CKIT

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Contents

Abstract

KIT is a type III receptor tyrosine kinase encoded by a gene locus on the long arm of chromosome 4. It is closely related to Fms-like tyrosine kinase 3 (FLT3), platelet-derived growth factor receptor alpha and beta (PDGFRα, PDGFRβ), and colony-stimulating factor 1 receptor (CSF1R). Depending on its degree of glycosylation, the molecular mass of KIT is 140–160 kD. KIT is normally expressed on the surface of hematopoietic stem and progenitor cells, mast cells, melanocytes, germ cells, and interstitial cells of Cajal. There are both transmembrane and soluble forms of KIT; however, the transmembrane form is believed to be biologically active, while the role of soluble KIT is poorly understood. The ligand for KIT is stem cell factor (SCF), also known as steel factor or mast cell growth factor. Both soluble and membrane-bound forms of SCF exist, resulting from alternative splicing of exon 6 (Broudy, Blood 90:1345–1364, 1997; Heinrich

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Keywords
ABL • BCR-ABL • JAK/STAT • KIT • MAP kinase • MetaGIST study • PI3-K • Platelet-derived growth factor receptor alpha (PDGFRα) • Platelet-derived growth factor receptor alpha (PDGFRα) • Stem cell factor (SCF)

Target: KIT (Formerly c-Kit)

KIT is a type III receptor tyrosine kinase encoded by a gene locus on the long arm of chromosome 4. It is closely related to Fms-like tyrosine kinase 3 (FLT3), platelet-derived growth factor receptor alpha and beta (PDGFRα, PDGFRβ), and colony-stimulating factor 1 receptor (CSF1R). Depending on its degree of glycosylation, the molecular mass of KIT is 140–160 kD. KIT is normally expressed on the surface of hematopoietic stem and progenitor cells, mast cells, melanocytes, germ cells, and interstitial cells of Cajal. There are both transmembrane and soluble forms of KIT; however, the transmembrane form is believed to be biologically active, while the role of soluble KIT is poorly understood. The ligand for KIT is stem cell factor (SCF), also known as steel factor or mast cell growth factor. Both soluble and membrane-bound forms of SCF exist, resulting from alternative splicing of exon 6 (Broudy 1997; Heinrich et al. 2002; Lennartsson and Ronnstrand 2006).

Biology of the Target

KIT is critical for hematopoiesis, the development and migration of melanocytes, the development of the gonads, gut peristalsis, and the survival and function of mast cells. In mice, KIT is the gene product of the white spotting locus (*W*), and SCF is encoded by the steel locus (*Sl*). It was observed that loss of function mutations at these two locations results in similar phenotypes – bone marrow failure/anemia, white spotting of the fur, loss of mast cells, abnormal peristalsis (decrease in the interstitial cell of Cajal), and sterility. Complete or near-complete loss of KIT expression is embryonic lethal. These observations prompted studies which suggested that SCF is the cognate ligand of KIT (Dexter and Moore 1977).

KIT becomes activated when stem cell factor (SCF) binds to the KIT extracellular domain. SCF is expressed by cells that make up the microenvironment of KIT-expressing cells including epithelial cells, endothelial cells, fibroblasts, Sertoli cells, etc. Binding of SCF leads to receptor dimerization, kinase activation, KIT autophosphorylation, and activation of downstream signaling pathways including the PI3-K, MAP kinase, and JAK/STAT pathways. Signaling via KIT promotes cell growth, survival, and proliferation. However, certain mutations in *KIT* lead to its constitutive activation in the absence of SCF. These activating mutations have been

linked to acute myeloid leukemia (AML), mast cell tumors, melanoma, seminoma, and gastrointestinal stromal tumors (GIST) (Lennartsson and Ronnstrand 2006; Lennartsson et al. 2005).

Activating KIT mutations can be located in the intracellular or extracellular domains. Extracellular mutations are typically located in exons 8 and 9. *KIT* exon 8 mutations are associated with AML, and these mutations are believed to induce hypersensitivity to SCF, rather than constitutive activation in the absence of SCF. Exon 9 mutations are found in approximately 10% of GIST patients. The activation mechanism of these mutations is being investigated and may be related to KIT dimerization or conformational changes; however, these mutations do cause constitutive activation in the absence of SCF. Intracellular mutations are most commonly associated with exons 11 and 17. Mutations in exon 11 are found in approximately 70% of GIST patients. These mutations occur in the juxtamembrane domain and prevent this autoinhibitory region from locking the kinase in "off" position in the absence of SCF. D816V, a mutation in exon 17, is associated with mast cell neoplasms, leukemia, and seminoma. This mutation is located in the activation loop and stabilizes the kinase activation loop in the active conformation, promoting spontaneous kinase activity.

Target Assessment

KIT protein expression is readily assessed in fixed tissue using immunohistochemistry (fixed tissue) or flow cytometry (blood, bone marrow) (Craig and Foon 2008; Turner and Goldsmith 2009; Miettinen and Lasota 2005; Rubin and Heinrich 2015). As noted below, measurement of KIT expression has some diagnostic utility. More importantly, detection of the presence or absence of *KIT* mutations is predictive of response of GIST, melanoma, and mast cell neoplasms to KIT kinase inhibitors.

Role of the Target in Cancer

Rank: 10

High-Level Overview

A number of KIT kinase inhibitors have been approved by the FDA. Three of these inhibitors, imatinib, sunitinib, and regorafenib, have specific FDA-approved indications for treatment of GIST (Blay 2010; Overton and Heinrich 2014). In addition, imatinib is FDA approved for treatment of adult patients with aggressive systemic mastocytosis without the D816V KIT mutation or with unknown *KIT* mutational status (Piccaluga et al. 2007). Multiple phase 2 trials have shown efficacy of imatinib and nilotinib in *KIT*-mutant melanoma, though no KIT inhibitors have been FDA approved for treatment of this disease (Hodi et al. 2013; Guo et al. 2011; Carvajal et al. 2011, 2015; Lee et al. 2015a).

Diagnostic, Prognostic, and Predictive

Over the past decade, immunohistochemistry for detection of KIT protein (CD117 antigen) has helped standardize the diagnosis of GIST (Rubin and Heinrich 2015). GIST is the most common spindle cell neoplasm (sarcoma) of the GI tract, but morphologically it can be difficult or impossible to distinguish from smooth muscle tumors, schwannomas, desmoids tumors (aggressive fibromatosis), and metastatic melanoma. Indeed, until the application of KIT immunohistochemistry to the pathologic classification of these lesions, GIST was not even recognized as a separate pathologic entity and these tumors were classified as either benign or malignant smooth muscle tumors (Turner and Goldsmith 2009; Miettinen and Lasota 2005). As noted below, the use of KIT kinase inhibitors has revolutionized the treatment of GIST – making the accurate diagnosis of GIST even more critical. KIT immunohistochemistry can also be used in the diagnosis of melanoma, AML, mast cell neoplasms, and germ cell tumors (Turner and Goldsmith 2009). In addition, KIT is a useful marker for flow cytometric identification of bone marrow blast cells and classification of cases of myelodysplastic syndrome and AML (Craig and Foon 2008).

The presence and type of *KIT* mutation found in primary GIST has been shown to have prognostic value in retrospective population studies (Andersson et al. 2006; Hou et al. 2009). Similar results have been shown in the placebo arm of a double blind, randomized study of placebo versus 1 year of adjuvant imatinib following curative intent resection of primary GIST. Notably, the presence of a *KIT* exon 11 in frame deletion mutation was associated with a much higher risk of recurrence than seen in tumors with other *KIT* genotypes (HR 3.45, $p = 0.024$ compared with wild-type tumors) (Turner and Goldsmith 2009; Miettinen and Lasota 2005; Corless et al. 2010). *KIT* mutation status also influences the effectiveness of adjuvant imatinib given after curative intent surgery, with patients whose GIST harbor *KIT* exon 11 mutations deriving the greatest benefit from 3 years of adjuvant imatinib compared with 1 year of adjuvant imatinib (Joensuu et al. 2016). *KIT* mutation data is now being incorporated into risk stratification algorithms to help predict the risk of recurrence after surgery and to help guide decision making concerning the use of adjuvant imatinib in GIST (Joensuu et al. 2015).

Translational studies utilizing tumor samples from large clinical studies have identified tumor genotype as a strong predictor of clinical benefit for patients with metastatic GIST treated with imatinib. Specifically, patients with *KIT* exon 11-mutant GIST (approximately 70% of GIST) have the highest rates of objective response, progression-free survival (PFS), and overall survival (OS) compared with patients whose tumors had no kinase mutations (wild-type GIST, approximately 10–15% of GIST) or GIST with somatic *KIT* exon 9 mutations (~10% of patients). In this SWOG/NCIC study, PFS was 24.7 months for *KIT* exon 11-mutant tumors versus 16.7 months for wild-type GIST and 12.8 months for patient with *KIT* exon 9-mutant tumors. In terms of the effect on overall survival, *KIT* exon 11-mutant GIST patients had a median OS of 60 months versus 38.4 months for wild-type GIST patients and 49 months for *KIT* exon 9-mutant GIST patients (Heinrich et al. 2003, 2008a; Debiec-Rychter et al. 2004, 2006).

The effect of tumor genotype and imatinib dose on clinical outcomes was also analyzed in the MetaGIST study (400 versus 800 mg dosing for metastatic GIST). Within patients with *KIT* exon 9-mutant GIST, PFS was significantly longer for patients treated with the high-dose arm ($P = 0.017$). For patients whose tumor had genotypes other than *KIT* exon 9 mutation, no difference in clinical outcomes was observed between treatment arms. In terms of OS, there was a trend toward a survival advantage for patients with *KIT* exon 9-mutant GIST treated with high-dose therapy ($p = 0.15$) (2010). Tumor genotyping is recommended in oncology professional guidelines to help optimize care of patients with newly diagnosed metastatic GIST (von Mehren et al. 2012, 2014). In addition, *KIT* mutation status has recently been incorporated into a prognostic nomogram for patient with metastatic GIST treated with first-line imatinib (Lee et al. 2015b).

Besides its impact on response to imatinib, *KIT* mutation status also influences clinical outcome in patients treated with sunitinib as second-line therapy for metastatic GIST. In contrast to the experience with first-line imatinib, patients with *KIT* exon 9-mutant or wild-type GIST are predicted to have better outcomes with sunitinib treatment compared with patients with *KIT* exon 11-mutant GIST (Heinrich et al. 2008b; Reichardt et al. 2016).

Therapeutics

To date, all of the FDA-approved anti-KIT therapeutics are small molecule tyrosine kinase inhibitors. Currently, there are numerous agents with KIT inhibitory activity that are FDA approved for treatment of one or more human malignancies, including imatinib, sunitinib, regorafenib, nilotinib, dasatinib, sorafenib, pazopanib, and ponatinib. However, only imatinib (GIST, mastocytosis), sunitinib (GIST), and regorafenib (GIST) are FDA approved for treatment of *KIT*-mutant disease.

Preclinical Summary

A large body of evidence has established KIT as therapeutic target, and subsequent research has studied the efficacy of various tyrosine kinase inhibitors in blocking its activity in vivo and in vitro. Research in 2000 by Ma et al. showed efficacy of a small group of indolinones against KIT (Ma et al. 2000). They also reinforced a direct link between KIT function and mast cell survival. In the same year, Heinrich et al. and Buchdunger et al. investigated the use of imatinib (formerly STI-571) as a KIT inhibitor. Imatinib was found to selectively inhibit KIT tyrosine kinase activity as well as inhibit the activation of downstream effector proteins. They also found that imatinib was more potent against certain activating KIT mutations than against WT KIT and concluded that the clinical profile of imatinib should be expanded to include KIT (in addition to its known targets: ABL, BCR-ABL, and PDGFRA and PDGFRB) (Buchdunger et al. 2000; Heinrich et al. 2000).

In this same time frame, Tuveson et al. developed a GIST tumor cell line – GIST882 – harboring an activating mutation in the KIT tyrosine kinase I domain. Incubation of this cell line with imatinib led to decreased proliferation and increased apoptosis supporting a role of KIT in GIST pathology and the therapeutic potential for imatinib in GIST patients (Tuveson et al. 2001). Later, in 2003, Abrams et al. evaluated the activity of sunitinib (formerly SU11248) against KIT in a small cell lung cancer model (Abrams et al. 2003). Treatment with sunitinib inhibited KIT tyrosine phosphorylation and cellular proliferation. The results of this study suggested a clinical potential for sunitinib in the treatment of tumors with activating KIT mutations.

KIT mutations are found in the vast majority of human mast cell neoplasms. In particular, the KIT D816V mutation is found in >90% of cases. Pre-clinical studies of mastocystosis cell lines and/or patient samples have shown that KIT inhibition by kinase inhibitors reduces proliferation and induces apoptosis of cells. Unfortunately, the D816V mutation is resistant to most of the available kinase inhibitors. However, these studies do indicate that KIT is a compelling target in mastocytosis and have spurred efforts to develop inhibitors with activity against the D816V mutation (Gotlib et al. 2005; Schittenhelm et al. 2006; Shah et al. 2006).

More recently, *KIT* mutations have been found in a subset of human melanoma. In particular, these mutations are more common in acral or mucosal melanomas. In vitro studies of *KIT*-mutant melanoma cell lines have demonstrated that KIT inhibitors can exert an anti-proliferative and pro-apoptotic effect on these cells (Beadling et al. 2008; Jiang et al. 2008).

All of these studies and many more have established KIT as a therapeutic target in cancers driven by the hyperactivation of KIT and demonstrated the efficacy of specific tyrosine kinase inhibitors in controlling cell growth resulting from KIT hyperactivity.

Clinical Summary

Prior to 2000, there was no active medical treatment for metastatic GIST (DeMatteo et al. 2002). However, the introduction of small molecule tyrosine kinase inhibitors (TKIs) has revolutionized the treatment of GIST. Currently, there are three FDA-approved treatments for advanced GIST: imatinib for front-line treatment, sunitinib for second-line treatment, and regorafenib for third-line treatment. A number of other TKIs have been tested in phase 2 studies for treatment of GIST in the fourth-line or later clinical setting. Overall, the use of KIT inhibitors has changed the prognosis for patients with metastatic GIST, with median survival increasing from an estimated 1–1.5 years to the current 6–8 years (Barrios et al. 2015). Notably, resistance to KIT inhibitors in *KIT*-mutant GIST is typically associated with the development of secondary *KIT* mutations that confer drug resistance (Heinrich et al. 2006, 2008b; Corless et al. 2011; Gramza et al. 2009). Developing new inhibitors to prevent or overcome secondary mutations is a major focus of ongoing GIST research (Blay 2010).

In addition to GIST, some therapeutic progress has been made in treating mast cell neoplasms with KIT kinase inhibitors. Currently, available KIT kinase inhibitors have reduced potency against the KIT D816V mutation associated with mast cell neoplasms (Verstovsek et al. 2008; Vega-Ruiz et al. 2009). However, it is anticipated that development of novel KIT inhibitors that are active against the D816V mutation will be clinically effective for treating mast cell neoplasms. Currently, imatinib is FDA approved for treatment of aggressive mastocytosis lacking the D816V mutation or with an unknown *KIT* genotype.

Clinical studies using KIT inhibitors to treat unselected cases of malignant melanoma have been disappointing (Wyman et al. 2006). However, KIT kinase inhibitors have shown strong activity against *KIT*-mutant melanoma (Hodi et al. 2008). Three phase 2 trials for imatinib and two for nilotinib have shown promising responses in *KIT*-mutant melanoma, specifically in mucosal, acral, and chronically sun-damaged subtypes (Hodi et al. 2013; Guo et al. 2011; Carvajal et al. 2011, 2015; Lee et al. 2015a). The disease control rate for patients with *KIT* mutations treated with imatinib was 77% (including partial response of 54%). To date, none of the tested KIT inhibitors has been approved by any national health authority agency for treatment of *KIT*-mutant melanoma.

Anticipated High-Impact Results

- Final reports from ongoing phase 2 and phase 3 studies of imatinib, sunitinib, or nilotinib for treatment of *KIT*-mutant melanoma
- Final analysis of the impact of *KIT* mutations on the clinical efficacy of adjuvant imatinib after resection of primary GIST
- Planned phase 1–2 studies of mechanistically novel KIT inhibitors with activity against D816V and other mutations that are resistant to current inhibitors

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