## Phylogeny

Human KIT has a strict one-to-one orthologue in mouse (W-locus), exemplifying the strong conservation of this type III receptor tyrosine kinase (Caenepeel et al., 2004). Comparative kinome analyses show KIT/PDGFR-family members throughout vertebrates (rat, chicken, zebrafish, Xenopus) but not in most invertebrates, indicating a vertebrate-restricted lineage (Goldberg et al., 2006; Manning et al., 2011). KIT belongs to the tyrosine-kinase (TK) group, type III RTK/PDGFR sub-family together with PDGFRA, PDGFRB, FLT3 and CSF1R (Mol et al., 2004). A YxxM PI3K-binding motif in the kinase insert is conserved across this clade (Lev et al., 1992). In mouse, Kit is essential for melanoblast, erythroblast and germ-cell development, underscoring functional conservation across mammals (Piao et al., 1996).

## Reaction Catalyzed

ATP + protein-L-tyrosine ⇄ ADP + protein-L-tyrosine-phosphate (Mol et al., 2004).

## Cofactor Requirements

Requires Mg²⁺, coordinated by Asp810 of the DFG motif to position ATP for phosphoryl transfer (Mol et al., 2004).

## Substrate Specificity

Peptide-array profiling groups KIT with RTKs that favor aliphatic hydrophobic residues at –1 and +3 and disfavor Ser –1 and Glu +3, giving the consensus Φ-x-pY-x-Φ (Yaron-Barir et al., 2024). Major autophosphorylation sites are Tyr568, Tyr570 (juxtamembrane); Tyr703, Tyr721, Tyr730, Tyr747 (kinase insert); Tyr823 (activation loop); Tyr900 and Tyr936 (C-terminal tail) (Lennartsson & Rönnstrand, 2012). Tyr721 within pTyr-XXM recruits the PI3K p85 subunit (Lev et al., 1992). Activating D814Y/D816V mutations broaden specificity toward Src/Abl-type motifs (Piao et al., 1996; Lennartsson & Rönnstrand, 2012).

## Structure

KIT comprises five Ig-like extracellular domains (D1–D5), a single transmembrane helix, an autoinhibitory juxtamembrane segment (Thr544–Trp580), a split kinase domain interrupted by a 68-aa kinase insert (residues 694–753) and a C-terminal tail (Yuzawa et al., 2007; Mol et al., 2004). Key catalytic motifs are VAIK (Lys818), HRD (Asp792) and DFG (Asp810-Phe811-Gly812); correct C-helix and spine alignment defines the active state (Mol et al., 2004). Trp557 wedges into the active-site cleft and Tyr823 acts as a pseudosubstrate in the inactive conformation (Mol et al., 2004). Representative structures: active kinase (PDB 1PKG), autoinhibited kinase (PDB 1T45), imatinib-bound inactive kinase (PDB 1T46) (Mol et al., 2004); SCF-induced ectodomain dimer (PDB 2E9W) (Yuzawa et al., 2007).

## Regulation

Stem cell factor (SCF)-induced dimerization aligns the transmembrane helices, allowing trans-autophosphorylation. Phosphorylation of Tyr568/Tyr570 relieves juxtamembrane inhibition and triggers sequential phosphorylation of Tyr703, Tyr721, Tyr730, Tyr747, Tyr823, Tyr900 and Tyr936 to create docking sites for signaling proteins (Lennartsson & Rönnstrand, 2012). Subsequent Ser/Thr phosphorylation dampens activity, whereas c-Cbl-mediated ubiquitination targets active KIT for endocytosis and lysosomal degradation (Lennartsson & Rönnstrand, 2012). SHP-1 phosphatase binds pTyr568/570 to dephosphorylate KIT; oncogenic D814Y/D816V mutations promote SHP-1 degradation, sustaining signaling (Piao et al., 1996). Imatinib stabilizes the autoinhibited DFG-out state (Mol et al., 2004).

## Function

Expression is prominent in hematopoietic progenitors, mast cells, melanocytes, endothelial progenitors, gastrointestinal stromal tumors (GIST) and acute myeloid leukemia cells (Lennartsson & Rönnstrand, 2012). Key signaling routes include PI3K–AKT via Tyr721-p85 binding (Lev et al., 1992; Lennartsson & Rönnstrand, 2012), RAS–RAF–MEK–ERK (Src-dependent in wild-type, Src-independent in D816V), STAT1/3/5 activation, and PLCγ1-mediated DAG/IP₃ generation (Lennartsson & Rönnstrand, 2012). Biological outcomes encompass survival, proliferation, migration, hematopoiesis, stem-cell maintenance, gametogenesis, mast-cell maturation, melanogenesis and, in dendritic cells, IL-6-driven TH2/TH17 responses (Lennartsson & Rönnstrand, 2012).

## Inhibitors

Type II inhibitors imatinib (IC₅₀ ≈ 124 nM) and sunitinib (IC₅₀ ≈ 42 nM) potently block unactivated KIT but imatinib is ineffective against D816V (Gajiwala et al., 2009; Lennartsson & Rönnstrand, 2012). Dasatinib and nilotinib inhibit many exon 17 mutants (Lennartsson & Rönnstrand, 2012). Sorafenib, regorafenib, cabozantinib and ponatinib maintain affinity for V654A or T670I variants (Martorana & Lauria, 2020). The type I inhibitor avapritinib shows sub-nanomolar potency against D816H and engages an auxiliary Gα pocket (Teuber et al., 2024). Docking studies identify SML0140 as a lead compound effective against V654A/T670I/D816H (Martorana & Lauria, 2020).

## Other Comments

Gain-of-function KIT mutations drive GIST, systemic mastocytosis and subsets of AML, whereas loss-of-function alleles cause piebaldism (Lennartsson & Rönnstrand, 2012). Variant drug sensitivities include V560G (imatinib-sensitive), D816V (imatinib-resistant with altered specificity) and V654A/T670I (impaired imatinib binding but responsive to later-generation TKIs) (Lennartsson & Rönnstrand, 2012; Martorana & Lauria, 2020). The V560D mutant depends on PI3K activity even when KIT catalytic activity is inhibited (Lindblad et al., 2015).

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