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REVIEW

Therapeutic targets in gastrointestinal stromal tumors

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Abstract

Gastrointestinal stromal tumors (GISTs) are the most common type of mesenchymal tumor of the gastrointestinal tract. The tumorigenesis of GISTs is driven by gain-of-function mutations in *KIT* or platelet-derived growth factor receptor α (*PDGFRA*), resulting in constitutive activation of the tyrosine kinase and its downstream signaling pathways. Oncogenic *KIT* or *PDGFRA* mutations are compelling therapeutic targets for the treatment of GISTs, and the KIT/PDGFRA inhibitor imatinib is the standard of care for patients with metastatic GISTs. However, most GIST patients develop clinical resistance to imatinib and other tyrosine kinase inhibitors. Five mechanisms of resistance have been characterized: (1) acquisition of a secondary point mutation in *KIT* or *PDGFRA*; (2) genomic amplification of *KIT*; (3) activation of an alternative receptor tyrosine kinase; (4) loss of KIT oncoprotein expression; and (5) wild-type GIST. Currently, sunitinib is used as a second-line treatment for patients after imatinib failure, and regorafenib has been approved for patients whose disease is progressing on both imatinib and sunitinib. Phase Ⅱ/Ⅲ trials are currently in progress to evaluate novel inhibitors and immunotherapies targeting KIT, its downstream effectors such as phosphatidylinositol 3-kinase, protein kinase B and mammalian target of rapamycin, heat shock protein 90, and histone deacetylase inhibitor. Other candidate targets have been identified, including ETV1, AXL, insulin-like growth factor 1 receptor, KRAS, FAS receptor, protein kinase c theta, ANO1 (DOG1), CDC37, and aurora kinase A. These candidates warrant clinical evaluation as novel therapeutic targets in GIST.

Key words: Gastrointestinal stromal tumors; Tyrosine kinase inhibitors; *KIT*; Platelet-derived growth factor receptor α; Targets

Core tip: Oncogenic *KIT* and platelet-derived growth factor receptor α (*PDGFRA*) mutations are compelling therapeutic targets in gastrointestinal stromal tumors (GISTs), and the KIT/PDGFRA kinase inhibitors imatinib, sunitinib, and regorafenib are the standards of care for patients with unresectable or metastatic GIST. However, most patients eventually develop resistance to these kinase inhibitors, resulting in an urgent need to identify biologically rational targets for novel therapies.

Herein, we review advances in the research on GIST and the therapies that are used to treat it. Additionally, we discuss novel agents, targets, and strategies for the future treatment of GIST.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) were originally described as smooth muscle or neural tumors of the gastrointestinal (GI) tract; however, in 1983, Mazur *et al*[1] referred to GISTs as "stromal tumors"[2,3]. Subsequent studies identified the interstitial cells of Cajal as the origin of GISTs. In 1998, activating mutations of the *KIT* receptor tyrosine kinase (RTK) were found in GISTs[4]. In 2003, platelet-derived growth factor receptor α (*PDGFRA*) mutations, an alternative target, were identified in GISTs that lacked *KIT* mutations[5].

GISTs are the most common mesenchymal tumors of the GI tract and are frequently seen in the stomach (60%), small intestine (25%), colorectum (5%-10%) and occasionally in the esophagus and appendix[5]. Histologically, GISTs may be composed of spindle cells (70%), epithelioid cells (20%), or a mixture of these types (10%)[6]. Morphologically, GISTs may be mistaken for smooth muscle neoplasms, such as leiomyoma and leiomyosarcoma (Figure 1)[6]. Consensus guidelines for GIST prognosis, accentuate risk stratification based on the tumor volume and mitotic index of the primary tumors (Table 1)[2].

The majority of GISTs contain oncogenic mutations of *KIT* (approximately 85%) or *PDGFRA* (approximately 5%-10%)[2,4-6]. The resulting mutant oncoproteins are crucial for GIST oncogenesis, proliferation, and survival, as demonstrated by the clinical successes of small molecule therapeutics targeting KIT and PDGFRA[7-9]. Imatinib, sunitinib, and regorafenib are the standard first-, second- and third-line therapies, respectively, in patients with inoperable GISTs[10-12], and adjuvant imatinib is used in patients with localized GISTs with a high risk of recurrence[13].

Except from imatinib, sunitinib, and regorafenib, which target the activated oncoproteins KIT and PDGFRA in inoperable or metastatic GIST, the increasing novel drugs are currently in clinical trials, and additional potential therapeutic targets have been identified. Herein, we summarize these agents, targets, and strategies for the future treatment of GIST.

KIT AND PDGFRA ARE MAJOR THERAPEUTIC TARGETS IN GISTS

Oncogenic mutant KIT and PDGFRA play a critical function in the initiation of the transformation event that leads to GIST. Mutations in *KIT* are usually found in the regulatory and dimerization domains, which are located in the extracellular region encoded by exon 9 (approximately 13% of GISTs), the juxtamembrane region encoded by exon 11 (approximately 66% of GISTs), or the tyrosine kinase (TK)[Ⅰ] [adenosine triphosphate (ATP) binding pocket]; and TK[Ⅱ] (activation loop) domains encoded by exon 13 (approximately 1% of GISTs) and exon 17 (approximately 0.6% of GISTs), respectively[2,14,15]. Five percent to ten percent of GISTs contain mutations in *PDGFRA* exon 12 (juxtamembrane region) (1.5%) or exon 18 (activation loop) (5.6%). The remainder (10%-12%) are wild-type for both *KIT* and *PDGFRA*[2,6]. The percentage of population of *KIT* and *PDGFRA* mutations is shown in Figure 2[2].

GISTs harboring insertions, deletions, and missense mutations in *KIT* exon 11 can be found throughout the GI tract[16]. A enhanced metastasis and proliferation has been associated with loss of heterozygosity at the *KIT* locus[17,18]. The vast majority of GIST cases with alterations of KIT in exon 9 involve an insertion of six base pairs, resulting in the duplication of Ala and Tyr residues. These mutations often occur in high-risk primary GISTs of the small intestine[17,19,20], advanced or relapsed GISTs[18,21]. A recent study demonstrated that GISTs harboring *KIT* exon 17 and exon 13 mutations show slightly overrun population among a subset of GISTs. Most of single base pair substitution *KIT* mutations in exon 13 and 17 in small intestinal GISTs, have no marked effects on the clinicopathologic characteristics when compared to the "average" small intestinal GIST[22].

The majority of *PDGFRA* exon 14 and 18 alterations are missense mutations. GISTs harboring *PDGFRA* mutations are confined to the stomach and omentum. These tumors are shortage of KIT expression, they typically present an epithelioid morphology, and they are commonly associated with a benign prognosis[23,24]. GISTs harboring a D842V *PDGFRA* exon 18 mutation are resistant to imatinib and other RTK inhibitors[25-28].

Inhibition of KIT or PDGFRA kinase activity by imatinib results in an objective response in approximately 80% of metastatic GIST patients (approximately 50% partial response, approximately 30% stable) with a 3-year survival rate of 69%-74%[8]. However, the median survival of metastatic GIST patients was 19 mo in the pre-imatinib period[10,15]. Constitutive activation of KIT or PDGFRA results in the activation of downstream signaling intermediates necessary for proliferation, survival, adhesion, and blockage of differentiation, including the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) and RAF/mitogen-activated protein kinase (MAPK) pathways. Targeting KIT/PDGFRA and its downstream intermediates has proven to be an effective strategy in the treatment of GISTs[29-32].

MECHANISMS OF IMATINIB RESISTANCE

Imatinib, an ATP-competitive inhibitor of KIT and PDGFRA, is the first-line therapy for patients with

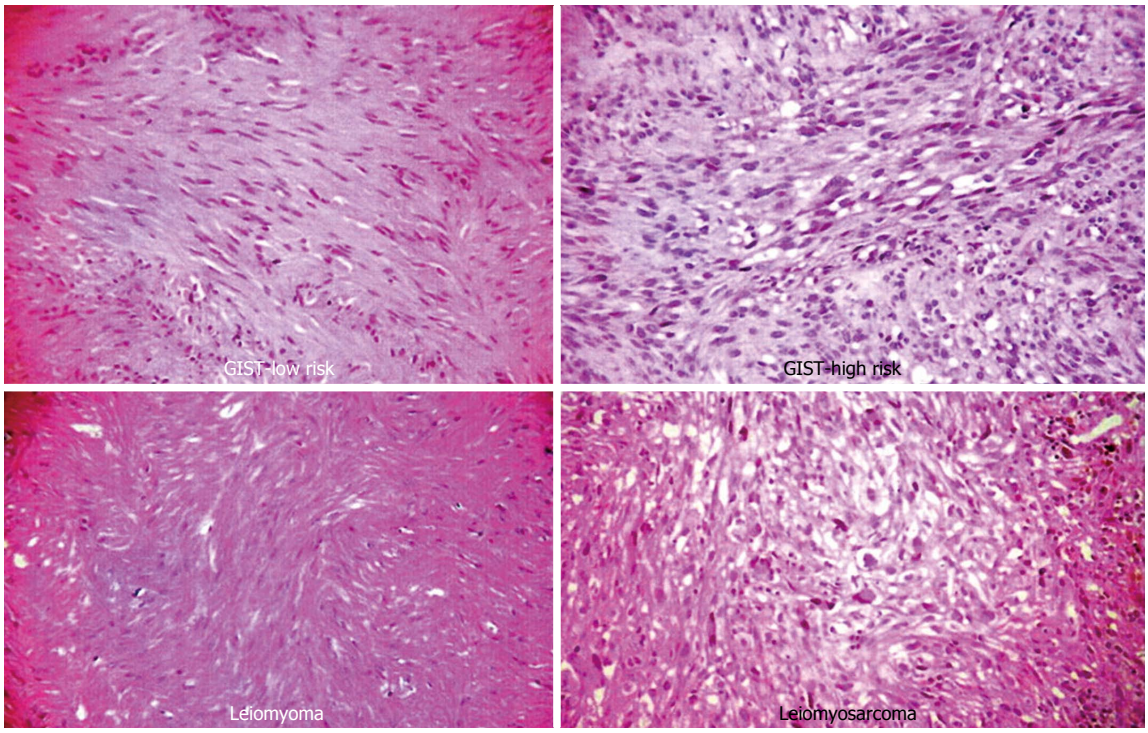

Figure 1 Morphologic similarities of low-risk gastrointestinal stromal tumor and leiomyoma and of a high-risk gastrointestinal stromal tumor and leiomyosarcoma. GIST cells can divided into 3 types: spindle cell (70% of cases), epithelioid cell (20% of cases), and mixed cell (containing a mixture of spindle and epithelioid cells). GIST: Gastrointestinal stromal tumor.

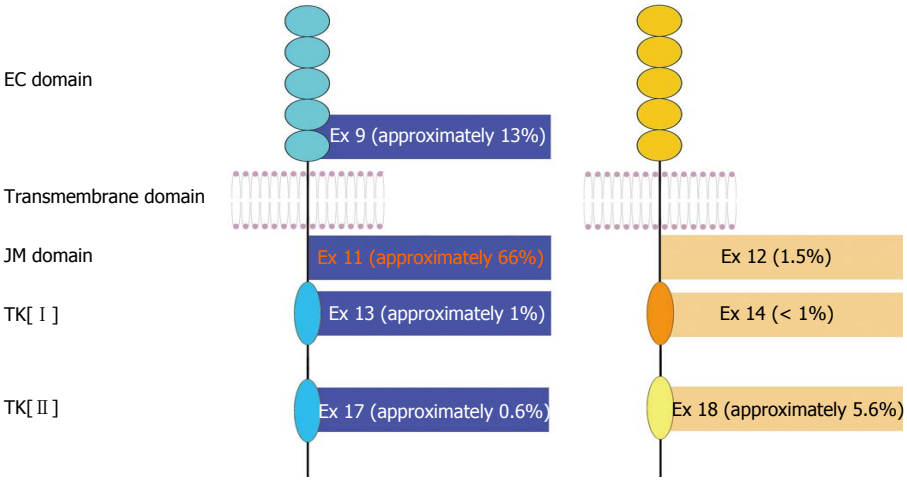

Figure 2 Schematic structure of *KIT* and platelet-derived growth factor receptor α receptor tyrosine kinases and distribution of *KIT* mutations in gastrointestinal stromal tumor. EC: Extracellular; JM: Juxtamembrane; TK[Ⅰ]: Tyrosine kinase domain Ⅰ; EX: Exon.

advanced GIST or primary GIST with a significant risk of recurrence after surgery[28,33-35]. Among patients with advanced GIST, 75% to 90% will show a response to imatinib[15]. Analysis of the crystal structure of the KIT-imatinib complex reveals that the drug fills a hydrophobic region of the ATP binding pocket, effectively blocking ATP binding and inactivating KIT and its downstream signaling[36,37].

Despite the dramatic clinical success of imatinib, most inoperable GIST patients eventually develop resistant to imatinib. Imatinib resistance in GIST is classified as either primary or secondary imatinib resistance. Approximately 10% of GISTs demonstrate primary imatinib resistance of clinical progression within 3 to 6 mo of the start of treatment[28,38]. Primary imatinib resistance is usually observed in tumors that lack *KIT* or *PDGFRA* mutations (wild-type GISTs), but it is also common in tumors harboring *KIT* exon 9 mutations[28,38]. Approximately 40% to 50% of GIST patients experience secondary imatinib resistance of clinical progression after 12-36 mo of response or disease stabilization. Molecular studies showed that activated KIT expression in imatinib-resistant tumors was similar to or greater than those typically found in

Table 1 Risk stratification of primary gastrointestinal stromal tumor by mitotic index, size and anatomic location[2]

Prognosis of primary GIST		
Risk	**Size (cm)**	**Mitotic count (per 50 HPF)**
Very low risk	< 2	< 5
Low risk	2-5	< 5
Intermediate risk	< 5	6-10
	5-10	< 5
High risk	> 5	> 5
	> 10	> Any mitotic rate
	Any tumor	> 10

HPF: High power fields; GIST: Gastrointestinal stromal tumor.

untreated GISTs[15]. Secondary *KIT* mutations were rare in GISTs with primary resistance but often found in GISTs with secondary resistance (10% *vs* 67%; $P = 0.002$). Polyclonal secondary kinase mutation was detected in 18.8% patients. The secondary kinase mutations were nonrandomly distributed and were associated with attenuated imatinib sensitivity compared with *KIT* exon 9 and exon 11[15]. Mechanisms of acquired resistance include secondary mutations in *KIT* or *PDGFRA*, genomic amplification of *KIT*, or activation of an alternative RTK[6,14,39-46]. An even more challenging resistance mechanism, seen in approximately 5%-10% of clinically progressing *KIT*-mutant GISTs involves a transition from dependence on oncogenic KIT to a new imatinib-insensitive oncogenic driver, accompanied by the loss of former KIT expression[39,40].

NOVEL INHIBITORS IN PRE-CLINICAL MODELS AND CLINICAL TRIALS

Tumorigenesis is a complex, multi-step process, and oncogenic RTK proteins frequently play key roles[47] (Table 2). Oncogenic RTK mutations can lead to constitutive kinase activation and thereby enhance growth and survival in cancer cells[48,49]. Tyrosine kinases can be divided into two categories: receptor tyrosine kinases and non-receptor tyrosine kinases. At present, approximately 90 types of TK members have been identified, including 58 RTKs, such as PDGFR, epidermal growth factor receptor (EGFR), fibroblast growth factor receptor, and 32 non-RTKs[50]. Oncogenic RTK mutants are useful therapeutic targets, as shown by the clinical benefit of small molecular inhibitor therapies in chronic myeloid leukemia (BCR-ABL)[51], metastatic breast cancer [human epidermal growth factor receptor 2 (HER2)][52], GIST (KIT/PDGFRA)[8], and non-small-cell lung cancer [EGFR, hepatocyte growth factor receptor (MET), anaplasticlymphoma kinase, HER2][47,53-62].

Sunitinib is an oral multi-target tyrosine kinase inhibitor (TKI) with activity against KIT, PDGFRA, FMS-Like Tyrosine Kinase 3, Vascular endothelial growth factor receptor (VEGFR), and orphan receptor tyrosine kinase[63]. Sunitinib is approved for use as a second-line therapy for patients with imatinib-resistant GIST[9,64,65]. A clinical benefit of sunitinib was seen in common primary GIST with KIT exon 9 (58%), KIT exon 11 (34%), and wild-type KIT/PDGFRA (56%)[9]. Progression-free survival (PFS) was greater improvement for patients with a wild-type genotype ($P = 0.0356$) or with primary KIT exon 9 mutations ($P = 0.0005$) than for those with KIT exon 11 mutations. Overall survival (OS) showed the similar pattern. The PFS and OS were greater improvement for patients with secondary *KIT* exon 13 or 14 mutations than for those with exon 17 or 18 mutations[9]. The safety and efficacy of regorafenib in metastatic or unresectable GIST patients after failure of imatinib and sunitinib were evaluated in phase Ⅲ, and the results showed that regorafenib can markedly improve PFS compared with control in metastatic GIST patients with progression after standard treatments[12,66]. Currently, regorafenib has been approved for patients whose tumors are progressing on both imatinib and sunitinib. A large number of therapies are in various stages of pre-clinical and clinical trial development and are summarized in Table 2[10,13,14,21,30,64,67-84]. These therapies can be divided into four groups: TKIs, PI3K/mTOR inhibitors, heat shock protein 90 (HSP90) inhibitors, and others.

Multiple TKIs, including nilotinib, sorafenib, dasatinib, vatalanib, and motesanib, are being investigated as potential therapies for GIST. Nilotinib, an inhibitor of KIT, PDGFRA and BCR-ABL, has been shown to be active in a small series of imatinib-resistant and sunitinib-resistant GIST patients in a phase Ⅰ study[67,71,74,85]. Sorafenib, an inhibitor of RAF kinase, VEGFR, PDGFR, and KIT, inhibited KIT activity in some *KIT* primary and secondary mutations in a phase Ⅱ trial in imatinib- and sunitinib-resistant GIST[69,80,86,87]. Dasatinib, a dual SRC/ABL kinase inhibitor, binds and inactivates wild-type and mutant KIT regardless of the conformation of the KIT activation loop[42,43]. Linsitinib (OSI-906) is a selective inhibitor of insulin-like growth factor receptor (IGFR)/insulin receptor. The combination of imatinib and linsitinib has been shown to be effective in wild-type GIST with insulin-like growth factor 1 receptor (IGF1R) overexpression or amplification[88]. Vatalanib (PTK787) and motesanib (AMG706), multi-kinase inhibitors, have been evaluated in phase Ⅱ trials for patients who are resistant to both imatinib and sunitinib[89,90]. Vatalanib has shown activity in patients with imatinib-resistant or both imatinib- and sunitinib-resistant GIST[89,90]. Motesanib treatment was shown to have acceptable toxicity, and it resulted in disease stabilization in GIST patients[82].

The PI3K/AKT/mTOR pathway is crucial for proliferation and survival in GIST[29,30,68,91-93]. Preclinical experiments have confirmed that targeting the PI3K/AKT/mTOR pathway is a rational therapeutic strategy. Early studies with mTOR inhibitors have shown limited success, possibly due to feedback activation of AKT

Table 2 Novel agents are being developed for gastrointestinal stromal tumor therapy[10,13,14,21,30,64,67-84]

Agent	Molecular target	Phase
Kinase inhibitors		
Nilotinib	KIT, PDGFRs, BCR-ABL	Ⅰ
Sorafenib	Raf, KIT, PDGFRB, VEGFR, FLT3, RET	71%
Dasatinib	Src, ABL, KIT, PDGFRs	Phase Ⅱ ongoing in advanced sarcomas and accepting patients
Cediranib (AZD2171)	VEGFR, KIT, PDGFRs	Phase Ⅱ ongoing
OSI-930	VEGFR, KIT	Phase Ⅱ ongoing, not recruiting
Linsitinib (OSI-906)	IGF1R	Phase Ⅲ
Vatalanib (PTK787)	VEGFR, KIT, PDGFRs	67%
Motesanib (AMG706)	VEGFR, KIT, PDGFRs, RET	24%-27%
XL820	KIT, PDGFRB, VEGFR	Phase Ⅱ ongoing, not recruiting
mTOR and AKT inhibitors		
Perifosine	AKT	Phase Ⅱ ongoing in combination with imatinib
Everolimus	mTOR	26%
Temsirolimus	mTOR	Phase Ⅱ ongoing, closed recruitment
Hsp90 inhibitors		
17-AAG	Hsp90	Phase Ⅱ / Ⅲ
Ganetespib (STA-9090)	Hsp90	Phase Ⅱ
AUY922	Hsp90	Phase Ⅱ
AT13387	Hsp90	Phase Ⅱ ongoing in combination with imatinib
IPI-504	Hsp90	78%, phase Ⅲ ended due to safety concerns
Others		
Flavopiridol	Transcription inhibitor	Phase Ⅰ ongoing in combination with doxorubicin

Clinical benefit is defined as complete or partial response or stable disease

PDGFRs: Platelet-derived growth factor receptors; PDGFRA: Platelet-derived growth factor receptor α; PDGFRB: Platelet-derived growth factor receptor β; VEGFR: Vascular endothelial growth factor receptor; FLT3: FMS-Like Tyrosine Kinase 3; IGF1R: Insulin-like growth factor 1 receptor; AKT: Protein kinase B; mTOR: Mammalian target of rapamycin; Hsp90: Heat shock protein 90; RET: Orphan receptor tyrosine kinase.

after mTORC1 inhibition. Simultaneous targeting of multiple nodes in the PI3K/AKT/mTOR pathway prevents feedback activation and may translate into more complete pathway inhibition. A few therapies targeting this pathway are currently being evaluated in phase Ⅰ and Ⅱ clinical trials[94]. A number of drugs currently in development include inhibitors of pan-Class Ⅰ PI3K (BKM120 and GDC0941), PI3K/mTOR (BEZ235, SF1126 and GDC0980), AKT (Perifosin), and mTOR (Everolimus/RAD001 and Temsirolimus). Additionally, combined inhibition of KIT and PI3K/AKT/mTOR results in a greater response compared to either intervention alone[73,94-97].

Heat shock proteins control the proper folding, function, and stabilization of various client proteins. HSP90 optimizes and maintains the folding and localization of many activated tyrosine kinases and also prevents proteasomal degradation[98]. HSP90 is abundant in eukaryotic cells, comprising up to 1%-2% of total cellular protein, and it plays key roles in regulating cell proliferation, differentiation, and apoptosis[99,100]. The HSP90 inhibitor 17-allylamino-17-demethoxygeldanamycin (17-AAG), a geldanamycin derivative[101], binds a ATP-interaction pocket in the HSP90 NH_2-terminal domain[102] and shows anti-proliferative effects in various human cancers, where it can degrade HSP90-client oncoproteins with high selectivity[103,104]. Whereas the clinical application of 17-AAG has been hampered by its low water solubility, IPI-504, a 17-AAG derivative, exhibits improved aqueous solubility while maintaining the biological HSP90-inhibitory properties of 17-AAG[105]. Furthermore, clinical trials with new-generation synthetic HSP90 inhibitors are ongoing in various cancer types. HSP90 is an attractive target in GIST as it is a key chaperone for KIT and PDGFRA[79,106]. Targeting HSP90 results in pro-apoptotic and anti-proliferative effects in GIST and is associated with the inhibition of KIT and PDGFRA signaling[72,79,107,108]. Other HSP90 inhibitors are in development (NVP-AUY922, AT-13387, KW-2478, and SNX-5422) and show promise for GIST treatment, particularly in combination with TKI[109].

Other drugs are in various stages of development for the treatment of GIST. Flavopiridol, a transcription inhibitor, has been evaluated in an ongoing phase Ⅰ trial in combination with doxorubicin[110]. Histone deacetylase inhibitors (HDACIs) alone or in combination with imatinib have shown pro-apoptotic and anti-proliferative effects in GIST and are associated with inhibition of KIT and a reduction in the expression and activities of downstream pathways[111].

NOVEL CANDIDATE THERAPEUTIC TARGETS

Other therapeutic targets have been identified for the treatment of GIST, including Ets Variant 1 (ETV1), AXL, FAS, IGF1R, protein kinase c theta (PKCθ), RAS, CDC37, cyclin D1, Dog1, and aurora kinase A. Inhibitors targeting these candidates are being developed, and some are being evaluated in clinical trials.

The E26 transformation-specific family member ETV1 is overexpressed in the GIST and is required in the development of both imatinib-sensitive and imatinib-resistant GIST[112-114]. ETV1 enhancer binding is a master regulator of an ICC-GIST-specific transcription network. Activated KIT cooperates with ETV1 to induce development of GIST, regulating the ETV1 transcriptional program by prolonging ETV1 protein stability through MAPK signaling[112,114]. Inhibition of ETV1 reduces the expression of KIT, reduces mutagenesis, and stabilizes the GIST genome, thereby inhibiting GIST growth and progression and inducing apoptosis.

AXL (UFO/ARK/Tyro), an RTK stimulated by its ligand growth arrest-specific 6, shows potent oncogenic and transforming activity in normal and cancer cells[115-117]. AXL also plays a role in tumor cell invasion, metastasis, and survival[41,118,119]. AXL is active in GIST metastases that lose KIT expression at the time of clinical progression on imatinib[41,120]. In KIT-independent GISTs, AXL knockdown results in upregulation of p21, p27 and p53 protein expression and shows antiproliferative effects[120]. MP470, a KIT/AXL inhibitor, shows a synergistic cytotoxic effect in GIST cells when combined with docetaxel (taxotere)[41].

Fas and its ligand FasL belong to the tumor necrosis factor family of death receptors. Activation of Fas by FasL induces cell apoptosis through caspase 8 signaling. Down-regulation of Fas is associated with tumorgenesis[121,122]. Fas and FasL expression were positively correlated in primary GISTs, but there was no association KIT mutation status[123]. MegaFasL, a hexameric form of soluble FasL, is an active apoptosis-inducing agent and potentiated the apoptotic effects of imatinib in GIST cell lines[123].

The IGF/IGF1R signaling system has been implicated as a relevant therapeutic target in a variety of cancers. When IGF1 binds with IGF1R, it activates downstream signaling cascades, such as the PI3K/AKT/mTOR and RAF/MEK/MAPK pathways, to trigger protein synthesis, and it also activates anti-apoptotic and proliferative pathways[124-126]. Recent reports have shown that *IGF1R* is amplified in a subset of GISTs[127] and over-expressed in wild-type and pediatric GIST[88,128,129]. Recent studies have shown that the IGF/IGF1R pathway may be a promising therapeutic target for GIST[127,130-135].

PKCθ, a member of the protein kinase C family commonly expressed in T cells and myogenic cells[136,137], is expressed at high levels and activated in GIST irrespective of the *KIT* or *PDGFRA* status. Therefore, PKCθ serves as a diagnostic marker of GIST[138-141]. PKCθ knockdown is accompanied by inactivation of KIT in KIT+/PKCθ+ GIST cell lines. PKCθ knockdown resulted in inhibition of PI3K/AKT signaling, upregulation of pro-apoptotic proteins p21 and p27, cell cycle arrest, and apoptosis, recapitulating the effect of direct KIT targeting[142]. PKCθ is a compelling therapeutic target in GISTs, including those with mutations that confer resistance to KIT/PDGFRA inhibitors.

Wild-type GISTs often demonstrate primary imatinib resistance. In some cases, these tumors are succinate dehydrogenase (SDH)-deficient GISTs with mutations in *SDHA*, *SDHB*, or *SDHC*[143,144], while others have no known genetic mutations. A recent report suggested that *KRAS* mutations might confer imatinib resistance in GIST, and although rare, KRAS gain-of-function mutations contribute to clinical imatinib resistance[145,146]. Serrano *et al*[145] used a Sequenom panel to screen for RAS, BRAF, and PI3KCA mutations in 27 wild-type GIST patients. Only one of these 27 GISTs contained a mutation in this pathway, harboring concomitant *HRAS G12V* and *PIK3CA H1047R* mutations[145]. KRAS and HRAS can contribute to GIST oncogenesis and indicate the importance of the PI3K/AKT and RAS/RAF pathways in GIST tumorigenesis.

As discussed previously, HSP90 inhibitors strongly inactive KIT kinase activity, but clinical applications in GIST patients have been prevented due to the toxicity resulting from inactivation of HSP90 client proteins beyond KIT and PDGFRA. Genome-scale short-hairpin RNA (shRNA) screening identified CDC37, an HSP90 cofactor, as an essential GIST-specific gene[147]. Validation studies in treatment-naive and imatinib-resistant GIST cell lines demonstrated that CDC37 is a viable therapeutic target in GIST, recapitulating the effect of HSP90 inhibition while remaining selective for KIT/PDGFRA and a limited number of other HSP90 clients[147]. CDC37 inhibition represents a potential HSP90 targeting strategy that limits toxicity for GIST patients.

The strongly expressed DOG1 (ANO1/TMEM16A) has been used as a diagnostic marker to differentiate GIST from other sarcomas[148-151]. Loss of DOG1 expression occurs together with loss of KIT expression in a subset of GISTs that are resistant to imatinib. Although DOG1 inhibition do not inhibit cell growth *in vitro*, DOG1 knockdown delays the growth of xenograft models of GIST and is associated with the up-regulation of insulin-like growth factor binding protein 5, a potent antiangiogenic factor implicated in tumor suppression[152]. These findings suggest that DOG1 is a potential target in GIST through its role in IGFR signaling.

A recent analysis of the prognostic significance of aurora kinase A (AURKA) in imatinib-treated patients with advanced GIST suggested that the expression of AURKA may predict recurrence in patients with primary, surgically resected GISTs[153,154]. AURKA overexpression is a prognostic factor of poor PFS and OS. Inhibition of AURKA suppresses the growth of both imatinib-sensitive and imatinib-resistant GIST cells in a concentration-dependent manner, and it results in a synergistic cytotoxicity with imatinib[154].

CONCLUSION

Oncogenic KIT or PDGFRA receptor tyrosine kinase mutations are compelling therapeutic targets in GISTs, and the KIT/PDGFRA kinase inhibitors imatinib,

sunitinib, and regorafenib are standards of care for patients with unresectable or metastatic GIST. However, most patients eventually develop resistance to KIT/PDGFRA kinase inhibitors, indicating that there is an urgent need to identify novel therapeutic strategies. A number of novel drugs are undergoing clinical trials, and several novel therapeutic targets have been identified, showing promise for the future treatment of GIST.

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