[Frontiers in Bioscience, Landmark, 20, 919-926, June 1, 2015]

KIT gene mutations in gastrointestinal stromal tumor

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1. ABSTRACT

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract. It arises in the stomach, small intestine, colon, rectum and esophagus. KIT gene mutation is a feature of GIST, in addition to PDGFRA gene mutation. KIT gene mutations have been observed to be involved in the development of GIST, its recurrence after surgery and chemotherapy resistance in GIST. Exons 13, 17, 9, and mainly exon 11 are concerned in these biological behaviors of GIST. In this review, we will discuss on the involvement of KIT gene mutations in the tumorigenesis, recurrence and chemotherapeutic resistance of GIST.

2. INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract, representing 0.1.-3% of gastrointestinal malignancies (1). The incidence of GIST is 14%–17.4.%; about 60%–70% occur in the stomach, 20%–30% in the small intestine, 5% in the colon and rectum, and less than 5% in the esophagus (2-4). Approximately 20%–25% of gastric and 40%–50% of small intestinal GISTs are clinically malignant (1). The five-year survival rate of GISTs ranges from 35% to 65% depending on the tumor size, the mitotic index and the tumor location (5). About 50% of GISTs are metastatic at presentation, and the most common sites of metastases are the peritoneum and the liver (1,6,7). GISTs arise from interstitial cells of Cajal, which comprise a complex cellular network of the autonomic nervous system that regulates gastrointestinal motility (1,6). The behavior of GISTs is driven by mutations in the KIT gene or the PDGFRA gene (1). Approximately 85% of GISTs are associated with an abnormal KIT pathway, which arises from mutation of the gene itself, and a smaller subset of KIT-associated GISTs are associated with constitutive activation of the KIT enzymatic pathway (8) (Figure 1).

The KIT gene, also known as the c-kit gene, encodes the proto-oncogene c-kit or tyrosine-protein kinase Kit, or CD117 (9). CD117 is a receptor tyrosine kinase type III, which is expressed on the surface of hematopoietic stem cells and other cell types, and binds to stem cell factor. Since KIT is a proto-oncogene, the overexpression of its protein can lead to cancer (10). As far as is known, the inactivating mutations are associated with the genetic defect piebaldism, while activating mutations of KIT gene are associated with tumors such as testicular seminoma, mast cell disease, melanoma, and acute myeloid leukemia, as well as GISTs (11). About 95% of GISTs express the transmembrane receptor CD117 on histological examination; this is the main immunohistological marker (12). Thus, in this review, we will discuss the involvement of the KIT gene in GIST tumorigenesis, recurrence and resistance to therapy.

3. GENE MUTATION IN THE TUMORIGENESIS OF GASTROINTESTINAL STROMAL TUMOR

Mutations in the KIT gene are the most common genetic changes associated with GISTs, as mentioned above. A series of novel mutations of KIT were observed in primary GISTs that occurred in the rectum, pancreas, jejunum or sacrum (13-16), suggesting that KIT gene mutations are important regardless of the organ in which the tumor occurs. The common mutation of the KIT gene at codon 576, located in the juxtamembrane domain, indicates the importance of this region (17). A point mutation of the KIT gene was found at codon 557 in exon 11 of leukocyte DNA from a patient with GIST (18). Later, an activating mutation (19) and a missense point mutation (Trp557Gly) (20) also were observed in exon 11 of the KIT gene in cases of GIST. Thus, exon 11 of the KIT gene may be a key region in the mutations associated

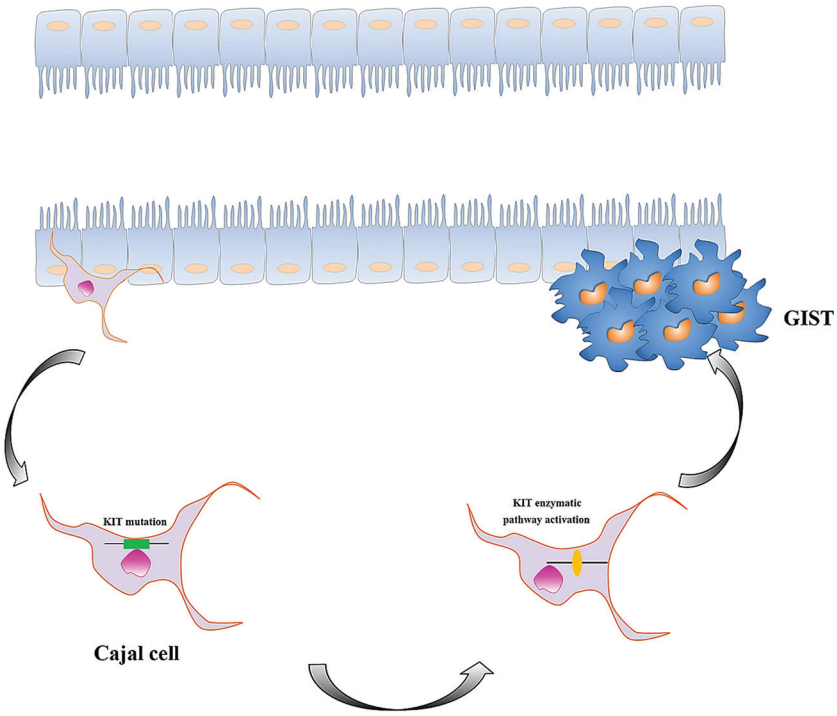

Figure 1. GIST is associated with KIT gnen mutation. GIST arises from mutation of the gene itself and a smaller subset of KIT-associated GISTs are associated with constitutive activation of the KIT enzymatic pathway.

with GIST. In patients with familial GISTs, germline mutations are located in this region of the KIT gene (21). Furthermore, germline and missense mutations at exon 11 in the juxtamembrane domain of the KIT gene were observed in a 25-year-old Japanese woman with familial GISTs (22). Therefore, exon 11 of KIT gene is a "hot spot" in both sporadic and familial GISTs, although less than 5% occur as part of hereditary familial or idiopathic multitumor syndromes.

A study based on 32 patients found that KIT mutation is associated with tumor size, proliferating cell nuclear antigen index, mitotic cell number, presence of necrosis, microscopic invasion of adjacent tissues, recurrence, and distant metastasis, suggesting a predictive role of KIT mutation in the prognosis of GISTs (23). Yamaguchi and colleagues (24) found that a specific mutation in exon 11 of the KIT gene may have played an essential role in the development of liver metastases in a case of GIST, and suggested that mutations in KIT exon 11 may be significant in the development of GISTs and associated with prognosis. Later, Ma and collegues (25) confirmed this prognostic role of exon 11 mutation, as well as its role in the pathogenesis of the disease, by analyzing KIT genes from 82 patients with GIST. More recently, a study of KIT exon 11 mutation from 77 patients with GIST showed that the five-year disease-free survival rates of patients carrying different genotypes were in line with the five-year overall survival rates but that patients with exon 11 mutations have worse relapse-free survival and overall survival rates (26). This further suggests that mutations in exon 11 may be associated with the development of GIST. Moreover, the detection of a hexanucleotide deletion in exon 11 of the KIT gene can be used to confirm the diagnosis of GIST in clinical cases (27). Thus, mutations in exon 11 have an association with the diagnosis and development of GISTs, suggesting a potential role of the KIT exon 11 in the tumorigenesis of GIST. However, the mechanism of this association requires further investigation.

In a study of 119 patients with GIST, Zheng and colleagues found that 42% had KIT mutations, which were all in exon 11 and were heterogeneous and clustered between codons 556 and 560 at the 5' end of exon 11 (28). However, no significant association between these mutations and biological behavior of the GISTs was observed (28). Therefore, different roles of exon 11 mutations of the KIT gene in GIST may be associated with specific loci. Further study is required in a larger sample to confirm these associations, and to investigate the underlying mechanism.

In addition to exon 11, exon 9 is another "hot spot" of KIT gene mutation in GISTs. In patients with GIST, AY 502–503 duplication/insertion, FAF 506–508 duplication/insertion and P456S substitution have all been observed in exon 9 (29-31). A novel mutation

consisting of a large deletion of 43 nucleotides and an insertion of 25 nucleotides was also found in a case of GIST (32). Thus, several mutations in exon 9 have been found in GISTs. A patient with a GIST tumor and non-islet cell tumor-induced hypoglycemia had an exon 9 mutation, which occurs in 11–20% of GISTs and is often associated with poor patient outcome (33). This suggests a possible role of KIT exon 9 in the prognosis of patients with GIST. However, the precise role of exon 9 mutations in the pathogenesis and biological behavior of GISTs is less clear than that of similar mutations in exon 11, and will be considered in future studies.

4. GENE MUTATION IN THE RECURRENCE OF GASTROINTESTINAL STROMAL TUMOR

Although surgery is an effective treatment for GIST, recurrence after surgery is common. The median survival of patients with resected metastatic-only GISTs is 19 months, and the five-year overall survival is 25% (34). Postoperative recurrence is fairly common in patients with tumors with high-risk features. In a study of patients with GIST, a homozygous/hemizygous KIT-activating mutation was found in 9 of the 62 cases, in which duplication of both intron 11 and exon 11 was observed (35). This study also found that three patients with heterozygous KIT-activating mutations at initial presentation, whose tumors later recurred with highly aggressive clinical courses, showed total dominance of homozygous (diploid) KIT-activating mutations within a short period of 6–13 months, suggesting that homozygosity of this mutation played a role in tumor recurrence (35). A 579–580 LY insertion in the KIT exon 11 was observed in a patient with a malignant small-intestinal rhabdoid GIST; the tumor recurred twice following resection and treatment with tyrosine kinase inhibitors (36). Moreover, Utsunomiya and colleagues (37) reported that a deletion mutation in exon 11 was found in patients with recurrent GIST who were under long-term treatment with imatinib mesylate. These cases show the important role of mutations in the KIT exon 11 in the recurrence of GISTs. In the same case report by Utsunomiya and collegues (37), KIT exon 13 contained a mutation (Val654Ala) in a recurrent hepatic tumor of a patient with GIST, in addition to a mutation in exon 11. In a recurrent duodenal GIST, a frameshift mutation led to a stop codon in KIT exon 13 (38). Thus, exon 13 also is involved in the recurrence of GIST, and may not only contain mutations but also be an effector of gene mutation. Understanding of the mechanisms involved in the recurrence of GIST has been limited to gene mutations in certain exons. Further investigation is needed, for instance of the mechanism of regulation and its down- or up-stream factors. The “hot spots” identified may be a potential target for research.

5. GENE MUTATION IN THE RESISTANCE TO CHEMOTHERAPY OF GASTROINTESTINAL STROMAL TUMOR

Although the only possibility for cure of GIST is by complete surgical resection (39), the postoperative recurrence rate for GIST with high-risk features is high. Thus, post-surgical adjuvant treatment may be recommended (40). Imatinib has been shown to have clinical benefit in GIST. Imatinib is a tyrosine kinase inhibitor and was marketed initially for treatment of chronic myelogenous leukemia. It is useful in treating GISTs in certa*in situ*ations because it can inhibit both KIT tyrosine kinase mutations and PDGFRA mutations. Not only does postoperative treatment with imatinib have clinical benefit, but preoperative (neoadjuvant) therapy with imatinib is also feasible (41). Treatment of patients with metastatic GIST with KIT mutations in exon 11 has shown the beneficial effect of imatinib (42,43). *In vivo* study with GIST cell lines has further demonstrated the effects, which include inhibition of proliferation, inhibition of activation and induction of apoptosis, of imatinib on GIST cell lines with KIT mutations in both exon 11 and exon 13 (44) (Figure 2). However, acquired resistance to imatinib in GIST occurs as a result of secondary KIT mutation (45). While the primary mutations occur in KIT exon 11, most secondary mutations are located in KIT exon 17, and these were observed in 15 patients whose GISTs had acquired resistance to imatinib (46). A novel mutation of exon 17 of the KIT gene was also found to be induced by longterm chemotherapy using imatinib in a patient with recurrent GIST (47). Thus, exon 17 may contain the key mutations associated with acquired resistance to imatinib in GIST. In addition, a mutation in KIT exon 14 resulting in T670I substitution was also found in patient with GIST, and this also caused acquired resistance to imatinib (48).

Although use of imatinib leads to improved survival in patients with GIST, the majority of patients who initially benefit from imatinib eventually become resistant, with a median time to progression on imatinib mesylate of 2 years (49). Given that the median survival is only 15 months once imatinib resistance develops (50), second-line tyrosine kinase inhibitors, including sorafenib, dasatinib, and nilotinib, may be used as alternatives to imatinib. *In vivo* study with GIST cell lines showed that all three drugs decreased cell proliferation and inhibited KIT activation in exon 13 (KIT(V560del/V654A)) and exon 17 (KIT(V559D/D820Y)) double mutants. Moreover, sorafenib inhibited imatinib-resistant KITT670I gatekeeper mutation in GIST (51). In a patient with GIST that was resistant to sunitinib, an exon 13 mutation in the KIT gene that led to an aggressive phenotype was observed (52).

In summary, the mutations in KIT gene associated with chemotherapy resistance in GISTs mainly occur in exons 11, 13 and 17. Interestingly, exons 11 and 13 are also important in the biological behavior of GISTs,

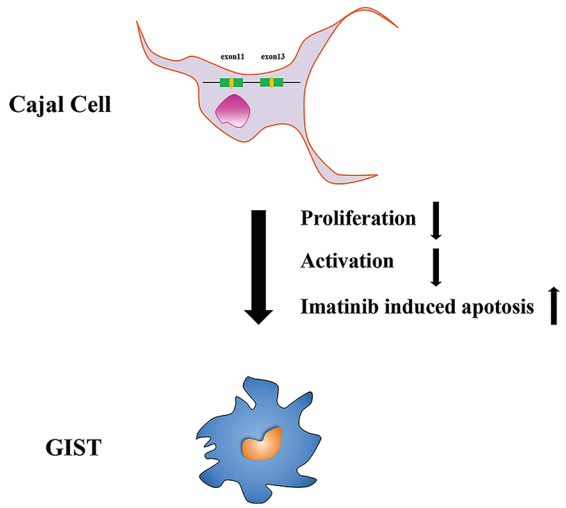

Figure 2. KIT mutations of exon 11 and exon 13 in GIST cell line. In GIST cell line, both KIT mutations of exon 11 and exon 13 have effect of inhibiting proliferation, inhibiting activation and inducing apoptosis of imatinib.

being associated with tumorigenesis and recurrence after surgery. Therefore, these exons may be important targets in the pathogenesis and chemotherapeutic strategy of GIST.

6. CONCLUSIONS

In conclusion, KIT gene mutations are involved in the pathogenesis and resistance to chemotherapy of GIST. Among the loci with mutations, exon 11 is a hot spot, where several KIT mutations participate in the tumorigenesis, recurrence and chemotherapeutic resistance of GIST. In addition, KIT mutations in exons 13 and 17 are involved in GIST recurrence and resistance. However, because the mechanisms by which these gene mutations influence the biological behavior of GIST are unclear, future *in vivo* and *in vitro* study is needed. In addition, most information on KIT gene mutations in GIST is obtained from case reports; studies based on large numbers of patients are rare. Although the low incidence of GIST is the reason that most knowledge about the tumor comes from case reports, the diagnosis is important to consider in clinical practice.

6. ACKNOWLEDGMENTS

Weiming Kang and Changzhen Zhu are co-first authors. Weiming Kang and JianChun Yu conceived and designed the manuscript. Weiming Kang, Changzhen Zhu performed the literature search and wrote the manuscript.

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Abbreviations: GIST: gastrointestinal stromal tumor

Key Words: KIT, Gene Mutation, Gastrointestinal Stromal Tumor, Review

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