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Targeted therapies in gastrointestinal stromal tumors

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The discovery of constitutive KIT activation as the central mechanism of gastrointestinal stromal tumor (GIST) pathogenesis suggested that inhibiting or blocking KIT signaling might be the milestone in the targeted therapy of GISTs. Indeed, imatinib mesylate inhibits KIT kinase activity and represents the front-line drug for the treatment of unresectable and metastatic GISTs. Despite a high rate of response in patients with *KIT* exon 11 mutated GISTs, the failure rate is significantly higher in patients with a wild-type genotype, suggesting an alternative activated pathway not targeted by imatinib therapy. The most common mechanism of resistance is through polyclonal acquisition of second-site mutations in the kinase domain, which highlights the future therapeutic challenges in salvaging these patients after failing kinase inhibitors monotherapies. This review article summarizes the recent knowledge accumulated on targeted therapy in GIST, based on the central role of KIT oncogenic activation and subsequent signal transduction in the pathogenesis of GIST. In addition, we provide an updated discussion on diagnostic pitfalls, including changes secondary to imatinib response and resistance.

Molecular targeted therapy refers to a new generation of anticancer drugs that are designed to interfere with a specific molecular target, usually a protein, which plays a critical role in tumor growth or progression. This approach differs significantly from conventional cytotoxic chemotherapy. Chemotherapy agents disrupt DNA synthesis and cell division in rapidly dividing cells, but have low selectivity and typically do not discriminate normal cells from tumor cells, thus being associated with several cytotoxic side effects. In contrast, the molecular targets of targeted therapy are protein kinases, which are expressed or constitutively activated in tumor cells and play a central role in tumorigenesis. Receptor tyrosine kinases (RTKs) occupy a position at the top of cellular growth and proliferation signal transduction cascades, and their aberrant activation is often implicated in human disease. RTKs thus are attractive targets for therapeutic intervention by small-molecule inhibitors. Many of these inhibitors are competitive with ATP, binding at the conserved kinase nucleotide binding site, and are often targeted to the active kinase conformation. Drugs that target distinct inactive kinase conformations, however, are likely to attain a greater degree of specificity. The specific inhibition of these targets contributes to the high efficacy and less side effects. As a result, the success of targeted therapy in gastrointestinal stromal tumors (GISTs) has become a model for molecular therapy in oncology.

The structural basis of imatinib inhibition of KIT

Imatinib is a 2 phenyl-amino-pyrimidine derivative, which specifically binds to the inactive conformation of the Abl kinase or the inactive form of KIT (Figure 1). In more than 75% of the cases, KIT mutations identified in GISTs are localized within exon 11, which encodes for the juxtamembrane domain of the receptor. This juxtamembrane region plays an autoinhibitory function for the kinase activity, by inserting into the kinase-active site and disrupting its acti-

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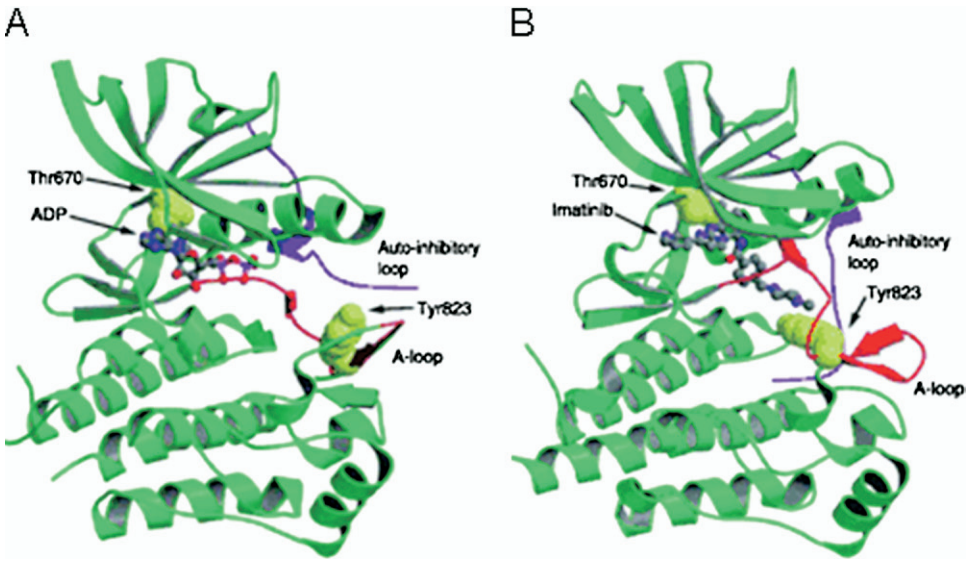

Figure 1 Interaction of imatinib and the KIT kinase. The activation loop (A-loop; 809-831) is highlighted in red, and the autoinhibitory domain (547-579) is highlighted in purple. (A) Active form with ADP bound (ADP is shown as ball-and-stick representation). (B) Inactive form with imatinib bound (imatinib shown as ball-and-stick representation). (Adapted from Antonescu and coworkers.[35])

vated structure and thus stabilizing KIT in its inactive form.[1] Studies using a synthetic peptide of KIT juxtamembrane region suggest that it folds as an autonomous domain and directly interacts with the amino-terminal lobe of the kinase domain.[2] A 1.6-Å resolution cocrystal structure of a KIT–imatinib complex illustrates that portions of the inhibitor would clash with regions of the juxtamembrane domain that maintain KIT in the autoinhibited conformation, thus disrupting the physiologic mechanism for maintaining KIT in an autoinhibited state (Figure 1).[3]

The molecular basis of the GIST paradigm for targeted therapy

GIST is the most common sarcoma of the intestinal tract. Nearly all tumors have a mutation in the *KIT* or, less often, *PDGFRA* or *BRAF* gene.[4–6] KIT was originally identified as the cellular homologue of the retroviral oncogene v-kit in the Hardy-Zuckerman-4-feline sarcoma virus.[7] In humans, the *KIT* gene maps to 4q12-13, in the vicinity of the genes encoding for PDGFRA and FLK1 receptor tyrosine kinases, and is composed of 21 exons, spanning 65 kb. The KIT protein belongs to the class III of tyrosine kinase receptors, together with M-CSF (macrophage colony stimulating factor) and PDGFR, based on their sequence homology and similar conformational structure. The KIT autophosphorylation on tyrosines and the association of KIT with substrates transduces the signals for various cellular responses, including cell proliferation, survival, adhesion, chemotaxis, and secretory responses. The downstream signaling cascades known to activate KIT include the Ras/MAP kinase, Rac/Rho-JNK, PI3K/AKT, and SFK/STAT signaling networks.

The revelation of KIT expression as a diagnostic signature of GIST has not only revolutionized the pathologic criteria in classifying GIST, but also shed light on the histogenesis of these tumors. The similarities in KIT immunoreactivity and ultrastructural appearance between GISTs and the intestinal pacemaker, the interstitial cells of Cajal (ICC), suggested that GISTs derive from or differentiate toward the ICC lineage. KIT plays a significant role in proliferation, survival, and differentiation of hematopoietic stem cells, mast cells, melanocytes, and ICC; and activating *KIT* mutations have been identified in tumors affecting most of these cell lineages.

Oncogenic KIT activation is the initiating event in GIST tumorigenesis. GIST patients harbor different oncogenic mutations in *KIT* and *PDGFRA,* which have distinct responses to imatinib. Imatinib mesylate (STI571, Gleevec; Novartis Pharmaceuticals, Basel, Switzerland) is a selective tyrosine kinase inhibitor whose targets include KIT and PDGFRA. Imatinib treatment achieves a partial response or stable disease in about 80% of patients with metastatic GIST. KIT mutation status has a significant impact on treatment response. Patients with the most common exon 11 mutation experience higher rates of tumor shrinkage and prolonged survival, as tumors with an exon 9 mutation or wild-type *KIT* are less likely to respond to imatinib.[8] Furthermore, tumors with activation loop mutations particularly show the least response to imatinib inhibition. Although imatinib achieves a partial response or stable disease in the majority of GIST patients, complete and lasting responses are rare. About half of the patients who initially benefit from imatinib treatment eventually develop drug resistance. More recently, sunitinib (Sutent; Pfizer, New York, NY), which inhibits VEGFR in addition to KIT and PDGFRA, has