For both MC subtypes, the major growth and differentiation factor is stem cell factor (SCF), which binds KIT (CD117), a transmembrane receptor with intrinsic tyrosine kinase (TK) activity.[4]

Mastocytosis comprises a heterogeneous group of rare diseases characterized by abnormal accumulation of more or less atypical MCs in 1 or more organs.[5] Although mastocytosis can affect either children or adults, the behavior of the disease appears different not only in children (disease frequently restricted to the skin and attenuating at puberty) versus adults (disease constantly systemic and chronic) but also between adults with systemic involvement.[5] Adult patients may suffer from an indolent form of the disease or may show aggressive or even leukemic variants.[6] However, in most adults, a recurrent abnormality in the *KIT* gene (mainly *KIT* D816V) is found in neoplastic MCs.[7] This discrepancy between the recurrent genotype and the variable severity of the disease has led several teams to investigate for, then to find, the presence of associated non-*KIT* molecular defects, particularly in advanced systemic mastocytosis (advSM).[8–10]

In the first part of this review, an overview of the implications of *KIT* in MC development and functions is provided. The mechanisms involved in the transforming potential of *KIT* mutants found in the various subcategories of mastocytosis and their consequences for treatment are then discussed. The additional genetic defects found in several cohorts of patients and their impact in terms of severity and progression of the disease are described, as well as their possible implications for future therapeutic considerations.

CRITICAL ROLES OF SCF AND *KIT* IN THE DEVELOPMENT AND BIOLOGY OF MCs

Mice with loss-of-function mutations affecting either synthesis of SCF (Sl/Sld mice) or *Kit* (W/Wv mice) are virtually devoid of MCs, showing the importance of the SCF/Kit axis in MCs.[11] In contrast, gain-of-function mutations in the *KIT* proto-oncogene are associated with enhanced survival and autonomous growth of MCs and their progenitors.[12] In addition, the injection of SCF increases the number of MCs by more than 100 times near the site of injection.[13] MCs are the only terminally differentiated hematopoietic cells expressing KIT, and SCF promotes not only differentiation of MCs from their MCPs but also adhesion, migration, and survival, as well as mediator release from mature MCs.[2]

Structure of SCF

SCF is encoded by a gene on chromosome 12q22-12q24 in humans.[14] The gene is alternatively spliced, leading to 2 SCF isoforms, which differ in the absence or presence of a particular proteolytic cleavage site. The isoform containing the cleavage site undergoes proteolysis and becomes soluble (sSCF of 18 kDa), as a 165 amino acid protein, with the first 141 residues necessary for its receptor-binding activity.[15] The isoform lacking the cleavage site remains cell associated as a 31-kDa membrane-bound form (mSCF).[15]