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Genetic Aberrations of Gastrointestinal Stromal Tumors

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Abstract

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal neoplasm in the gastrointestinal tract and is associated with mutations of the *KIT* or *PDGFRA* gene. Additionally, other genetic events are thought to be involved in GIST tumorigenesis. Cytogenetic aberrations associated with these tumors thus far described include loss of 1p, 13q, 14q, or 15q, loss of heterozygosity of 22q, numerical chromosomal imbalances, and nuclear/mitochondrial microsatellite instability. Molecular genetic aberrations include loss of heterozygosity of *p16(INK4A)* and *p14(ARF)*, methylation of *p15(INK4B)*, homozygous loss of the *Hox11L1* gene, and amplification of *C-MYC*, *MDM2*, *EGFR1*, and *CCND1*. GIST in patients with neurofibromatosis type 1 seem to lack the *KIT* and *PDGFRA* mutations characteristic of GIST and may have a different pathogenetic mechanism. Gene mutations of *KIT* or *PDGFRA* are critical in GIST, because the aberrant versions not only are correlated with the specific cell morphology, histologic phenotype, metastasis, and prognosis, but also are the targets of therapy with imatinib and other agents. Furthermore, specific mutations in *KIT* and *PDGFR* appear to lead to differential drug sensitivity and may in the future guide selection of tyrosine kinase inhibitors. Activation of the receptor tyrosine kinases involves a signal transduction pathway whose components (MAPK, AKT, PI3K, mTOR, and RAS) are also possible targets of inhibition. A new paradigm of classification integrating the standard clinical and pathological criteria with molecular aberrations may permit personalized prognosis and treatment.

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Keywords

GIST; genotype; karyotype; receptor tyrosine kinase

Introduction

Sarcomas may be divided into two groups based on cytogenetic and molecular genetic characteristics: (1) those with a frequently diploid karyotype and limited chromosomal abnormalities but with frequently observed specific translocations and (2) those with complex karyotypes and multiple cytogenetic and molecular genetic aberrations. Gastrointestinal stromal tumors (GIST) are generally believed to belong to the former group and are the most common mesenchymal tumors of the gastrointestinal tract. The 2 most important prognostic features of primary GIST are tumor size and mitotic index, which were the foundation for a consensus approach to risk stratification of GIST published in 2002. The anatomic location also significantly affects the risk of disease recurrence and progression and this is noted in the 2007 NCCN risk stratification criteria.1,2

More than 90% of GISTs harbor a specific *KIT* or *PDGFR-alpha* (*PDGFRA*) gene mutation. These mutations are important for tumor phenotype, and their presence correlates with benefit from targeted therapy with the kinase inhibitor imatinib mesylate (Gleevec). Besmer et al. first showed that *v-kit* is an oncogene,3 and it has been demonstrated since then that germline *KIT* mutation leads to imatinib-sensitive GIST in an autosomal dominant pattern.4 Moreover, the identification of *KIT* and *PDGFRA* mutations in GIST has led to development of imatinib, sunitinib, and other tyrosine kinase inhibitors for the treatment of solid tumors. Most GISTs have other genetic aberrations besides *KIT* and *PDGFRA* mutations. Understanding the genetic aberrations beyond *KIT* and *PDGFRA* may lead to identification of additional therapeutic targets for GIST and possibly other cancers. Herein we provide a comprehensive compendium of known cytogenetic and molecular abnormalities in GIST.

Cytogenetic Aberrations

Loss of chromosome 14 and/or 22 with minimal recurrent regions in 14q11.2–q32.33 (5 of 7, 71% of tumors) and 22q12.2–q13.31 (7 of 7, 100%) appears to play an important role in early stages of tumor formation as well as in late tumor progression.5–7 In the report by Wozniak et al, all the 66 primary GISTs had genomic imbalances, most frequently loss of 14q, 1p, 22q, 15q, or 13q. Furthermore, lower incidence of losses at 14q and higher frequency of losses at 1p and 15q were the most common findings in nongastric GIST. These findings suggest that loss of 14q is a relatively less frequent genetic event in the development of nongastric GIST.8 Chen et al. investigated the chromosomal imbalance aberrations in 28 GIST and found that losses were more common than gains. The median number of chromosomal imbalance aberrations in high-risk GIST was significantly higher than that in low-risk GIST, especially for losses. Among the chromosomal imbalance aberrations, losses of 13q, 10q, and 22q suggest that these chromosomal loci were most likely to harbor the tumor suppressor gene(s) that may be related to early recurrence and/or metastasis during malignant transformation of GIST.9 Another investigation detected nuclear and mitochondrial microsatellite instability in 3 and 10 of 62 GIST, respectively, and the chromosomal numerical abnormality in the primary sites was more extensive in GIST with recurrence and metastasis than in those without. These results indicated that mitochondrial microsatellite instability plays a role in the development of GIST and that numerical chromosomal abnormalities may be a phenotype associated with more aggressive tumors with a propensity to metastasize and recur locally.10,11

As shown in Table 1, the cytogenetics of GIST in some cases is so complex that an oncogenetic tree model was constructed using CGH data from 203 primary GIST.12 The oncogenetic tree model identified 3 major cytogenetic pathways: one initiated by −14q, one by −1p, and another by −22q. The −14q pathway mainly characterized gastric tumors with predominantly stable karyotypes and more favorable clinical course. On the other hand, the −1p pathway was more characteristic of intestinal GIST, with an increased capacity for cytogenetic complexity and more aggressive clinical course. Loss of 22q, more closely associated with −1p than −14q, appeared to initiate the critical transition to an unfavorable cytogenetic subpathway.12 Furthermore, Pylkkäen et al. found that allelic losses at 22q were associated with high mitotic activity and recurring disease. Thus, insights into the cytogenetic evolution obtained from oncogenetic tree models may eventually help to improve our understanding of the heterogeneous biological behavior of GIST.8,13

Molecular genetic aberrations of *KIT* and *PDGFRA*

Activation of the KIT receptor tyrosine kinase (RTK) is a central pathogenetic event in most GIST and generally results from oncogenic, gain-of-function, in-frame deletions or point mutations that can involve either the extracellular juxtamembrane or cytoplasmic domains of the receptor. Oncogenic mutations enable the KIT receptor to phosphorylate various substrate proteins, leading to activation of signal transduction cascades that regulate cell proliferation, survival, chemotaxis, and adhesion (Table 2). *KIT* mutations can be assigned broadly to one of 2 groups: (1) those that involve the "regulatory" regions responsible for modulating KIT enzymatic activity and (2) those that involve the enzymatic region itself. Published reports indicate that *KIT* mutations in untreated GIST are clustered primarily in 4 exons: 9, 11, 13 and 17. Most common are exon 11 (intracellular juxtamembrane domain) mutations that include deletions, point mutations, and duplications of the 3′ region. Exon 13 and 17 mutations are almost exclusively point mutations, occur in several hot spots, and the frequency of exon 13 or exon 17 mutations is no higher than 1–2%. Almost all of the KIT exon 13 mutations were the 1945A>G substitution leading to L642G. A majority of the KIT exon 17 mutations were the 2487T>A substitution leading to A822L. They may be more commonly present in small bowel GIST and exon 13 mutation may predict a more aggressive course in gastric GIST.14⁻19 An A842V substitution in exon 18 is the most common PDGFRA mutation. GISTs with such mutation are resistant to imatinib. PDGFRA mutations are associated with gastric GISTs, epithelioid morphology and a less malignant course of disease.18 Recently, with the use of imatinib therapy, a new class of mutations associated with resistance to this treatment has been discovered. These are virtually all point mutations that involve a limited number of codons in exons such as 13, 14, 17, and 18 of *KIT* and sometimes *PDGFRA* and are rarely encountered in untreated GIST. The primary mutations are retained, but these additional or secondary mutations make the KIT receptor less sensitive to inhibition by imatinib, sometimes by actually affecting binding of the drug to the cytoplasmic tyrosine kinase domain.19

GISTs are thought to originate from interstitial cells of Cajal (ICC) or their precursors. Ogasawara et al. suggested that ICC undergoing *KIT* mutation as a possible early initiation step in GIST tumorigenesis may thus have preneoplastic potential.20 Agaimy et al. also considered that GIST tumorlets represent the grossly recognizable counterpart of sporadic ICC hyperplasia caused by somatic *KIT* or *PDGFRA* mutations.21 In this recent study, 12 of 19 sporadic ICC hyperplasia lesions were investigated by molecular analysis and the investigators found found three KIT exon 11 mutations (2 point mutations and 1 deletion, all involving W557) in 3 cases. Furthermore, the remarkable variation in the incidence of ICC hyperplasia at different GI sites suggests an origin from heterogeneous subsets of ICC with varying potentials for neoplastic transformation.22

Molecular aberrations of other genes

More and more genes, including tumor suppressor genes, have been found to harbor abnormalities in GIST that are closely correlated with tumorigenesis, such as p16. Sabah et al. demonstrated that LOH with at least one microsatellite marker at the 9p region was a common finding in high-risk GIST and recurrent GIST showed more frequent deletions than their cognate primary tumors. These results suggest that loss of the *p16(INK4A)* gene on 9p may contribute to the progression and/or malignant transformation of GIST.23 To assess the involvement of *p14ARF* and *p15INK4B* in addition to *p16INK4A* in GIST, Perrone et al. undertook a molecular and cytogenetic study of the 9p21 locus. The results indicated the loss of *p16INK4A* mRNA expression in 41% of the GIST studied, mainly due to homozygous deletion of both the *p16INK4A* gene. No mutations were found, and promoter methylation was restricted mainly to the *p15INK4B* gene. Alterations in the 9p21 locus were found cumulatively in 54% of the tumors in this series and comprised mainly loss of tumor suppressor gene expression.3›24 These results were further supported by the investigation of Assämäki et al., which found that most recurrent copy number losses were localized to 14q, 22q, 1p, and 9p, harboring the *PARP2*, *APEX1*, *NDRG2*, *SIVA*, *ENO1*, and *CDKN2A/2B* genes.25 At the same time it was demonstrated that the *Hox11L1* gene, which is located on chromosome 2 and exerts a role in proliferation of ICC, had homozygous loss in 7 of 72 GIST. These data implicate *Hox11L1* in the tumorigenesis of GIST.26

To determine whether known oncogenes take part in genomic rearrangements and to investigate the potential clinical significance of their amplifications, the oncogenes *C-MYC*, *MDM2*, *GLI1*, *CDK4*, *HER2*, *EGFR1*, *CCND1*, *FGF3*, and *EMS* were analyzed by fluorescent in situ hybridization on a tissue microarray containing 94 primary GIST. Amplification was found for *C-MYC* in 3 of 90 cases, for *MDM2* in 5 of 94, for *EGFR1* in 5 of 94, and for *CCND1* in 7 of 79. Amplifications of *MDM2* and *CCND1* were associated with clinical and histologic malignancy. The data show that gene amplification does occur in a subset of GIST. *MDM2/CCND1* amplification may represent a molecular feature important in the pathogenesis of some GIST.27 West et al. also characterized gene expression patterns in GIST and found that the gene *FLJ10261* (*DOG1*, discovered on GIST-1), encoding a hypothetical protein, was specifically expressed in GIST. Immunoreactivity for DOG1 was found in 136 of 139 (97.8%) GIST; all 7 GIST cases with a *PDGFRA* mutation were DOG1 positive, while most of these were KIT negative. These findings suggested the *DOG1* may be involved in GIST tumorigenesis.28›29 Other genes such as *PKCtheta* have also proven to be useful markers and may play roles in the development of GIST; expression of the *obscurin* and *prune2* genes can be helpful in differentiating GIST and leiomyosarcomas.30›31

Molecular genetic aberrations and clinicopathologic features

Reports showing that molecular genetic aberrations in GISTs are correlated with specific cell morphologies and histologic phenotypes are accumulating. Wardelmann et al. provided evidence that GIST may be divided into distinctive entities with different genetic, biological, and phenotypic features. They found *PDGFRA*-mutated tumors were preferentially located in the stomach, whereas GIST with exon 9 and 13 *KIT* mutations occurred predominantly in the small bowel. Furthermore, GIST carrying *PDGFRA* mutations displayed an epithelioid or mixed phenotype, while *KIT*-mutated GIST almost always exhibited a spindled or mixed histologic pattern.32 The investigators also found that some mutations were located in the second kinase domain of *PDGFRA*, including 16 point mutations and 4 larger deletions of 9 to 12 bp. The occurrence of *PDGFRA* mutations was significantly associated with a higher frequency of epithelioid or mixed morphology and gastric location. These data indicate that GIST can be conceptualized as distinctive subsets, differing in genetic, biological, and

morphological features.33 Additional studies have confirmed these findings.16,19,34 The correlations between mutation and primary site by examining expression of *KIT* and *PDGFRA* in a large series of primary GIST also confirmed the results. GIST with *KIT* mutation had a significantly higher expression of KIT and at the same time a significantly lower expression of PDGFRA than GIST with *PDGFRA* mutation. Concerning the site of the primary tumor, gastric GIST had a significantly higher expression of PDGFRA and a significantly lower expression of KIT than intestinal GIST. Even though GIST with higher PDGFRA expression constitute only a minority of gastric cases, the higher PDGFRA expression may contribute to the site-dependent clinical behavior of these tumors.34,35

In summary, exclusive gain-of-function *KIT* or *PDGFRA* mutations occur in a majority of GIST; these include in-frame deletions, point mutations, duplications, and insertions. Mutation of the KIT juxtamembrane domain is the most common mutation site independent of the site of the primary tumor. On the other hand, *KIT* extracellular domain Ala502-Tyr503 duplication appears to be relatively specific for intestinal GIST. Mutations in *PDGFRA* have been identified in juxtamembrane and tyrosine kinase domains, mostly in gastric GIST and the epithelioid histologic variants.

Genetic aberrations of extragastrointestinal stromal tumors

Extragastrointestinal stromal tumor (EGIST) is a unique tumor that occurs outside the gastrointestinal tract. EGIST have a histologic appearance similar to that of GIST. Yamamoto et al. examined the clinicopathologic features, prognostic factors, and *KIT* and *PDGFRA* mutations in 39 cases of EGIST. The *KIT* mutations were found in exon 11 in 12 of 29 cases and in exon 9 in 2 of 29 cases. The *PDGFRA* gene mutation was found at exon 12 and 18 in one case each. The pattern of *KIT* and *PDGFRA* mutation in EGIST was essentially similar to that of GIST, albeit at a lower frequency.36

Genetic aberrations of GIST in other tumors

GIST has an apparent association with other cancers, such as neurofibromatosis type 1 (NF1). NF1 is caused by mutations of the *NF1* gene, and patients with such mutations have an elevated risk of developing GIST. In study of Kinoshita et al., none of the 29 GIST derived from NF1 patients had detectable *KIT* mutations and none of the 10 GIST derived from patients without NF1 had detectable *NF1* mutations.37 The biggest case analysis, by Miettinen et al., showed that in 45 patients who had NF1 and GIST, none of the 16 tumors from 15 patients had a *KIT* mutation in exon 9, 11, 13, or 17 or a *PDGFRA* mutation in exon 12 or 18 mutation as is typical in sporadic GIST. These data clearly indicate that GISTs in NF1 patients have a different pathogenesis than sporadic GIST.38 Data from others confirm this, and they suggest that the molecular event underlying GIST development in this patient group may be a somatic inactivation, such as LOH of the wild-type *NF1* allele. This leads to inactivation of neurofibromin and subsequent activation of the MAP-kinase pathway. Interestingly, the JAK-STAT3 and PI3K-AKT pathways were less activated in NF1-related GIST than in sporadic GIST.39,40 Recently, Pasini et al. reported a patient who had a unique combination of multiple fibrous polyps and lipomas of the small intestine and several gastric GISTs. The patient was found to carry a germline *PDGFRA* mutation (V561D) in the heterozygous state, which has been seen only rarely before and only in sporadic GIST. CGH identified losses of chromosomal regions 1p33–36, 9q12–24, 11q13, and 16q.41 Carney triad is an extremely rare syndrome with three types of tumors present including GIST, extra-adrenal paragangliomas and pulmonary chondromas. Incomplete Carney triad cases have two of the three tumor types present, usually the GISTs and chondromas. Agaimy et al. evaluated GIST from 3 women with incomplete Carney triad for *KIT* and *PDGFRA* mutations and found all cases had wild-type *KIT* exons 9, 11, 13, 17 and *PDGFRA* exons

12,18. CGH revealed 14 aberrations, including 11 gains (X, 1q, 5p, 8q, 9p, 12p, 13q, 18p, 19q), 2 amplifications (1q, 19p) and one loss (13q). Carney triad-related GIST not only lack conventional *KIT* and *PDGFRA* mutations, but they also lack the nonrandom loss of 14q and 22q characteristic of their sporadic counterparts, suggesting an origin through a distinct pathogenetic pathway.42

Prognostic value of genetic aberrations

Singer et al. evaluated the prognostic relevance of *KIT* mutations in a series of GIST and determined that particular *KIT* mutation types are associated with prognosis. The independent predictors of disease-free survival were the presence of deletion/insertion exon 11 mutations, mixed histologic patterns, and male sex. These results suggest that *KIT* mutation and activation are important in GIST pathogenesis and also may provide important prognostic information.15 In a population-based series involving long-term follow-up of 177 GIST patients not treated with imatinib, investigators found that *KIT* exon 11 deletions adversely affected outcome. It was suggested that *KIT* exon 11 deletion is an independent adverse prognostic factor in patients with GIST.43 Cho et al. and others also reported that *KIT* mutation-positive GIST showed more frequent liver metastases and higher mortality than *KIT* mutation-negative GIST, which indicates that *KIT* mutations, especially deletions in exon 11, are markers of poor prognosis for pre-imatinib gastric GIST.44 Miettinen M et al. examined 906 patients with GISTs of the jejunum, ileum and found similar results.45 Deletions affecting codons 557 to 558 are also relevant for the prognosis in GIST patients. This genetic alteration could be considered in prognostic stratification of GIST patients for randomized trials exploring imatinib mesylate in the adjuvant setting.46

Kikuchi et al. suggested that LOH of the *KIT* gene is an important event that leads to imatinib resistance and metastatic progression of GIST, which played an important role in aggressive tumor behavior and perhaps the process of liver metastasis.47,48 What is more, Lasota et al. documented shifting from heterozygosity to homozygosity of *KIT* exon 11 mutations during tumor progression in metastases, but not in primary GIST.49 At the same time, a small subset of GIST with otherwise typical clinicopathologic and cytogenetic features did not express detectable KIT protein. When compared with KIT-positive GIST, these KIT-negative GISTs are more likely to have epithelioid cell morphology, express *PDGFRA* oncogenic mutations, and arise in the omentum/peritoneal surface. Notably, some KIT-negative GIST contained imatinib-sensitive *KIT* or *PDGFRA* mutations; therefore, patients with KIT-negative GIST should not, *a priori*, be denied imatinib therapy.50

Haller et al. examined the prognostic relevance of the CDKN2A tumor suppressor pathway in GIST and found that low mRNA expression of the *CDKN2A* transcripts *p16* and *p14* but high mRNA expression of *CDK4*, *RB1*, *MDM2*, *TP53*, and *E2F1* was associated with aggressive clinical behavior and unfavorable prognosis. Univariate analysis revealed high expression of E2F1 to be associated with mitotic count, proliferation rate, *KIT* mutation, and aggressive clinical behavior. The findings implicate differential regulation schemes of the CDKN2A tumor suppressor pathway converging to upregulation of E2F1 as a critical link to increased cell proliferation and adverse prognosis in GIST.51 Not only do the molecular genetic aberrations correlate with prognosis, but cytogenetic aberrations also have prognostic value in pre-imatinib GIST patients (Table 4).26,52

However, findings on the prognostic value of mutations of *KIT* and *PDGFRA* genes present different opinions. In one study of 134 Taiwanese GIST patients, *KIT/PDGFRA* mutations, 99% in *KIT* and 1% in *PDGFRA*, regardless of the location (exon 9 versus 11) and type (missense, insertion, or deletion, including deletion specifically involving codons 557 and 558), were not significantly associated with a poor progression-free survival rate.

Comparing overall survival in imatinib-treated patients, there was no significant difference between patients with exon 11 mutation and those with exon 9 mutations.53 This study raises the question of the racial differences in this prognostic significance. These questions need further investigation.

Genetic alterations and targeted therapy

Because most GISTs have an activating mutation of *KIT* or *PDGFRA* tyrosine-kinase receptors, imatinib, a selective inhibitor of ABL, KIT, and PDGFR tyrosine kinases, provides a clinical benefit in most patients with advanced GISTs.54,55 The proteins inhibited by imatinib and other inhibitors of specific tyrosine kinases are shown in Table 5. Imatinib treatment markedly inhibited KIT, MAP, and Akt phosphorylation in all transfectants, leading to reduced glucose uptake via decreased levels of plasma membrane-bound Glut4 and induction of apoptosis and/or growth arrest.56 Long-term results from a randomized phase II trial by Blanke et al. showed that nearly 50% of patients with advanced GIST who were treated with imatinib survived for more than 5 years, regardless of a 400 or 600 mg/d starting dose.57 Chen et al. found the effect of imatinib on KIT(820Tyr) was weaker than that on KIT(del559–560) or KIT(642Glu), indicating varying biological effects of imatinib on GISTs that have different *KIT* and *PDGFRA* mutational settings.58 In the recently published randomized EORTC phase III trial study, tumors with mutation in *KIT* exon 11 showed response rates of up to 80%, whereas fewer than 50% of tumors with mutation in *KIT* exon 9 responded.59 The presence of exon 9-activating mutations in KIT was the strongest adverse prognostic factor for response to imatinib, increasing the relative risk of progression by 171% and the relative risk of death by 190% when compared with KIT exon 11 mutants. Similarly, the relative risk of progression was increased by 108% and the relative risk of death by 76% in patients without detectable KIT or PDGFRA mutations. In patients whose tumors expressed an exon 9 KIT oncoprotein, treatment with the high-dose regimen (800mg/d) resulted in a significantly superior progression-free survival, with a reduction of the relative risk of 61%. GISTs without detectable *KIT* mutation in either of these exons often are resistant to imatinib.59 From these data it is apparent that therapeutic insight can be gained by genotyping of *KIT* and *PDGFRA* before imatinib therapy.

As more experience with imatinib has accumulated, primary and secondary resistance to this agent is becoming a major clinical challenge. As many as 40% of patients with GIST develop secondary resistance to imatinib, which often is due to secondary *KIT* mutations occurring in addition to the primary mutation.56 Chen et al. reported for the first time the presence, after imatinib treatment, of an additional specific and novel *KIT* mutation in imatinib-resistant GIST. They studied 12 GIST patients with initial near-complete response to imatinib. Seven harbored mutations in *KIT* exon 11 and 5 harbored mutations in exon 9. Within 31 months, 6 rapidly progressive, imatinib-resistant peritoneal implants developed in 5 of these patients. All 6 imatinib-resistant implants showed an identical novel *KIT* missense mutation, 1982T→C, which resulted in V654A in *KIT* tyrosine kinase domain 1. This novel mutation was not present in pre-imatinib or post-imatinib residual quiescent GIST, and was strongly correlated with imatinib resistance. Allele-specific sequencing data showed that this new mutation occurred in the allele that harbored the original activating mutation of *KIT* suggesting that resistance emerged under the selective pressure of imatinib.60 Tamborini et al. also reported a novel point mutation in *KIT*, in exon 14, which resulted in T670I substitution. Functional analyses showed that *KIT* T670I is insensitive to imatinib and that introduction of this mutation into a receptor responding to imatinib subverted its sensitivity to the drug.61 Debiec-Rychter et al. performed a cytogenetic analysis and screened for mutations of the *KIT* and *PDGFRA* kinase domains in 26 resistant GIST. Six distinct secondary *KIT* mutations were detected in 12 progressive tumors; of these, V654A and T670I were frequent. One progressive tumor showed an acquired *PDGFRA* D842V

mutation. GIST cells carrying *KIT*-del557–558/T670I or *KIT*-insAY502–503/V654A mutations were resistant to imatinib, while PKC412 significantly inhibited autophosporylation of these mutants. Resistance to imatinib and sensitivity to PKC412 of *KIT* T670I and *PDGFRA* D842V mutants was confirmed using Ba/F3 cells.62

Multiple studies indicate several point mutations involving secondary mutation in the kinase domain of *KIT*, including T670I, T823A, V654A, and other sites of exons 13, 14, 17, and 18, conferring imatinib resistance in GIST. Furthermore, secondary mutations T670I and V654A confer imatinib-acquired resistance, and the former is more resistant to imatinib than the latter.63¯69 Heinrich et al. found that imatinib-resistant tumors had levels of activated KIT that were similar to or greater than those typically found in untreated GIST. Secondary kinase mutations were rare in GIST with primary resistance but frequent in GIST with secondary resistance. Evidence for clonal evolution and/or polyclonal secondary kinase mutations was seen in 3 of 16 patients. Secondary kinase mutations were nonrandomly distributed and were significantly more associated with decreased imatinib sensitivity than typical *KIT* exon 11 mutations. Using RNAi technology, these investigators demonstrated that imatinib-resistant GIST cells remain dependent on KIT kinase activity for activation of critical downstream signaling pathways. From these data it is clear that different molecular mechanisms are usually responsible for primary and secondary imatinib resistance in GIST. 70

In the study of Desai et al., a unique "resistant clonal nodule" pattern (defined as a new enhancing nodular focus enclosed within a preexisting tumor mass) was seen in 23 of 48 patients and was thought to represent emergence of clones resistant to imatinib. This investigation revealed new activating kinase mutations in 80% (8 of 10) of the examined tumors. The resistant clonal nodule is a unique pattern of disease progression seen in patients with GIST after an initial response to imatinib and reflects emergence of imatinib-resistant clones. A new enhancing nodule growing within a preexisting tumor mass should be classified as a new lesion and be regarded, at least, as partial progression of GIST.71

All of these data highlight the potential mechanisms of resistance to imatinib and would be useful in clinical treatment, but the precise molecular mechanisms of this drug resistance are not well understood. Mahadevan et al. found that the imatinib-resistant GIST cell line (GIST-R) developed from the imatinib-sensitive GIST882 cell line acquires imatinib resistance by overexpressing the oncogenic RTK AXL in a “kinase switch.” Real-time PCR and western blotting of the GIST-S (sensitive) and GIST-R cells confirmed the switch from KIT to AXL. This switch is associated with a morphological change from spindle to epithelioid histologic pattern. Molecular modeling of the kinase domain of mutant *KIT* exon 13 (V654A) and AXL showed no binding to imatinib.72 From the present reports about drug resistance of GIST, Tarn et al. considered that the phenomenon of resistance to treatment, which arises primarily through selection for secondary mutations in GIST, could also involve amplification or activation of other RTK. Alteration of drug sensitivity can be fought by specific RTK inhibitors, and RTK activation involves a transduction pathway whose components (MAPK, AKT, PI3K, mTOR and RAS) are possible targets of new molecular treatment. A new paradigm of classification integrating the classic pathological criteria with the molecular changes may eventually facilitate more personalized prognosis and treatment.73 Furthermore, there are patients with primary GIST that lack mutations in either *KIT* or *PDGFRA*, or express "imatinib-resistant" mutations in these genes. These tumors typically do not respond well to imatinib therapy. The use of “second-generation” KIT and PDGFRA inhibitors is still in its early stages, but is promising, as some of these drugs use alternative molecular mechanisms that may be able to counter primary or secondary resistance to imatinib. Use of rational combinations of inhibitions to prevent or slow the development of resistance may be useful. This may not be the complete solution

and identifying additional genetic factors that contribute to the pathogenesis of GIST, independent of KIT and PDGFRA, may be important in developing additional anti-GIST therapies. New drugs that can serve as alternative therapies in imatinib-resistant GIST or that can be used in combination with imatinib are needed.

Summary

GIST is the most common malignant mesenchymal tumor in the gastrointestinal tract and is typically characterized by specific *KIT* or *PDGFRA* gene mutations. In addition to *KIT* and/or *PDGFRA* mutation, other genetic events are likely involved in tumorigenesis. Described cytogenetic aberrations include loss of 1p, 13q, 14q, 15q, and 22q; chromosomal numerical and imbalance aberrations; and nuclear/mitochondrial microsatellite instability. Other molecular genetic aberrations include LOH of *p16(INK4A)* or *p14(ARF)*; methylation of *p15(INK4B)*; homozygous loss of *Hox11L1*; amplification of *C-MYC*, *MDM2*, *EGFR1*, and *CCND1*; and others. GISTs in patients with NF1 seem to lack *KIT* and *PDGFRA* mutations and appear to have a different molecular mechanism. Molecular genetic aberrations of the *KIT* or *PDGFRA* gene are correlated not only with the specific cell morphology, metastasis, and prognosis, but also with the efficacy of targeted therapy, especially imatinib. Because the biological effects of imatinib vary with the site of *KIT* and *PDGFRA* mutation in GIST, genotyping can be helpful in guiding aspects of therapy with imatinib or other related inhibitors. The mechanisms of acquired resistance to imatinib in GIST include secondary mutation of *KIT* and *PDGFR* and possibly amplification or activation of other RTK. Primary or secondary mutations in the kinase domain of *KIT* involving imatinib resistance include V654A, T670I, T823A, del557–55873, insAY502–593, and other sites of exon 9 (partial resistance), 13 and 17 in the kinase domain of *KIT*, and D842V in *PDGFRA*. Alteration of imatinib sensitivity can be fought by specific RTK inhibitors, and new paradigm of classification integrating the classic pathological criteria with the molecular changes will facilitate personalized prognosis and treatment.17›74

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Table 1

Correlation of cytogenetic aberrations and clinicopathological features in GIST

Cytogenetic aberrations	Specific sites	Potential clinicopathological significance
Loss of 14q	14q11.2–q32.33	Early events in tumorigenesis
LOH of 22q	22q12.2–q13.31	Play role in early stages of tumorigenesis and late progression
Loss of 1p, 10q, 13q, 15q	----------	May harbor tumor suppressor gene(s) related to early recurrence and/or metastasis during malignant transformation
Nuclear and mitochondrial microsatellite instability	----------	May play role in pathogenesis
Chromosomal aneuploidy	-------	Associated with more aggressive tumor behavior
−14q pathway in oncogenetic tree model	Loss of 14q	Seen in gastric tumors with predominantly stable karyotypes and more favorable outcome
−1p pathway in oncogenetic tree model	Loss of 1p	Characteristic of intestinal GIST, with increased capacity for cytogenetic complexity and more aggressive clinical course
−22q pathway in oncogenetic tree model	Loss of 22q, 9p Gain of 8q	Associated with increased mitotic activity and recurring disease

GIST, gastrointestinal stromal tumors; LOH, loss of heterozygosity

Table 2

Genes regulated by mutations of *KIT* and *PDGFRA*

Gene	Target genes	Downstream signaling factors		Signaling consequences
		JAK1/2	STAT	Induce progression through cell cycle; prevent apoptosis
			P90RSK	
	MAPK	ERK1/2(P44/22)	MSK ELK-1, STAT	Inhibit cell differentiation
		p38	PLA2, MNK1, PRAK, Hsp27, STAT1, ELK-1	Inhibit apoptosis
	GRB2	SOS, RAS, RAF, MEK, ERK	P90RSK, MSK, ELK-1, STAT	Inhibit apoptosis
		p70S6K	RPS6, ELF-4	Regulate cell growth
			mTOR signaling (p70S6K, RPS6, ELF4,STAT)	Regulate cell growth
			RAF, ERK, p70S6K↓	Inhibit apoptosis
KIT mutation		PKB(AKT) ↓	p21, p27	Regulate cell cycle and proliferation
	PI3K		cyclinD1, p53	
			BAD, FXHR/AFX↓	Induce cell survival
			p53, NF-KB	Modulate cell death
		BAD↓	BCL-XL, BCL-2	Inhibit apoptosis
		NF-KB	IKB, IKK, et al	Inhibit cell differentiation
	SHP1/2	-------	----------	Negative regulation of KIT signaling pathway
	CBL	--------	----------	Unknown
	SHC	--------	----------	Unknown
	EPHA4	--------	----------	Unknown
	Paxillin	--------	----------	Unknown
	MAPK	JAK1/2, ERK1/2, p38	STAT, P90RSK, MSK, ELK-1, PLA2,MNK1, PRAK, Hsp27	Inhibit apoptosis; inhibit cell differentiation;induce progression through cell cycle
		mTOR signaling (p70S6K, RPS6, ELF4, STAT)	----------	Regulate cell growth
		RAF, ERK, p70S6K	----------	Modulate cell growth
PDGFR A mutation	*AKT* (with controversy)	p21, p27 cyclinD1	----------	Regulate cell cycle and proliferation
			----------	Modulate cell cycle (indirectly)
		BAD, FXHR/AFX	----------	Induce cell survival
		p53, NF	----------	Modulate cell death (indirectly)
	STAT	----------	----------	Induce progression through cell cycle; prevent apoptosis

Table 3

Gene aberrations other than *KIT* and *PDGFRA* mutations in GIST

Gene sites	Related gene aberrations	Clinical correlations
9p21	LOH	More often in high-risk GIST, absent in low-malignant-potential group, recurrent GIST showed more frequent deletions than cognate primary tumors
P16 and *p14*	LOH of P16INK4A and p14ARF	May contribute to progression and/or malignant transformation of GIST
P15	P15INK4B promoter methylation	Loss of tumor suppressor gene expression
PARP2, *APEX1*, *NDRG2*, *SIVA*, *ENO1*, and *CDKN2A/2B*	Copy number loss	Loss of tumor suppressor gene expression
Hox11L1	homozygous loss	Has role in tumorigenesis
C-MYC, *MDM2*, *EGFR1*, *CCND1*	Amplification	Associated with clinical and histologic malignancy
FLJ10261	High expression	Involved in tumorigenesis of GIST
PKC-theta	-------	Play role in development of GIST
obscuring, C9orf65	--------	Helpful to differentiate GIST and leiomyosarcoma

GIST, gastrointestinal stromal tumors; LOH, loss of heterozygosity

Table 4

Genetic aberrations and their possible significance in GIST

Gene	Specific aberrations	Potential clinical significance and prognosis
	Exon 11 deletions	Independent adverse prognostic factor in patients with GIST
	Exon 11 mutations	Independent predictors for disease-free survival, mixed histologic pattern; more frequent liver metastasis; poor prognosis for gastric GIST (pre-imatinib)
KIT	Exon 11 duplication	Characteristic site: almost exclusively in gastric GIST
	Exon 9 mutation	Characteristic site: almost exclusively in small intestinal GIST
	Deletion of 557–558 codon	Prognostic value in choosing imatinib therapy
	LOH	Possible role in liver metastasis
PDGFR	Exon 18 mutation	Imatinib resistance
	p16, p14 low mRNA expression	Associated with aggressive clinical behavior and unfavorable prognosis
CDKN2A tumor suppressor pathway	CKK4, RB1, MDM2, TP53, E2F1 high mRNA expression	Associated with aggressive clinical behavior and unfavorable prognosis
	Upregulation of E2F1	Increased cell proliferation and adverse prognosis in GIST
P16	Negative expression	Worse prognosis and 2.3-fold relative increased risk of dying of disease
Hox11L1	LOH	Worse tumor-specific and relapse-free survival rates

GIST, gastrointestinal stromal tumors; LOH, loss of heterozygosity

Table 5

Proteins regulated by imatinib and other inhibitors of specific tyrosine kinases and downstream effects

Target protein	Downstream signaling factors		Potential functions
	PI3K, AKT	BAD, MYC	Promote apoptosis
	BAD	BCL-XL, BCL-2	Induce apoptosis
	JAK2	STAT	Prevent cell proliferation
BCR-ABL↓		SOS, RAS, RAF,	
	GRB-2	MEK, ERKs, P90RSK, MSK, ELK-1, STAT	Prevent cell proliferation
	STAT		Prevent cell proliferation
Caspase-3↑	PLA2, MNK1, PRAK, Hsp27, STAT1, ELK-1		Cell apoptosis
p38↑	PLA2, MNK1, PRAK, Hsp27, STAT1, ELK-1		Inhibit proliferation and induce apoptosis by activation o p38 MAPK pathways
exogenous IL-6↓			Inhibit KIT signaling pathway activated by exogenous IL-6
ERK1/2↓	p90RSK, MSK, ELK-1, PLA2, MNK1, PRAK,Hsp27, STAT		Induce apoptosis inhibits proliferation by downregulation of ERK pathways
ERK5↓			Inhibit proliferation and induce apoptosis by downregulation of ERK5 pathways
Kit↓	Decreased autophosphorylation by competing at ATP-binding site		Downregulation of activation of ERK1/2 and AKT, induce apoptosis
PDGFRA↓			Downregulation of activation of ERK1/2 and AKT, induce apoptosis
C-ABL↓			Prevent cell proliferation, induce apoptosis
SPRY4A, FZD8, PDE2A,RTP801, FLJ20898, and			Prevent cell proliferation, induce apoptosis
ARHGEF2↓			
MAFbx↑			Prevent cell proliferation, induce apoptosis