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REVIEW

Sine oculis homeobox homolog family function in gastrointestinal cancer: Progression and comprehensive analysis

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Abstract

The sine oculis homeobox homolog (SIX) family, a group of transcription factors characterized by a conserved DNA-binding homology domain, plays a critical role in orchestrating embryonic development and organogenesis across various organisms, including humans. Comprising six distinct members, from *SIX1* to *SIX6*, each member contributes uniquely to the development and differentiation of diverse tissues and organs, underscoring the versatility of the SIX family. Dysregulation or mutations in *SIX* genes have been implicated in a spectrum of developmental disorders, as well as in tumor initiation and progression, highlighting their pivotal role in maintaining normal developmental trajectories and cellular functions. Efforts to target the transcriptional complex of the *SIX* gene family have emerged as a promising strategy to inhibit tumor development. While the development of inhibitors targeting this gene family is still in its early stages, the significant potential of such interventions holds promise for future therapeutic advances. Therefore, this review aimed to comprehensively explore the advancements in understanding the SIX family within gastrointestinal cancers, focusing on its critical role in normal organ development and its implications in gastrointestinal cancers, including gastric, pancreatic, colorectal cancer, and hepatocellular carcinomas. In conclusion, this review deepened the understanding of the functional roles of the SIX family and explored the potential of utilizing this gene family for the diagnosis, prognosis, and treatment of gastrointestinal cancers.

Key Words: Sine oculis homeobox homolog; Gastrointestinal cancer; Transcription factor; Development; Regulation; Diagnosis; Therapeutics

Core Tip: The sine oculis homeobox homolog gene family, crucial for embryonic development and implicated in tumors, shows promise for targeted therapies in gastrointestinal tumors. Understanding its diverse roles can lead to advances in diagnosis, prognosis, and treatment of gastrointestinal cancers.

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INTRODUCTION

Growth and development involve the regulation of numerous factors, with a significant portion being transcription factors responsible for directly interpreting the genome and initiating the first step in DNA sequence decoding. Numerous transcription factors serve as master regulators and selector genes, controlling cell type determination, developmental patterns, and the regulation of specific pathways. Aberrant expression of transcription factor expression and mutations in their binding sites are closely linked to tumorigenesis[1]. Among them, the sine oculis homeobox homolog (SIX) family proteins function as transcription factors, regulating the expression of target genes involved in various developmental processes and contributing to eye, inner ear, muscle, and kidney development. They regulate the expression patterns of genes crucial for normal tissue differentiation and morphogenesis by interacting with other transcription factors, cofactors, and signaling molecules[2]. Furthermore, mutations or dysregulation of *SIX* genes have been implicated in various human developmental disorders and cancers, underscoring their significance in human health and cancer. Understanding the molecular mechanisms underlying the function of SIX family members can offer insights into the pathogenesis of these diseases and potential therapeutic targets[3].

Currently, gastrointestinal cancers (GICs) represent some of the most prevalent and metastatic malignancies, significantly impacting mortality rates. Metastatic GICs, characterized by their high invasiveness and heterogeneity, are the primary cause of mortality among patients with these malignancies[4]. Despite advances in modern surgical techniques, radiotherapy, and chemotherapy for early detection and treatment, the overall 5-year survival rate for advanced GIC remains low due to challenges in early diagnosis, rapid disease progression, high metastatic risk, and resistance to chemotherapy and radiotherapy[5]. Current therapeutic targets and diagnostic biomarkers fail to meet the clinical needs for GIC treatment, necessitating a better understanding of cancer progression mechanisms and optimized treatment strategies. Studies have shown that *SIX* genes are associated with the development and progression of GICs, holding potential as therapeutic targets. Therefore, this review aimed to deepen understanding of the function of the SIX family and to explore their potential in diagnosing, prognosticating, and treating gastrointestinal tumors.

SIX HOMEOBOX FAMILY MEMBERS

The first member of the SIX family, sine oculis (SO), was initially discovered in fruit flies, with its name originating from Latin, meaning "without eyes" as mutations in the *SO* gene lead to eye development defects in fruit flies[6]. Subsequent studies in fruit flies identified the presence of two more *SIX* genes, namely *OPTIX* and *DSIX4*. Similar to SO, Optix is also expressed in developing eyes, but its role in the retina differs from that of SO[7]. Dsix4, on the other hand, is not involved in eye development but plays a role in muscle and gonad development[8]. Gene duplications during evolution have expanded the SIX family, which in humans comprises six members organized into three subfamilies, that is *SIX1*/*SIX2* (SO), *SIX3*/*SIX6* (Optix), and *SIX4*/*SIX5* (Dsix4)[2].

Structurally, all of these proteins possess two functional domains, the SIX domain (SD) and the homeobox nucleic acid recognition domain (HD)[2]. The SD is an evolutionarily conserved domain located immediately after the 5′ end and adjacent to the HD, playing a role in mediating protein-protein interactions. For instance, the eyes absent (Eya) protein, a coactivator for the SIX family, predominantly interacts with SD, facilitating gene activation[9]. In HD, the substitution of conserved amino acids leads to structural variations that influence DNA binding. In addition to the conserved SD and HD domains, SIX family proteins also feature variable-length regions on both sides, defined as the C-terminal and N-terminal domains[10].

SIX1

The *SIX1* gene is located on human chromosome 14q23.1, spanning a length of 6057 bp and comprising five transcripts that encode two protein isoforms. The *SIX1* protein consists of 284 amino acids, with serine or threonine residues replacing amino acids at positions 5 and 12 within the HD[11]. Despite lacking an activation domain, *SIX1* collaborates with auxiliary factors to regulate gene expression. During transcriptional activation, *SIX1* interacts with Eya, facilitating their nuclear translocation and participation in regulation [12].

SIX1, the earliest identified member of the SIX family, has been extensively studied[6]. During early development, *SIX1* is closely associated with progenitor cell proliferation and intercellular communication, contributing significantly to tissue and organ formation. For instance, during the development of skeletal muscle, an analysis of gene expression in

early mouse embryonic stages revealed that *SIX1* is expressed in mesoderm-derived tissues, including skeletal muscles and dorsal root ganglia[13]. It was subsequently discovered that the expression of *SIX1* and *PAX3* precedes that of myogenic regulatory factors, which are critical determinants of the myogenic fate in muscle progenitor cells[14].

Additionally, studies have shown that *SIX1* enhances and sustains *MyoD* expression in adult muscle satellite cells, promoting the regeneration of muscle[15]. Furthermore, *SIX1* collaborates with *EYA3* to bind to the *MEF3* promoter site, thereby facilitating the transcription of myogenin[16]. In the development of sensory organs, *SIX1* orchestrates the balance among the neural crest, epidermis, and pre-placodal ectoderm through transcriptional activation and repression mechanisms, playing a critical role in regulating cranial placode development[17]. During the early kidney development process, overlapping expression of *PAX2*, *EYA1*, *SIX1*, and *SIX2* in the renal metanephric mesenchyme have been noted. The absence of *SIX1* leads to a failure of ureteric bud invasion into the mesenchyme, followed by mesenchymal apoptosis. Additionally, research has found that *PAX2* expression depends on *EYA1* and *SIX1*, while *SIX2* expression in the renal metanephric mesenchyme is also dependent on *SIX1*[18]. During embryonic gonadal development, the collaborative function of *SIX1* and *SIX4* is essential for male gonadal differentiation, affecting *SRY* activation and downstream targets, such as *FOG2* and *NR5A1*, which are critical for sex determination and gonadal size regulation[19].

Research has shown that defects in the *SIX1* gene are implicated in the etiology of branchiootic syndrome 3 and autosomal dominant deafness 23[20]. Branchiootic syndrome 3 is a genetic disorder characterized by developmental defects in the auditory system. *SIX1* plays a pivotal role in the regulation of organogenesis by interacting with the *EYA* and *PAX* gene families[21]. On the other hand, dominant deafness 23 is an autosomal dominant genetic condition characterized by symmetric hearing loss. Mutations in *SIX1* impair its normal function in the development of the auditory system, particularly in the structures of the inner ear[20].

SIX2

The *SIX2* gene is located on human chromosome 2p21, spanning a total length of 4271 bp. Initially identified by Boucher *et al*[22], the gene was discovered through screening of the human genome library using human *SIX1* cDNA. The predicted *SIX2* protein comprises 291 amino acids and consists of two exons.

In craniofacial development, *SIX2* is robustly expressed in the neural crest-derived frontonasal mesenchyme, and its absence is associated with frontonasal developmental defects[23]. In gastric development, the expression of *SIX2* is linked to the formation of the pyloric sphincter[24]. In the maturation process of human pancreatic β cells, *SIX2* is essential for the expression of multiple hallmark genes, and its absence significantly impairs the control of insulin processing and secretion in β cells[25].

During kidney development, *SIX2* is expressed in the early stages within the uninduced metanephric mesenchyme of the nephrogenic cortex, where it has the potential to regulate ureteric bud outgrowth and kidney differentiation[26]. Furthermore, *SIX2* is crucial for maintaining the undifferentiated state of renal pelvic mesenchymal progenitor cells, opposing the inductive signals from the ureteric bud to prevent premature and ectopic epithelial differentiation and preserve the progenitor pool[27]. It also inhibits nephron formation by directly or indirectly suppressing the expression of *WNT4* and *SFRP2* within the renal mesenchyme[27].

SIX3

The *SIX3* gene is located on human chromosome 2p21, spanning a length of 4370 bp and comprising 2 exons. A single transcript encodes a protein of 332 amino acids in length[28]. Research on *SIX3* binding sites has identified the DNA sequence ATTA as the motif that binds to *SIX3*[29].

During the process of eye development, *SIX3* is primarily expressed in the lens and neuroretina, where it facilitates the formation of ectopic vesicle-like structures in mouse embryos[30]. It is indicated that conditional loss of *SIX3* does not affect the initial development of the optic vesicle but impedes subsequent neuroretinal specification, as *SIX3* inhibits the expression of *WNT8B* to promote neuroretinal formation[31]. Recent research highlighted the collaborative role of *SIX3* and *SIX6* in maintaining multipotent neuroretinal progenitors in the retina, regulating the expression of crucial markers and suppressing aberrant activation of Wnt/β-catenin signaling, thereby ensuring normal retinal development and differentiation[32].

During the maturation process of human pancreatic β cells, *SIX3* prevents the inappropriate expression of genes typically active in fetal β cells, adult α cells, and other non-β cell types[25]. Additionally, *SIX3* suppresses fetal gene expression programs and alternative islet cell fates, thereby enhancing insulin secretion and the proper regulation of β cell gene expression, ultimately strengthening the function of mature β cells[25].

Haploinsufficiency of *SIX3* can lead to holoprosencephaly 2, a congenital brain malformation characterized by the failure of the forebrain to properly divide into the right and left hemispheres during early embryonic development[33]. Research indicated that *SIX3* influences the expression of key developmental genes such as *SHH* and *FOXG1*, with variations in *SIX3* dosage potentially resulting in different forms of holoprosencephaly[34].

SIX4

The *SIX4* gene is located on human chromosome 14q23.1 and spans a total length of 14813 base pairs. It comprises five exons and three transcripts, encoding two protein variants. The *SIX4* protein consists of 781 amino acids[35].

It was found that *SIX4* mainly collaborates with other members of the SIX family during development. For instance, *SIX4* and *SIX5* have been identified to act together during mice abdominal wall development, crucial for abdominal wall growth and morphological changes, with their deficiency resulting in umbilical herniation[36]. *SIX4*, along with *SIX1*, has been implicated in mice myogenesis[37], kidney development[38], and gonadal development[19]. During embryonic development, *SIX4* functionally serves as an auxiliary factor, collaborating with other family members, and playing a

crucial supportive role.

SIX5

Originally known as myotonic dystrophy-associated homeodomain protein, *SIX5* is located downstream of the dystrophia myotonica protein kinase gene on human chromosome 19q13.32, spanning three exons that encode three protein isoforms, with a total length of 4468 bp. The *SIX5* protein consists of 739 amino acids and contains an intrinsic C-terminal activation domain[39].

The *SIX5* gene is associated with myotonic dystrophy 1 (DM1) and branchio-oto-renal (BOR) syndrome. DM1 is a multisystem disorder characterized by myotonia, muscle wasting, testicular atrophy, and cataracts. The underlying genetic cause involves the repeat expansion downstream of the dystrophia myotonica protein kinase gene on chromosome 19, which impedes the expression of neighboring genes, including *SIX5*, leading to reduced expression in DM1[40]. For instance, knockout mice lacking *SIX5*, both heterozygous and homozygous, develop cataracts, implicating the involvement of *SIX5* deficiency in the cataract phenotype of DM1[41]. Furthermore, loss of *SIX5* leads to reproductive defects in mice, including testicular atrophy, infertility, and hormonal alterations, suggesting the significance of *SIX5* in spermatogenesis and interstitial cell regulation[42]. Moreover, the muscle contractility, electromyographic insertional activity, and histology of *SIX5*-deficient mice are normal, contrasting with the muscle stiffness and wasting observed in human DM1 [43].

Another disorder associated with *SIX5* mutations is BOR. Similar to *SIX1*, mutations in *SIX5* hinder the interaction between *EYA1* and *SIX5*, leading to reduced transcriptional activity of the *EYA1*-*SIX5* complex[44]. However, some studies have questioned the pathogenic impact of *SIX5* mutations in BOR syndrome, as *SIX5* mutations were not detected in their samples[45,46]. Further research is needed to explore the relationship between *SIX5* mutations and BOR syndrome.

SIX6

The *SIX6* gene is located on human chromosome 14q23.1, spanning a length of 3705 base pairs, and consists of two exons and one transcript encoding a protein of 246 amino acids[47].

During eye development, *SIX6*, similar to its subfamily member *SIX3*, is expressed in the optic vesicles and optic nerve [48]. Subsequent research has found that both *SIX6* and *SIX3* promote retinogenic factors to maintain the progenitor population of the neuroretina[49]. Furthermore, point mutations and allelic deletions in *SIX6* are associated with various ocular malformations, including anophthalmia[47], microphthalmia[50], primary open-angle glaucoma[51,52], optic disc anomalies, and macular atrophy[53].

THE ROLE OF SIX FAMILY GENES IN GICS

Gastric cancer

Gastric cancer (GC) ranks as the fifth most prevalent cancer globally and stands as the third-leading cause of cancer-related mortality[4]. Its metastatic pathways, encompassing direct infiltration, hematogenous spread, transluminal dissemination, and lymphatic dissemination, significantly contribute to the unfavorable prognosis seen in advanced cases. Despite notable advancements in GC diagnosis and treatment, its incidence and mortality rates persist without effective control, with metastasis and chemotherapeutic resistance posing substantial challenges[54].

Lv *et al*[55] analyzed the correlation between *SIX1* expression and clinicopathological parameters in GC, finding that overexpression of *SIX1* is significantly associated with larger tumor size, serosal invasion, and lymph node metastasis as well as closely related to local recurrence and distant metastasis. High levels of *SIX1* expression were found to decrease both overall and disease-free survival rates in patients with GC[55]. Furthermore, the induction of vascular endothelial growth factor-C (VEGF-C) by SIX1 is crucial for its ability to promote lymphatic and distant metastases. A positive correlation between *SIX1* and VEGF-C has been established, with *SIX1* acting as an upstream regulator that activates the expression of VEGF-C[56]. Du *et al*[57] observed elevated levels of *SIX1* in GC tissues, where silencing of *SIX1* expression could promote mitochondrial apoptosis by inhibiting the anti-apoptotic protein B-cell lymphoma-2 and activating caspase-7.

Further investigations revealed that *SIX1* overexpression increased the expression of cyclin D1, *MMP2*, extracellular regulated protein kinases, and proteins associated with epithelial-mesenchymal transition (EMT). It promoted GC cell proliferation by targeting cyclin D1 and facilitated the EMT process as well as cell invasion by modulating *MMP2* and E-cadherin[58]. Additionally, circ*NHSL1* acted as a "sponge" for miR-1306-3p to alleviate its inhibitory effect on the expression of its target *SIX1*, thereby promoting GC progression. Among them, *SIX1* enhanced vimentin expression by directly binding to its promoter region, thus influencing the malignant progression of GC[59].

Wang *et al*[60] confirmed that short-form RON (sf-RON) activation of the β-catenin/*SIX1* signaling pathway enhanced glucose metabolism in GC cells, leading to cell proliferation. Upregulation of *SIX1* was observed upon overexpression of short-form RON or RON. Silencing expression of β-catenin decreased *SIX1* levels as well as the expression levels of glycolytic proteins (glucose transporter type 1 and *LDHA*), while introduction of *SIX1* cDNA rescued this process. Furthermore, *SIX1* can induce the expression of transforming growth factor (TGF)-β1, which leads to the phosphorylation and activation of the receptors for TGF-β1. This activation initiates *SMAD2* and *SMAD3*, which then bind with *SMAD4* to form a *Smad* complex. This complex subsequently translocates to the nucleus to regulate the expression of specific genes. Within the nucleus, the Smad complex functions as a transcription factor, regulating the expression of various genes associated with EMT, such as E-cadherin, N-cadherin, vimentin, and snail. *SIX1* promotes the EMT process by upregu-

lating these genes through the TGF-β/Smad2/3 signaling pathway[61]. These findings underscore the critical role of *SIX1* in GC cell migration and invasion (Figure 1).

Rajkumar *et al*[62] discovered that *SIX3* is differentially expressed between patients with GC and matched normal controls. Recent research has revealed that *SIX3* is involved in GC progression. The long noncoding RNA DLGAP1-AS2 interacts directly with *SIX3*, influencing the inhibitory effect of *SIX3* on the expression of the *WNT1* gene. Specifically, upon binding with *SIX3*, DLGAP1-AS2 impedes the binding of *SIX3* to the promoter region of the *WNT1* gene, thereby relieving the inhibition of *WNT1* transcription and activating *WNT1* transcription. Furthermore, the study found that Wnt/β-catenin signaling mediated by DLGAP1-AS2 depends on *WNT1*. This process leads to the malignant transformation of GC cells, including enhanced proliferation, migration, and invasion capabilities[63].

Elevated expression levels of *SIX4* in GC tissues are positively correlated with the malignant behavior of GC cells and associated with poor prognosis in patients[64]. Additionally, miR-384 has been found to directly target the 3′ untranslated regions (3′UTR) of the *SIX4* gene and inhibit its expression. Circ-0000670 acts as a "sponge" by binding to miR-384, releasing the inhibition on *SIX4*, which leads to increased expression of *SIX4*. This higher expression of *SIX4* may promote the malignant behavior of GC cells[64]. These findings suggest that the SIX family and its related signaling pathways could be potential therapeutic targets for GC.

Colorectal cancer

Colorectal cancer (CRC) ranks as the third most prevalent cancer globally, constituting about 10% of all cancer cases and standing as the second-leading cause of cancer-related deaths worldwide[4]. CRC exhibits a diverse array of genetic and epigenetic characteristics, with its onset influenced by various internal and external factors, including mutation accumulation, susceptibility loci linked to family history, abnormal expression of non-coding RNA, and chronic or persistent inflammation[65]. Despite advancements in medical technology that have introduced new treatment methods, such as endoscopic and surgical local resection, preoperative radiotherapy and systemic therapy, extensive surgery for localized and metastatic disease, metastatic local ablation therapy, as well as palliative chemotherapy, targeted therapy, and immunotherapy, the cure rate is still limited by recurrence and chemotherapy resistance. Therefore, the treatment of CRC still faces several challenges, including a high recurrence rate, poor prognosis, impact on patients' postoperative quality of life, and low 5-year survival rates for patients with metastasis patients[66].

Ono *et al*[67] discovered through gene expression analysis that *SIX1* is expressed in CRC cells and is associated with EMT. *SIX1* enhances the expression of *ZEB1*, a known inhibitor of E-cadherin, by activating it at the post-transcriptional level. *ZEB1* can bind directly to the promoter region of the E-cadherin gene, inhibiting its transcriptional activity and leading to reduced E-cadherin expression. *SIX1* also suppresses the transcriptional activity of the miR-200 family members, which negatively regulates the expression of *ZEB1* and/or other EMT-related transcription factors by targeting their 3′UTR regions. The downregulation of the miR-200 family diminishes inhibition of *ZEB1*, allowing increased levels of *ZEB1* that in turn inhibit E-cadherin expression[67]. Inhibition of E-cadherin is a key hallmark of EMT, marking the loss of epithelial characteristics and acquisition of mesenchymal traits.

Additionally, studies have confirmed that miR-30b can directly target the 3′UTR region of the *SIX1* gene, causing degradation of *SIX1* mRNA or preventing its translation into protein, thereby reducing *SIX1* expression levels, indirectly increasing E-cadherin expression, and inhibiting EMT. Thus, miR-30b controls CRC cell migration and invasion by negatively regulating *SIX1* expression[68]. Similarly, *SIX1* is also a direct target of miR-362, with the expression of miR-362 being inversely correlated with that of *SIX1* in CRC[69].

Kahlert *et al*[70] analyzed the expression pattern of *SIX1* across normal mucosa, adenomas, and primary adenocarcinomas, establishing a correlation between progressive epithelial dedifferentiation and increasing *SIX1* expression. Overexpression of *SIX1* in HCT116 cells induced a mesenchymal-like phenotype and enhanced cell migration capabilities. Furthermore, both univariate and multivariate analyses confirmed that high *SIX1* expression is associated with reduced overall survival.

SIX1 has been confirmed to promote the development and metastasis of CRC through multiple mechanisms. *SIX1* is a direct target of *TEAD4* in CRC, with *TEAD4* binding to two *MCAT* motifs within the *SIX1* promoter to enhance its transcription. *TEAD4* facilitates EMT and CRC cell migration. The absence of *SIX1* diminishes this effect, whereas its overexpression amplifies it, indicating that *SIX1* mediates the role of *TEAD4* in promoting CRC cell migration[71]. Moreover, in MC38 cells, overexpression of *SIX1* increases the levels of the *ALDH1* protein and expands the cluster of differentiation (CD) 44 +/CD166 + cell population, characteristics indicative of an increase in cancer stem cell traits. *SIX1* stimulates angiogenesis by upregulating the expression of VEGF. Tumor cells with *SIX1* overexpression recruit tumor-associated macrophages by increasing the expression of macrophage-specific colony-stimulating factor, chemokines C-C motif chemokine ligand 2/5, and VEGF, further promoting tumor growth and metastasis[72].

Additionally, research has found that *SIX1* activates the mitogen-activated protein kinase signaling pathway in CRC cells[72]. Song *et al*[73] discovered that *SIX1* promotes the malignant progression of CRC cells by activating the Wnt/β-catenin signaling pathway, a process confirmed by the localization of β-catenin in the cell nucleus. Similarly, *FOXC2* enhances the expression of circ*CASK*, which increases the sponging effect of circ*CASK* on miR-1271-5p, reducing the inhibition of miR-1271-5p on *SIX1*. This, in turn, promotes *SIX1* expression and further activates the Wnt/β-catenin signaling pathway[74].

Wu *et al*[75] discovered that the expression of *SIX1* and *EYA1* is upregulated in CRC tissues. The *SIX1*/*EYA1* complex can regulate the expression of key genes, including cyclin A1 and TGF-β1, by binding to specific DNA sequences. Furthermore, the dual knockdown of *SIX1* and *EYA1* reduces cell proliferation, invasion, tumor growth, and *in vivo* tumor development. Li and Ma[76] discovered that circ*PLOD2* acts as a "sponge" for miR-513a-5p, enhancing the activity of its target gene *SIX1*, which in turn increases the transcriptional expression of the glycolytic enzyme *LDHA*, associated with the Warburg effect, thereby regulating the glycolysis process in CRC cells[76] (Figure 1).

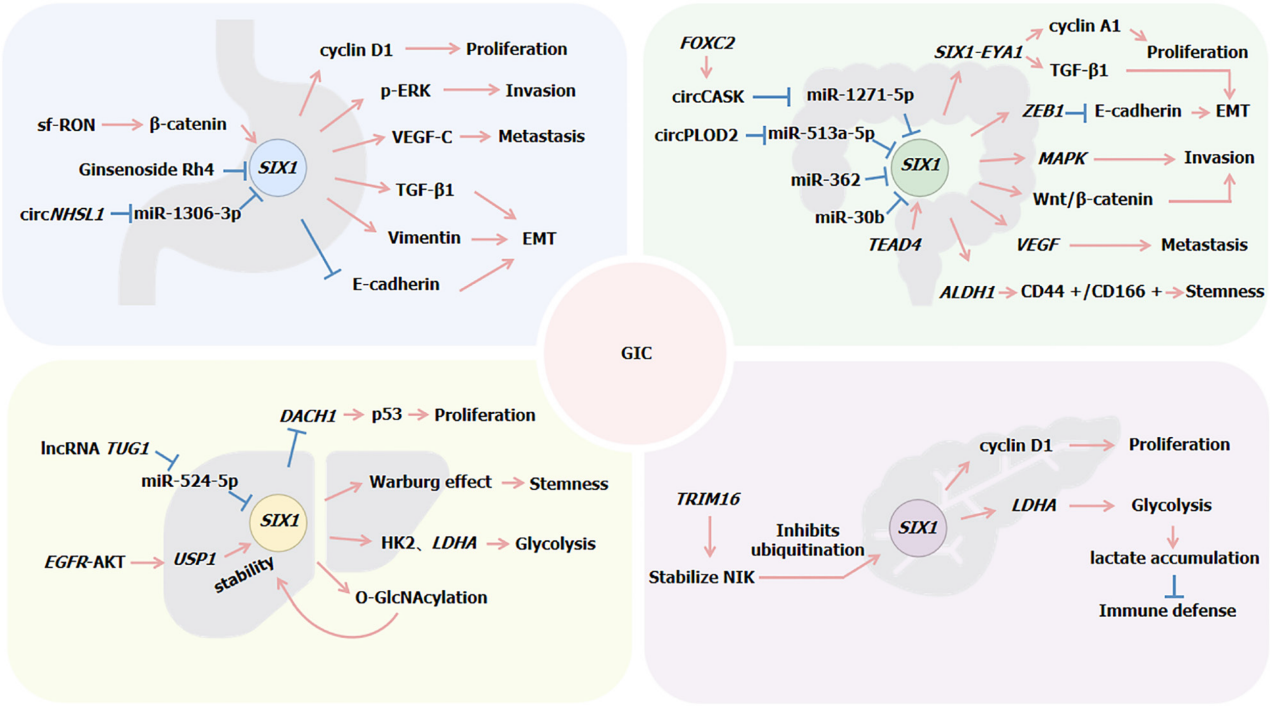

Figure 1 Regulation mechanism of *SIX1* expression in gastrointestinal cancers. EMT: Epithelial-mesenchymal transition; GIC: Gastrointestinal cancer; TGF: Transforming growth factor; VEGF: Vascular endothelial growth factor.

SIX2 has been recognized as an important EMT-related gene associated with CRC prognosis. Its methylation status and mutation state may influence its regulatory role in EMT, and changes in its expression levels are closely linked to tumor invasiveness, immune evasion, and drug treatment responsiveness[77]. Wu *et al*[78] discovered that the RNA helicase *DDX3* upregulates the transcription of *SIX2* by enhancing the binding of the c-fos protein to the *SIX2* promoter. This process involves the activation of *YAP1* through the phosphatidylinositol 3 kinase (PI3K)/AKT signaling pathway, which increases the expression and phosphorylation of c-fos, thereby facilitating its binding to the *SIX2* promoter[78]. Further studies indicated that *DDX3*-mediated invasiveness and cetuximab (CTX) resistance are regulated through the *YAP1*/*SIX2* axis in *KRAS*-WT cells and were further validated in animal models[78]. Additionally, cells overexpressing *DDX3* exhibited reduced sensitivity to CTX, but knockdown of *YAP1* or *SIX2* or the exogenous expression of E-cadherin significantly increased the sensitivity of *DDX3*-overexpressing cells to CTX, suggesting that the *YAP1*/*SIX2* axis plays a role in *DDX3*-mediated CTX resistance. Then, in patients with *KRAS*-WT CRC, *SIX2* expression levels were associated with overall survival and recurrence-free survival[78].

Jin *et al*[79] found that *SIX3* can inhibit cell growth, suggesting that it may act as a tumor suppressor in CRC. This differs from its role in GC. Additionally, studies have shown that *SIX3* is coregulated by *DNMT3B* and the *PRC1*/*PRC2* complexes, indicating that its expression may be controlled by these protein complexes. *SIX3* frequently undergoes DNA hypermethylation in CRC, leading to gene silencing[79]. Furthermore, the knockout of *DNMT1* and *DNMT3B* can affect the methylation status and expression of the *SIX3* gene. The absence of *DNMT3B* results in the loss of H2AK119 ubiquitination marks at specific gene promoter regions, potentially affecting the expression and function of the *SIX3* gene[79].

The expression levels of *SIX4* in CRC tissues are significantly higher than those in normal tissues. Furthermore, elevated *SIX4* expression is associated with lymph node metastasis, advanced tumor-lymph node-metastasis (TNM) stage, and poor prognosis in patients with CRC, including overall survival and recurrence-free survival[80]. Further investigations have revealed that *SIX4* promotes the metastasis of CRC cells by activating the PI3K-AKT signaling pathway. Rescue experiments further confirmed the regulatory role of *SIX4* in the PI3K-AKT signaling pathway[80].

Additionally, *SIX4* increases the expression of VEGF-A by interacting with hypoxia-inducible factor 1α (HIF-1α). VEGF-A is a key regulatory factor in tumor angiogenesis, and its expression is regulated by low oxygen conditions and HIF-1α. HIF-1α, a critical transcription factor under hypoxic conditions, can bind to the hypoxia response elements on the VEGF-A promoter, activating VEGF-A transcription[81]. Subsequently, *SIX4* upregulates HIF-1α expression through the PI3K/Akt signaling pathway dependency. Akt, a protein kinase, enhances the stability and activity of HIF-1α through phosphorylation, thereby increasing VEGF-A expression to promote tumor growth and angiogenesis[81].

SIX5, together with *EYA3* and p300, forms the *EYA3*-*SIX5*-p300 complex. This complex is formed after the induction of *EYA3* expression under hypoxic conditions, with the involvement of hypoxia-inducible factors HIF-1α and HIF-2α. Additionally, *SIX5* plays a role in recognizing and binding to the promoter regions of target genes within the complex, recruiting p300 to acetylate chromatin, leading to chromatin relaxation and further enhancement of gene expression. *SIX5* also synergistically interacts with *EYA3* to enhance transcriptional activation. *SIX5* participates in the regulation of genes associated with tumor cell proliferation, invasion, and tumor growth through the aforementioned mechanisms, thereby playing a role in the development of CRC[82].

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) constitutes the predominant form of primary liver cancer, ranks as the sixth most prevalent malignant tumor globally, and is the fourth-leading cause of cancer-related mortality worldwide, with chronic viral hepatitis, alcohol consumption, diabetes mellitus, and nonalcoholic steatohepatitis representing the principal risk factors for its onset[4]. While surgical resection and liver transplantation serve as primary treatments, long-term disease-free survival remains suboptimal. Tumor recurrence and metastasis stand as the primary causes of mortality among patients with HCC[83].

Overexpression of *SIX1* is associated with tumor progression in HCC. Studies have found that approximately 85% of HCC tumor tissues exhibit increased *SIX1* mRNA expression compared to non-tumor liver tissues, with about 60% of tumor tissues showing elevated *SIX1* protein expression. High levels of *SIX1* protein expression are observed in HCC cell lines with high metastatic potential. Furthermore, the overexpression of the *SIX1* protein is significantly associated with the pathological TNM stage and vascular invasion in HCC. It is also correlated with poorer overall survival in patients with HCC after liver resection[84]. Further investigation has revealed that inhibition of *SIX1* expression significantly reduces the growth and proliferation capabilities of HCC cells as well as diminishes their migration and invasion abilities. It also leads to a delay in the G2/M transition of cells, affecting the abnormal progression of the cell cycle and chemoresistance. Through cDNA microarray analysis, it has been found that *SIX1* can regulate the expression of multiple genes associated with tumor development[85]. Similarly, Cheng *et al*[86] also confirmed the role of *SIX1* in cell proliferation, apoptosis, and cell cycle regulation.

SIX1 influences the metabolic activities and stem cell characteristics of HCC cells by modulating metabolic processes linked to the Warburg effect, including sugar uptake, lactate production, adenosine triphosphate generation, and oxygen consumption rate[87]. Lu *et al*[88] found that *SIX1* plays a role in glycolysis by directly regulating the expression of glycolytic genes such as hexokinase 2 and *LDHA*, which are involved in regulating cell proliferation and/or apoptosis. Additionally, miR-524-5p can inhibit the expression of *SIX1* by targeting its 3′UTR. This regulatory action of miR-524-5p can suppress the positive regulation of glycolytic genes by *SIX1*, thereby reducing glycolysis levels. Conversely, the lncRNA *TUG1* acts as a "sponge" for miR-524-5p, inhibiting its suppressive effect on *SIX1* and thereby indirectly increasing *SIX1* activity, which in turn promotes glycolysis[88].

Furthermore, Chu *et al*[89] discovered that *SIX1* enhances the level of O-GlcNAcylation, a post-translational protein modification involving the addition of O-GlcNAc to serine/threonine residues of proteins. *SIX1* undergoes O-GlcNAcylation modification at serine 276, inhibiting its ubiquitination degradation and thus enhancing the stability of the *SIX1* protein. This enhancement promotes tumor growth and further exacerbates the malignant phenotype of HCC cells by increasing glucose uptake and O-GlcNAcylation levels. Subsequently, Liu *et al*[90] also identified a modification that enhances the stability of *SIX1*. They found that activation of the *EGFR*-AKT signaling pathway promotes the expression of ubiquitin-specific peptidase 1 (USP1). Ubiquitin-specific peptidase 1, a deubiquitinating enzyme, reduces the ubiquitination levels of *SIX1* by removing ubiquitin chains from the protein, thereby stabilizing *SIX1* expression and enhancing its stability.

Moreover, significant colocalization of *SIX1*, *DACH1*, and p53 was reported. Overexpression of *SIX1* inhibited the expression of both *DACH1* and p53, while overexpression of *DACH1* enhanced the expression of p53, suggesting that *SIX1* may indirectly decrease the expression of p53 by suppressing *DACH1* and thereby promote tumor progression[86]. Li *et al*[91] found that *SIX1* played a crucial role in drug resistance in HCC cells by modulating reactive oxygen species and autophagy. Treatment with *SIX1* siRNA, paclitaxel alone, or their combination significantly increased reactive oxygen species levels in HCC cells, and it resulted in decreased expression of the autophagy-related protein light chain 3-I and increased expression of light chain 3-II, along with a significant reduction in p62 levels. Then, treatment with the reactive oxygen scavenger N-acetylcysteine and the autophagy inhibitor reversed these effects.

Similarly, research has also confirmed the relationship between *SIX1* and cellular stemness and chemotherapy drug sensitivity. Knockdown of *SIX1* enhances the sensitivity of HCC cells to 5-fluorouracil (5-FU). Additionally, *SIX1* can directly bind to the promoter region of the *SOX2* gene, enhancing its transcriptional activities and expression accordingly. *SOX2* is a master regulator of stemness. Therefore, *SIX1* affects the stemness of HCC cells by regulating *SOX2*. Overexpression of *SIX1* can induce normal liver cells to acquire stem cell characteristics, including increased ability for sphere formation and expression of stemness markers. Furthermore, the decreased stemness and the increased sensitivity to 5-FU caused by *SIX1* knockdown can be partially reversed by overexpression of *SOX2*[92] (Figure 1).

It was revealed that the expression of *SIX2* was significantly elevated in HCC tumor tissues compared to adjacent non-tumorous liver tissue and normal liver tissue. High levels of *SIX2* are associated with shorter overall survival and disease-free survival in patients with HCC. Additionally, the expression of *SIX2* correlates with factors such as sex, tumor size, alpha-fetoprotein levels, and portal vein invasion, suggesting that *SIX2* may enhance tumor growth and invasion clinically. In cases of HCC with portal vein tumor thrombosis, the expression levels of *SIX2* are even higher, indicating that *SIX2* may facilitate tumor metastasis[93]. Li *et al*[94] also found that elevated expression levels of *SIX2* are associated with shorter overall survival in patients with HCC. Furthermore, *SIX2* suppresses the expression of E-cadherin by stimulating methylation in the promoter region of the E-cadherin gene. This suppression reduces the sensitivity of HCC cells to 5-FU and enhances the stem cell-like properties of the HCC cells[94].

Moreover, recent research has revealed that *NIK*, an NF-κB-inducing kinase, enhances the stability of *SIX2* protein by inhibiting its ubiquitination. Knockdown of *NIK* promotes the ubiquitination of *SIX2*, and this reduction in *SIX2* protein stability can be rescued by treating with the proteasome inhibitor. The overexpression of *SIX2* partially reverses the inhibitory effect of *NIK* knockdown on the stem cell-like properties of HCC cells. These findings suggest that *NIK* promotes the stem cell-like properties of HCC cells through *SIX2*, including self-renewal capacity and tumorigenicity[95].

It is noteworthy that the expression of *SIX3* mRNA in HCC tissues is significantly lower compared to adjacent non-tumorous tissues, a contrast to the expression patterns of other members of the SIX family in HCC[96]. Studies indicated that *SIX3* can bind to the promoter region of *WDR26* gene, and the overexpression of lnc*WDR26* enhances the binding of *SIX3* to this promoter region. This binding inhibits the transcription of the *WDR26* gene, thereby inhibiting the growth and metastasis of HCC cells[97].

SIX4 is also found to be significantly upregulated in HCC tissues compared to adjacent non-tumor tissues, which is positively correlated with the absence of a tumor capsule, microvascular invasion, higher TNM staging, and poor prognosis[96]. Further studies revealed that *SIX4* can directly bind to the promoter regions of the *YAP1* and c-*MET* genes, activating their expression, which promotes the invasion and metastasis of HCC. The expression of *SIX4* is positively regulated by hepatocyte growth factor, which activates the *ERK*/NF-κB signaling pathway through its receptor, c-*MET*, thus upregulating *SIX4* expression. This created a novel positive feedback loop of hepatocyte growth factor-*SIX4*-c-*MET* that may enhance the malignant progression of HCC[96].

Pancreatic cancer

The incidence of pancreatic cancer (PC) is increasing and continues to be one of the most lethal cancers[4]. It is characterized by its highly aggressive tumor growth rate, high rate of metastasis, and notable resistance to chemotherapy. Various treatment modalities, such as surgical resection, chemotherapy, and radiation therapy, have been progressively advancing over time. Nevertheless, due to the advanced or metastatic stage of diagnosis in most patients, treatment options are constrained, leading to an unfavorable prognosis[98].

Research has found that *SIX1* is expressed at significantly higher levels in PC tissues compared to normal pancreatic tissues. Overexpression is positively correlated with tumor size, TNM staging, lymph node metastasis, and tumor grading in PC, and it is closely associated with patient prognosis[99]. It is confirmed that *SIX1* can bind to specific regions of the cyclin D1 promoter, enhancing its activity. Additionally, the expression of *SIX1* is significantly correlated with cyclin D1 in human PC tissues. *SIX1* promotes the proliferation and colony formation of PC cells, partly by directly activating the transcription of cyclin D1, facilitating cell cycle progression and enhancing the proliferative capacity[100]. Conversely, inhibiting *SIX1* reduces the migratory capacity of PC cells *in vitro*, slows tumor growth *in vivo*, and diminishes the CD24-/ CD44 + tumor stem cell phenotype[101].

Additionally, *SIX1* enhances glycolysis in PC cells by directly targeting and activating the expression of *LDHA*, leading to lactate accumulation. Natural killer cells co-cultured with PC cells overexpressing *SIX1* exhibit a reduced proportion of activated surface receptors and diminished expression of cytotoxic mediators. This indicates that lactate accumulation caused by *SIX1* overexpression inhibits natural killer cell function, weakening the immune defense against malignant tumor cells[102]. Zhou *et al*[103] also discovered that the expression of *SIX1* in glycolysis is regulated by the E3 ubiquitin ligase *TRIM16*. *TRIM16* promotes glycolysis and metastasis in PC cells by stabilizing *NIK*, which inhibits the ubiquitination and degradation of *SIX1* (Figure 1).

The role of the *SIX3* gene in various cancers has been extensively studied, particularly as a tumor suppressor gene[79, 97]. Research has revealed that the methylation status of *SIX3* is associated with early diagnosis of PC, showing significant differences in methylation levels between patients with PC and healthy controls. In PCs, the high methylation level of the *SIX3* gene may lead to gene silencing, thereby impairing its function as a tumor suppressor[104].

Database analysis and quantitative real-time PCR techniques have confirmed the overexpression of *SIX4* in PC tissues. Knockdown of *SIX4 via* siRNA technology significantly reduces the survival rate, colony formation ability, and mitochondrial membrane potential of PC cells. Silencing *SIX4* alters the expression of apoptosis-related genes, thereby increasing apoptosis and autophagy in cancer cells[105]. Additionally, the knockdown of *SIX4* leads to cell cycle arrest at the G1 and sub-G1 phases, which may be associated with the inhibition of cell proliferation and the initiation of apoptosis [105].

Furthermore, *SIX1* and *SIX4* act as downstream effectors of hepatocyte nuclear factor 4α (HNF4α). HNF4α inhibits tumor growth and steers tumor cells towards epithelial properties, while *SIX1* and *SIX4* drive tumor cell proliferation and foster mesenchymal/neuronal cell differentiation in HNF4α-negative PC. HNF4α regulates PC proliferation and molecular subtypes by directly binding to the gene promoter regions of *SIX1* and *SIX4*, suppressing their expression [106]. Further research has found that *SIX4* and *SIX1* physically interact with their enzymatic cofactors, such as *SIX4* with the histone demethylase *UTX* and *SIX1* depending on the Eya family protein tyrosine phosphatases, which are potential drug targets[106]. Moreover, RNA sequencing analysis revealed a gene network coregulated by *SIX4* and *SIX1*, which likely involves multiple cell fate determinants that influence the characteristics of PC cells[106].

SIX6 has been identified as one of the differentially expressed genes consistently associated with PC and its radioresistance. Genome-wide methylation analysis revealed a set of genes whose expression was altered in radioresistant cell lines, with a particular enrichment of genes related to cholesterol biosynthesis pathways. *SIX6* is involved in the cholesterol biosynthesis pathway and is speculated to be associated with the radioresistance of PC cells[107]. However, comprehensive research is still lacking to elucidate the specific mechanism of action of *SIX6* in PC.

IMAGING IN HEALTHCARE

Although the role of the *SIX* gene family in GIC has been extensively studied, relying on a single gene is insufficient to fully elucidate the complex mechanisms underlying cancer development. Cancer is a multifactorial disease driven by interactions between gene expression, epigenetic modifications, and environmental influences[108]. To better understand the onset and progression of cancer, technologies that can accurately capture these multiple factors are essential.

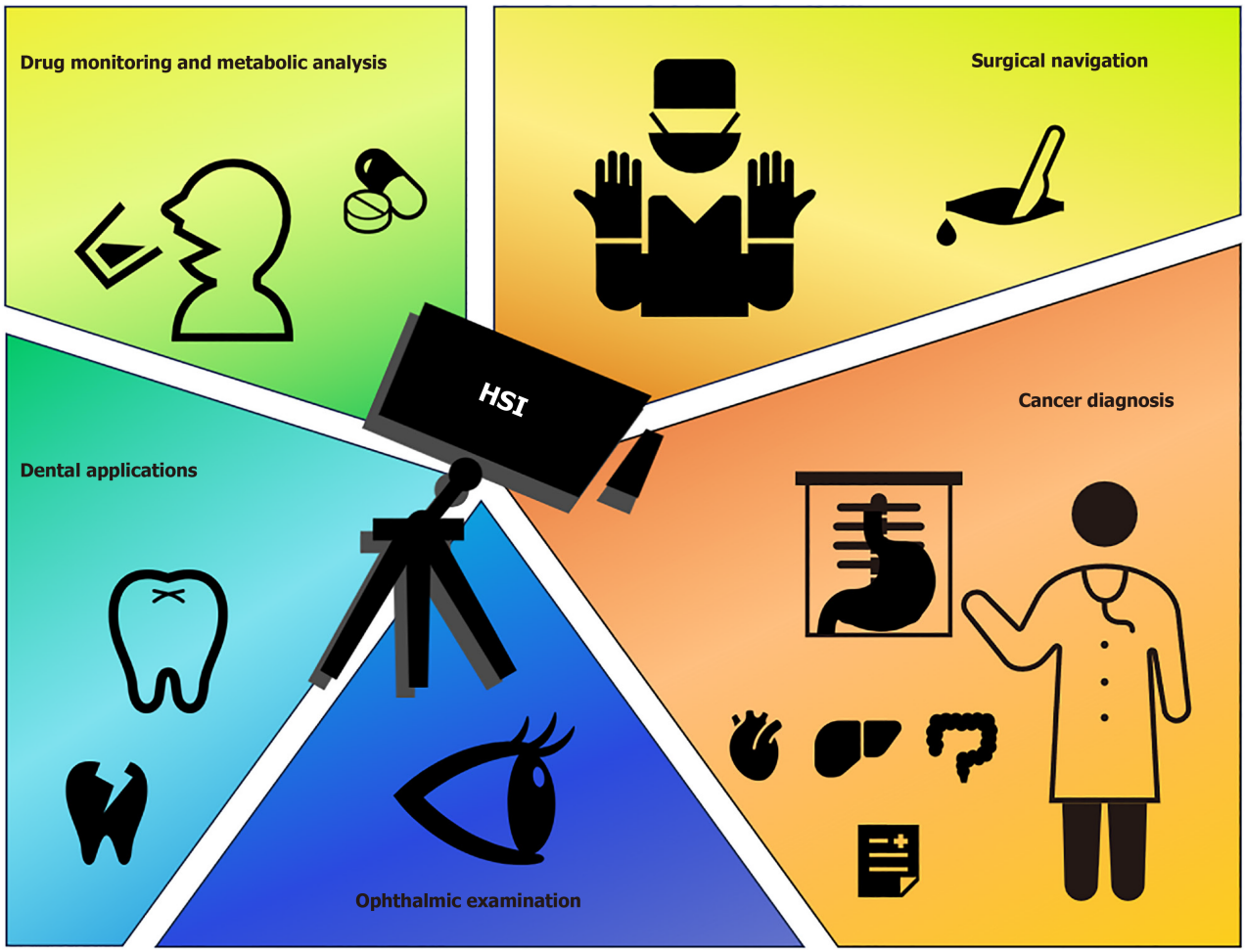

Figure 2 Hyperspectral applications in healthcare: A multifunctional diagnostic tool. HSI: Hyperspectral.

Traditional diagnostic methods face limitations in early detection and real-time imaging, particularly for GIC, which are often located deep within internal organs and are not visible to the naked eye or easily detected through non-invasive techniques[109]. However, advances in imaging technologies, especially hyperspectral imaging (HSI) and multispectral imaging, have enabled scientists to capture the spectral characteristics of tissues, leading to a better understanding of gene expression, mutations, and epigenetic changes (Figure 2). Integrating these imaging techniques with artificial intelligence can enhance early cancer detection and provide new perspectives for targeting the SIX gene family[110].

For example, in the early diagnosis of esophageal cancer, the combination of HSI with artificial intelligence has been shown to differentiate between normal and cancerous tissues through spectral analysis without direct tissue contact[111]. Studies have demonstrated that HSI outperforms traditional endoscopic techniques in sensitivity and specificity for early esophageal cancer detection, reducing reliance on biopsies[112,113]. Furthermore, multispectral imaging can be used not only for diagnosis but also as a surgical navigation tool, allowing real-time evaluation of tissue states and boundaries during surgery[114,115].

This presents new opportunities for exploring the application of HSI in GIC. Combining this technology with research on the *SIX* gene family offers a novel approach for early GIC detection and can deepen our understanding of the role of *SIX* genes in cancer initiation and progression. By precisely capturing the spectral characteristics of tumor tissues, HSI can support targeted gene therapy, providing strong backing for personalized cancer treatment[116]. This innovative integration of new imaging technologies and gene-targeted therapies offers a fresh perspective for developing *SIX* gene family-based therapies to address abnormalities in complex signaling pathways.

SUMMARY AND PROSPECT

At the mechanistic level, the diverse roles of the *SIX* gene family provide researchers with key insights into its functions in GIC, opening new avenues for therapeutic interventions. Precision-targeted therapies, particularly those designed for specific genetic targets, offer significantly improved efficacy and reduced side effects compared to traditional treatments [117]. For instance, ginsenoside Rh4 targets *SIX1*, thereby blocking the TGF-β/Smad2/3 signaling pathway. Compared to common chemotherapy agents like oxaliplatin, ginsenoside Rh4 demonstrates lower systemic toxicity and side effects while inhibiting tumor growth and metastasis[61].

Lowering *SIX1* expression with siRNA can increase the sensitivity of HepG2 cells to the chemotherapeutic drug paclitaxel, suggesting that *SIX1* siRNA may help overcome resistance to chemotherapy in certain cancers[91]. Moreover, to address challenges in target identification, it is crucial to deeply explore relevant ligands and signaling pathways. In GIC contexts, *SIX* genes often activate the Wnt/β-catenin signaling pathway, promoting tumor cell proliferation and migration. Developing small molecule inhibitors targeting SIX or inhibitors of the Wnt signaling pathway could potentially suppress malignant progression in the GIC tract[73].

Additionally, abnormal regulation of SIX proteins and their cofactors may lead to tumor development and progression. Developing inhibitors targeting these cofactors could be an effective therapeutic strategy. Interactions between *SIX1* and *SIX4* with their cofactors, such as *UTX* and the Eya family proteins, are critical for their activity. Using inhibitors like benzbromarone (inhibits Eya family proteins) has suppressed *SIX1* and *SIX4* expression, which may impact the proliferation of tumor cells dependent on these transcription factors[106].

Although targeting the *SIX* gene family has demonstrated potential advantages in the treatment of GIC, current research faces several limitations. Most inhibitors are still in the preclinical stage, lacking large-scale clinical validation, and many studies focus on single targets, limiting the coverage of relevant signaling pathways. Consequently, these limitations hinder the clinical application of existing findings. Further research is required to explore the mechanisms of the *SIX* gene family in different cancer types and to develop broader spectrum small-molecule inhibitors to enhance efficacy and expand applicability. However, due to the limited number and scope of current studies, the widespread clinical use of these inhibitors remains constrained. Future research must expand to cover more targeted pathways and undergo large-scale clinical trials to verify the effectiveness and safety of these therapies across various cancer types.

Additionally, future research directions should include extending the findings on the *SIX* gene family to other types of cancer. Although this study primarily focused on GIC, other studies have shown that the *SIX* gene family plays an important role in breast cancer, lung cancer, and other malignancies[118,119]. Therefore, future targeted therapies should explore the application of these genes in other types of tumors and develop inhibitors with broader applicability[120].

CONCLUSION

In summary, while targeted therapies involving the *SIX* gene family hold great potential, they are still in the early stages of development, with certain limitations in clinical application. Future research should prioritize deepening the understanding of its mechanisms, expanding the range of targeted pathways, and validating efficacy through large-scale clinical trials. As research progresses, *SIX* gene family-targeted therapies are expected to play a more significant role in cancer treatment, particularly in improving therapeutic outcomes across multiple cancer types.

FOOTNOTES

Author contributions: Liu J and Lan YZ designed this study; Lan YZ, Wu Z, Chen WJ, and Yu XN searched the publications; Lan YZ, Wu Z, Chen WJ, Yu XN, Wu HT, and Liu J interpreted the results, constructed the structure of the review, and prepared the tables; Lan YZ prepared the draft of the manuscript; Lan YZ and Wu Z prepared the figures; Liu J revised the manuscript critically; All authors read and approved the final manuscript.

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