Postprint of Research Progress on FOXF1 and ETV1 in Gastrointestinal Stromal Tumors

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Abstract

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract, originating from Interstitial cells of Cajal (ICC) or their precursor stem cells, with the majority of cases associated with KIT or PDGFRA gene mutations. Their incidence, targeted therapy resistance rate, and postoperative recurrence rate are increasing annually, greatly affecting patient prognosis. GISTs treatment is facing a bottleneck, and the search for new therapeutic approaches has become a current research focus in GISTs. ETV1 is a member of the ETS family of transcription factors that can stimulate KIT gene transcription, and KIT protein enhances ETV1 expression through the MEK-MAPK signaling pathway. The positive feedback co-regulation between ETV1 and KIT leads to sustained activation of intracellular signaling pathways in ICC/GISTs, thereby promoting tumor proliferation. FOXF1 is specifically highly expressed in GISTs and may serve as an upstream regulator of KIT and ETV1, promoting lineage-specific gene expression in ICC/GISTs. FOXF1 and ETV1 may provide novel insights and directions for GISTs therapy. This article provides a review of the current status and latest advances in the relationship between FOXF1, ETV1 gene expression and GISTs.

Full Text

Research Progress on FOXF1 and ETV1 in Gastrointestinal Stromal Tumors

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Abstract

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the digestive tract, originating from interstitial cells of Cajal (ICC) or their precursor stem cells. The majority of GISTs are associated with mutations in the KIT or PDGFRA genes. With increasing incidence, targeted therapy resistance, and postoperative recurrence rates, patient prognosis has been severely impacted, creating a therapeutic bottleneck for GISTs. Identifying novel treatment approaches has become a major research focus. ETV1 is a member of the ETS family of transcription factors that stimulates KIT gene transcription, while KIT protein enhances ETV1 expression through the MEK-MAPK signaling pathway. This positive feedback loop between ETV1 and KIT leads to persistent activation of intracellular signaling pathways in ICCs/GISTs, thereby promoting tumor proliferation. FOXF1 is specifically and highly expressed in GISTs and may serve as an upstream regulator of KIT and ETV1, promoting the expression of lineage-specific genes in ICCs/GISTs. Both FOXF1 and ETV1 may provide new insights and directions for GIST therapy. This review summarizes the current status and latest advances in understanding the relationship between FOXF1, ETV1 gene expression, and GISTs.

Keywords: gastrointestinal stromal tumors; GISTs; ETV1; FOX gene family; FOXF1

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract, arising from interstitial cells of Cajal (ICCs) or their homologous stem cells in the muscular layer of the digestive tract [1]. GISTs can occur anywhere in the gastrointestinal tract, most commonly in the stomach (70%) and small intestine (10%-25%), with fewer cases in the rectum, esophagus, and colon [2-3]. The incidence is approximately 1-2 per 100,000, accounting for 1-3% of all gastrointestinal tumors and 80% of gastrointestinal sarcomas [4], with a clear upward trend in recent years [5]. GISTs grow slowly and present with insidious symptoms, making early diagnosis extremely difficult with a misdiagnosis rate as high as 91.7% [6]. The clinical manifestations are diverse and nonspecific, often resulting in detection at intermediate to advanced stages that directly affects treatment efficacy and prognosis. Additionally, GISTs are not sensitive to conventional chemotherapy or radiotherapy, and complete surgical resection remains the only potentially curative approach. However, 40-80% of patients still experience recurrence or metastasis after surgery, with an average interval of 19-25 months and 80% of recurrences occurring within two years postoperatively [7].

The majority of GISTs are associated with functional mutations in KIT and/or PDGFRA genes [8-10]. Tyrosine kinase inhibitors (TKIs) have revolutionized GIST treatment, yet 14% of GISTs exhibit primary resistance [11]. Moreover, multiple site mutations and/or secondary mutations in these two genes have led to increasing rates of targeted therapy resistance and recurrence, which are

key factors affecting therapeutic efficacy. Studies have shown that the median progression-free survival for GIST patients taking adjuvant imatinib is approximately two years, with secondary resistance developing in 40-50% of cases within this period. Sunitinib achieves disease control in only 65% of imatinib-resistant cases (7% response rate, 58% stable disease), with short duration of benefit and easy development of resistance [12]. The efficacy of regorafenib and sorafenib for first- and second-line resistant GISTs remains uncertain and is associated with significant side effects [13]. GIST treatment has reached a bottleneck, making the search for novel therapeutic approaches a current research hotspot.

1. GISTs and ETV1 Expression

The KIT gene encodes a type III transmembrane receptor tyrosine kinase. Under normal conditions, the c-KIT protein must bind to its ligand, stem cell factor (SCF), to undergo autophosphorylation and activate mitogen-activated protein kinase and phosphatidylinositol 3-kinase, thereby triggering a kinase phosphorylation cascade that promotes cell proliferation. When the c-kit gene is mutated, its activation becomes ligand-independent, manifesting as persistent, automatic phosphorylation that pathologically enhances the c-KIT signal transduction system, driving cell proliferation and inhibiting apoptosis, ultimately leading to tumorigenesis [14-15].

The ETS (E-twenty six) transcription factor family comprises over 30 members and represents one of the largest families of signal-dependent transcriptional regulators. These proteins contain a conserved DNA-binding domain of 85 amino acids that binds to purine-rich sequences (typically GGAA/T) in target gene promoter regions to regulate transcription, participating in tumor initiation and progression [16-17]. ETV1 (ETS translocation variant 1, also known as Ets-related protein 81, ER81), located on chromosome 7p21.2, belongs to the PEA3 subfamily of ETS transcription factors. ETV1 can bind to numerous target genes and plays important roles in regulating tumor cell proliferation, differentiation, and migration by modulating target gene expression. Studies have demonstrated that ETV1 expression is significantly higher in tumor tissues such as prostate cancer, melanoma, and breast cancer compared to normal tissues [18-22].

ETV1 is highly expressed in both GIST tumor tissues and GIST cell lines, at levels significantly higher than in other tumors. In GIST cell lines, ETV1' s effects on target genes are regulated by a complex network, with the Ras/Raf/MAPK signaling pathway being the primary regulator of ETV1 [23-25]. Combined use of imatinib and MEK inhibitors in GIST patients significantly suppresses tumor growth. Research has revealed a positive feedback loop between ETV1 expression and KIT gene transcription: ETV1 can stimulate KIT gene transcription, while KIT protein promotes ETV1 expression and enhances its stability by slowing its degradation [26]. The transformation of ICCs into GISTs occurs through coordinated changes in KIT gene functional mutations and ETV1 expression [27]. Blocking ETV1 reduces cell division and increases apoptosis, demonstrat-

ing its critical role in GIST initiation and progression. Additional studies have shown that ETV1 may serve as an auxiliary diagnostic marker for wild-type GISTs and that its expression could be used as a prognostic indicator for 3-year disease-free survival in GIST patients after radical surgery [28].

In summary, ETV1 is likely involved in GIST initiation and progression, but whether it can serve as a new therapeutic target for drug-resistant GISTs or as an indicator for assessing malignancy and predicting tumor progression requires further clinical and basic research. In-depth exploration of ETV1' s potential mechanisms in GIST development will provide additional insights for GIST diagnosis and treatment.

2. GISTs and FOXF1 Expression

The FOX gene family (Forkhead box family) belongs to the forkhead genes and features a distinct forkhead DNA-binding domain in its molecular structure [29]. Currently, the family includes 19 subfamilies with 50 members, functioning in diverse biological processes including embryonic development, cell cycle regulation, carbohydrate/lipid metabolism, immune modulation, and aging. FOX family genes primarily act as transcription factors in the human body, regulating the expression of various target genes and being closely associated with tumor development, invasion, and metastasis [30]. FOXF1, a member of the FOX gene family located on human chromosome 16q24.1, encodes the FOXF1 transcription factor. FOXF1 can inhibit tumor cell proliferation and metastasis, and its inactivation promotes tumor progression, demonstrating tumor-suppressive effects [31]. Studies have shown that FOXF1 expression is positive in all enrolled GIST tissues regardless of KIT/PDGFRA mutation status [32], suggesting universal expression in GISTs. However, FOXF1 expression is rarely observed in other sarcomas, indicating that FOXF1 expression in GISTs is both universal and relatively specific. Therefore, FOXF1 may serve as a sensitive and relatively specific new biomarker for GISTs.

3. FOXF1 May Be Located Upstream of ETV1 Research indicates that FOXF1 appears to be an upstream regulator of ETV1 [32]. FOXF1 primarily binds to enhancer regions, suggesting it may regulate KIT and ETV1 expression through enhancer binding, thereby controlling GIST growth. FOXF1 downregulation not only reduces transcription of ICC/GIST lineage-specific genes but also decreases ETV1 expression. Inhibition of KIT and its downstream MAPK pathway with imatinib, or short-term inhibition of the MAPK pathway with MEK162 (a MEK inhibitor), leads to ETV1 protein degradation. Upon reactivation of these pathways, ETV1 protein levels correspondingly recover [33-34]. Throughout this process, FOXF1 protein expression levels remain stable, indicating that FOXF1 directly affects ETV1 expression without being influenced by ETV1 changes. These findings suggest that FOXF1 may be positioned upstream of ETV1 in the GIST growth signaling cascade, regulating ETV1 expression. However, the significance of FOXF1 expression in GISTs, its correlation

with clinicopathological features, and its potential as a new therapeutic direction remain unexplored.

In summary, the roles of FOXF1, ETV1, and KIT in GIST growth regulation can be described as follows: FOXF1 sits at the top of the signaling pathway, positively regulating ETV1 expression. ETV1 then regulates KIT expression, and the two form a positive feedback loop. This suggests that FOXF1 and ETV1 are likely new drug targets for GIST therapy, offering new hope for GIST patients facing therapeutic bottlenecks. However, how to develop GIST drugs targeting FOXF1 and ETV1, particularly for multi-drug resistant GISTs, requires further exploration through larger-scale, well-designed clinical and basic studies.

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