# KLF family of proteins in gastrointestinal tumors (Review)

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**Abstract.** The Krüppel-like family (KLF) are important transcriptional regulators that have important, context-specific roles in gastrointestinal (GI) malignancies. Their roles are very heterogeneous; each of the KLF members may play tumor-suppressive or tumor-promoting roles, depending on the type of tumor, clinical stage and the cellular microenvironment, which fine-tunes the core biological processes of tumor cell proliferation, apoptosis, epithelial-mesenchymal transition and metabolism. This is a context-dependent functional heterogeneity that poses a big challenge in the translation of KLF family transcription factors from basic research into clinical applications. In addition to these classical regulatory functions, KLFs have a key role in the restructuring of the tumor immune microenvironment (TIME). KLFs have the potential to affect the effectiveness of cancer immunotherapy by modulating immune cell infiltration, immune cell functions and immune evasion by tumors. The present review is a systematic review that summarizes the molecular regulatory mechanisms of KLFs in the major GI malignancies, such as colorectal, gastric, liver, esophageal and pancreatic cancer. The present review points to their control of major signaling pathways, including Wnt/β-catenin and PI3K/AKT, and their new roles in the remodeling of TIME. Moreover, the present review assesses their translational utility as diagnostic and prognostic biomarkers and therapeutic targets, and confronts the clinical issues involved in targeting transcription factors, thus giving a theoretical basis for oncology approaches in different types of GI cancer.

**Contents**

1. Introduction
2. KLF family
3. Progress of KLFs in GI tumors
4. Outlook
5. Conclusions

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## 1. Introduction

Gastrointestinal (GI) malignancies such as gastric, colorectal and esophageal cancer (EC) are the most prevalent and fatal types of cancer (1,2), which is a major danger to human health worldwide. The diseases are also being marked by an insidious onset, with high invasive and metastatic potential and considerable heterogeneity in treatment responses. These, along with the lack of early screening programs, have led to a relatively small rise in the overall 5-year survival rates, which has remained a consistent issue when it comes to cancer prevention and control (3-5). With the increased knowledge of cancer biology, it has come to light that tumor diversity is multidimensional, incorporating the genetic, cytological, tissue-level, pathological and therapeutic-response phenotypes (6). In 2022, Hanahan (7) revised the hallmark features of malignant tumors to 14 items, which improved the comprehension of the biological mechanisms of tumor development and offered a theoretical framework of identifying new therapeutic targets and designing novel treatment approaches.

At present, endoscopy and imaging methods are the main sources of early detection of GI tumors. Nevertheless, these methods have some limitations such as invasiveness, expensive nature and lack of sensitivity. The conventional tumor biomarkers, which include carcinoembryonic antigen and CA19-9, are also limited in sensitivity and specificity, and thus not suitable to satisfy the requirements of precision medicine (8). In this regard, the Krüppel-like factor (KLF) family, which is a potential source of new diagnostic and prognostic biomarkers, has become a promising target of new diagnostic and prognostic biomarkers (9). The changes in KLF expression are common in the initial phases of tumorigenesis and have an association with molecular subtypes, invasive and metastatic capacity, and response to treatment. KLFs are therefore promising candidates in the early detection and risk stratification biomarkers. A number of studies justify this possibility (10,11). As an example, poor prognosis in colorectal cancer (CRC) is associated with low KLF17 expression, which can be used as an independent prognostic biomarker (12). Increased KLF8 levels in liver cancer are associated with increased chances of recurrence (13). Besides, KLF10 expression is elevated in pancreatic cancer (PC), which is a predictor of clinical response to adjuvant chemotherapy and radiotherapy, and it has been confirmed in phase III clinical trials (14). These studies all indicate that KLF family members have the potential to be used effectively in order to address the limitations of traditional tumor markers, which offer a new molecular foundation of individual treatment decisions and patient stratification.

The KLF family is a key participant in several essential biological functions, such as cell cycle regulation, lineage differentiation, apoptosis signaling and tumorigenesis, therefore, it is a significant target of recent cancer biology studies (15-17). KLFs comprise a family of 18 members (KLF1-KLF18) with tissue specificity and reliance on the tumor microenvironment (TME) in their molecular functions (18). At the structural level, one of the KLF family characteristics is a highly conserved C-terminal DNA-binding domain that has three C2H2-type zinc finger motifs that specifically identify and bind to GC-rich or CACCC sequences in promoters of target genes (19). Depending on the differences in their N-terminal regulatory domains, KLFs can be subdivided into a number of subgroups that have different functional roles. Indicatively, KLF3 and KLF8 are the main mediators of transcriptional repression by interacting with the co-repressor C-terminal binding protein (CtBP) (20) and KLF4, KLF5 and KLF6 are the context-dependent mediators of transcriptional activation or repression, which affect major biological processes, including cell proliferation and differentiation. This structural and functional heterogeneity supports the multifunctional roles of KLF family members in physiological and pathological mechanisms, such as cancer development. It is based on this knowledge that the present review critically analyzes the molecular processes of KLF family members in GI tumors and the prospects of their application in clinical practice as diagnostic biomarkers, prognostic markers and therapeutic targets, thus offering a theoretical basis for future studies on targeted therapies in different types of gastric cancer (GC).

Although there has been considerable progress in the study of the KLF family in GI tumors (9,10,17), a number of its members have been found to be viable diagnostic biomarkers and therapeutic targets, yet there are still numerous challenges in the process of applying these basic findings into effective clinical practices. The factors that hinder this translational process are the context-dependent roles of the KLF family members, functional redundancy, antagonism among the members and the undruggable nature of transcription factors (TFs). Against this backdrop, the present review is not only a systematic summary of the molecular processes and clinical research advances of KLF family members in GI tumors, but also a critical assessment of the aforementioned clinical translation challenges. Based on this discussion, the present review offers future research opportunities, which will give insights into how the KLF family-related findings can be clinically translated successfully.

## 2. KLF family

KLFs are a family of zinc-finger TFs that are related to specificity protein 1 (SP1), and consist of 18 members. They are named after the Drosophila Krüppel gene (21). The DNA binding activity of KLFs is mediated by their C-terminal domain that contains three highly conserved motifs of a cysteine 2/histidine 2 (C2H2) zinc finger protein. Each zinc finger coordinates a tetrahedral zinc ion through two pairs of cysteine and histidine residues (22,23). The main difference between the KLFs and the SP TF family is in the N-terminal domains. Unlike the members of the SP family, which contain a highly conserved Buttonhead (BTD) domain (CXCPXC motif) for protein-protein interactions and transcriptional regulation, the members of the KLF family show a high degree of structural variation in this region, in particular, the absence of the BTD domain. This structural divergence likely changes the functional regulatory network of KLFs. The functional diversity of the KLF family is mainly due to differences in the C-terminal zinc-finger arrangements and selective target gene recognition, and thus results in distinct transcriptional regulatory patterns during development, cell differentiation and disease pathogenesis (24). KLFs usually act as transcriptional repressors by interacting with the co-repressor CtBP, although they can also have transcriptional activation or inhibition activities depending on the context (25). As a result, they are generally involved in physiological and pathological processes such as cell cycle regulation, tumorigenesis, metabolic regulation, stem cell differentiation and inflammatory response, playing key roles in cell proliferation, differentiation and metabolism (18,26-28). Individual members of the KLF family have different functional roles. For example, KLF5 induces cell proliferation by activating the EGFR/ERK pathway and works with the Wnt/β-catenin pathway to control CRC progression (29,30). KLF15 controls the processes of gluconeogenesis and lipid metabolism (31), KLF14 affects insulin sensitivity and metabolic homeostasis (32), and KLF9 controls hepatocellular carcinoma (HCC) metabolic reprogramming by inhibiting lactate dehydrogenase A, an important enzyme of glycolysis (33). These diverse molecular mechanisms highlight the important regulatory roles of KLFs in diverse physiological and pathological conditions.

In the context of disease, the KLF family has a complex spectrum of functions. In the case of cancer, KLF family members can behave as either an oncogene or tumor suppressor. Notably,

the combination of KLF4 agonists and immunotherapy has been taken to phase I clinical trials, showing great promise in clinical treatment (34-36). In cardiovascular diseases, KLF4 and KLF5 are central in hypertension-caused cardiac inflammation and fibrosis, regulating pathological processes through IL-1β/NF-κB and TGF-β1 signaling pathways (37,38). With regard to angiogenesis and immune regulation, KLF2 inhibits inflammation of endothelial cells, whereas KLF4 is involved in the regulation of macrophage polarization (39,40). In the nervous system, some KLF members may inhibit axon regeneration in the central nervous system and thus affect the repair of nerve injury (27,41).

A defining feature of the KLF family is that they are functionally specific and context dependent. Although the DNA-binding domains of different KLF members are structurally homologous to one another, individual members of these proteins may have opposing roles in tumorigenesis. For example, both KLF4 and KLF5 are highly expressed in the GI epithelium, but KLF4 is a tumor suppressor that induces cell cycle arrest and maintains epithelial differentiation, while KLF5 is a promoter of proliferation and an oncogene (29,38). These differences are the result of selective interactions of the N-terminal regulatory domains with coactivators and corepressors.

KLF proteins can display opposing functions depending on the type of tumor, stage of the disease or the cellular context. For example, KLF4 is a tumor suppressor gene in colorectal and GC; tumor progression is aided by the downregulation of KLF4. However, in squamous cell carcinoma of the esophagus, it has a controversial role, since it can have tumor suppressor or oncogenic effects depending on the stage of the disease (42-44). Similarly, while KLF5 is an oncogene in the majority of GI cancer types (29,45,46), it has growth inhibitory effects under certain cellular conditions or in interactions with certain binding partners (47).

This context-dependent functionality is affected by a number of factors. Tumor type and tissue origin control the choice of target genes by chromatin accessibility and the set of interacting proteins. Dynamic changes in the genomic landscape and TME during disease progression can affect KLF transcriptional output (48). Mutations in important pathways, such as p53, APC and KRAS, can play a key role in modulating the pro-cancer or tumor suppressor activity of KLFs (49). Additionally, microenvironmental signals, such as inflammatory cytokines and hypoxia, may influence KLF expression, post-translational modifications and cofactor binding, thereby altering transcriptional programs. Post-translational modifications, such as phosphorylation, acetylation and ubiquitination (50) further affect KLF stability, subcellular localization and transcriptional activity, adding another layer of regulatory complexity (51,52).

## 3. Progress of KLFs in GI tumors

*Progression of KLFs in colorectal cancer.* The invasive and metastatic potential of CRC is associated with poor prognosis, and members of the KLF family display complex biological functions in the regulation of the TME. Studies have been conducted to study the functional mechanisms of several KLF family members and their clinical relevance in CRC (Table I). In CRC tissues and cell lines, the expression levels of KLF1, KLF5, KLF8 and KLF12 are relatively high, while the expression levels of KLF3, KLF4, KLF13 and KLF14 are expressed at lower levels. These highly expressed members generally act as tumor-promoting factors.

Shen *et al* (53) reported that KLF3 regulates the behavior of CRC cells by the Wnt/β-catenin signaling pathway. WNT1 is a direct downstream target of KLF3, and its regulation promotes malignant phenotypes in CRC cells. In addition, decreased KLF3 expression increases CRC cell proliferation, migration and invasion, with the miR-365a-3p axis being instrumental in the regulation of migration, invasion and chemoresistance (54). Low levels of KLF4 favor CRC cell proliferation, invasion and epithelial-mesenchymal transition (EMT) (55). Mechanistically, KLF4 is a direct target of miR-29a. Clinical studies have demonstrated that upregulated miR-29a directly targets KLF4, modulating the MMP2/E-cadherin signaling axis and promoting CRC metastasis (56,57). Similarly, miR-92a can increase CRC cell proliferation and migration by regulating KLF4 and its downstream effector p21 (58). The TF KLF5 is a downstream target of the MAPK-ERK-RAS pathway and is regulated by early growth response factor 1 (EGR1). KRAS activation plays an important role in the pathophysiology of CRC, and KLF5 expression is required for the oncogenic and proliferative effects of KRAS, making it a pathogenic factor in CRC (29,59,60). The tumor suppressor APC, a key gene involved in the pathogenesis of CRC (61), controls the activity of Wnt signaling pathway via regulation of the activity of β-catenin. KLF5 is an important mediator of these interactions, and its absence can prevent the oncogenic effects of APC mutations and activation of the Wnt signaling pathway, providing further support for its oncogenic role in CRC (59,62). Additionally, KLF12 is involved in tumor growth through direct activation of EGR1 (63).

Conversely, some of the KLF family members are tumor suppressors in CRC. KLF2 is relatively highly expressed and KLF6, KLF7, KLF9 and KLF17 are expressed at lower levels. Overexpression of KLF2 suppresses the invasion, migration, EMT and xenograft tumor growth of CRC cells. Mechanistically, KLF2 causes ferroptosis by inhibiting the PI3K/AKT pathway (64) and controls the behavior of CRC cells through the hypoxia inducible factor-1α/Notch-1 signaling pathway as a tumor suppressor (65). Another tumor suppressor, KLF6, may be involved early in tumorigenesis (66,67). Downregulation of KLF6 splice variant KLF6-SV2 is associated with the progression of CRC. KLF6-SV2 upregulates p21 and Bax thus leading to cell cycle arrest, inhibition of cell proliferation and induction of apoptosis (68). Finally, KLF17 inhibits CRC cell adhesion, invasion and EMT, and is a tumor suppressor as well as a potential independent prognostic biomarker for patients with CRC (12).

Although the bidirectional regulatory network of the KLF family in CRC has been unveiled by current research, the complexity of these interactions remains a major challenge. It is important to note that the majority of existing studies are based on *in vitro* cell lines and xenograft models (17,18), which fail to capture the heterogeneity and complexity of the human TME. The development of targeted molecules, such as inhibitors of KLF5 or activators of KLF6, shows promise but their efficacy and safety need to be validated in models that more

Table I. Functional roles of KLF family members in colorectal cancer progression.

| KLF member | Expression level | Functions | Regulatory pathways | Clinical significance | (Refs.) |
|---|---|---|---|---|---|
| KLF1 | Increased | Oncogene | NA | Potential oncogenic factor | |
| KLF2 | Decreased | Tumor suppressor | Inhibition of the PI3K/AKT signaling pathway induces ferroptosis; regulation of the HIF-1α/Notch-1 signaling pathway | Inhibits invasion, migration, EMT and tumor growth | (64,65) |
| KLF3 | Decreased | Tumor suppressor | Regulates WNT1 expression through the Wnt/β-catenin signaling pathway; miR-365a-3p directly targets KLF3 | Downregulation promotes proliferation, migration, invasion and chemoresistance | (54) |
| KLF4 | Decreased | Tumor suppressor | miR-29a targets KLF4 to regulate the MMP2/E-cadherin axis; miR-92a targets KLF4 to regulate p21 expression | Downregulation promotes proliferation, invasion, EMT and metastasis | (55-58) |
| KLF5 | Increased | Oncogene | Acts downstream of the MAPK/ERK/RAS signaling pathway and is regulated by EGR1; cooperates with the APC/β-catenin signaling axis | Essential mediator of KRAS-driven oncogenic effects | (29,59,60) |
| KLF6 | Decreased | Tumor suppressor | KLF6-SV2 upregulates p21 and Bax, leading to cell cycle arrest and induction of apoptosis | Early tumor suppressor event | (66,67) |
| KLF7 | Decreased | Tumor suppressor | NA | Downregulation associated with progression | |
| KLF8 | Increased | Oncogene | NA | Oncogenic factor | |
| KLF9 | Decreased | Tumor suppressor | NA | Tumor suppressive function | |
| KLF12 | Increased | Oncogene | Directly activates EGR1 | Promotes tumor growth | (63) |
| KLF13 | Decreased | Tumor suppressor | NA | Downregulation promotes oncogenesis | |
| KLF14 | Decreased | Tumor suppressor | NA | Downregulation promotes oncogenesis | |
| KLF17 | Decreased | Tumor suppressor | Inhibits cell adhesion, invasion and EMT | Independent prognostic biomarker | (12) |

KLF, Krüppel-like factor; HIF-1α, hypoxia-inducible factor 1-α; miR, microRNA; EMT, epithelial-mesenchymal transition; EGR1, early growth response protein 1; KLF6-SV2, Krüppel-like factor 6 splice variant 2.

closely reflect the clinical setting. In addition, the complex cross-regulatory network between KLF family members is not fully understood. For example, whether KLF3 and KLF5 are synergistic or antagonistic in the Wnt signaling pathway and how such cross-regulation affect tumor cell responses to targeted therapies are not known. Addressing these questions will be important for improving the understanding of KLF-mediated mechanisms in CRC and for the development of effective therapeutic strategies in future studies.

*Progression of KLFs in GC*. The aggressive biological behaviors of GC, including invasion, metastasis and chemoresistance, are associated with poor patient prognosis. The KLF family plays a key role in the development of GC, and also in the regulation of the TME. Studies show that in GC patient tissues and cell lines, KLF3, KLF5, KLF11 and KLF16 are at relatively high expression levels while KLF2, KLF4, KLF9 and KLF15 are relatively low in expression. Collectively, these members of the KLF family are tumor-promoting factors in GC (Table II).

Wang *et al* (69) reported that KLF2 is expressed at low levels in gastric tumors and its downregulation is associated with poor survival of patients with primary GC. Diminished expression of KLF2 is involved in the acquisition of malignant phenotypes in GC cells. Beyond mechanistic insights, a registered clinical study at Nanfang Hospital, Southern Medical University (Guangzhou, China) (ChiCTR1900027330), further explored the clinical relevance of KLF2 in cancer. This observational study, based on human tissue samples, discussed the regulation of cancer cell invasion and metastasis mediated by the TF FOXK1 through CTGF and KLF2. Registered in November 2019, the research highlights the clinical importance of KLF2 in tumorigenesis and ongoing efforts to bring basic findings to clinical practice. Subsequently, Li *et al* (70) found that KLF3 is highly expressed in GC tissues. Overexpression of KLF3 facilitates GC cell proliferation, migration, invasion and EMT. Mechanistically, the WNT1 promoter is activated by direct binding of KLF3, which results in nuclear accumulation of β-catenin and activation of the Wnt/β-catenin signaling pathway. Inhibition of WNT1 reverses the malignant phenotype induced by KLF3 (53), and *in vivo* experiments confirm that KLF3 promotes tumor growth and metastasis.

Helicobacter pylori (Hp) is a known carcinogenic agent for GC. KLF4 is frequently a tumor suppressor in GI tumors. Studies have shown that Hp promotes the development of GC by inhibiting the expression of KLF4 (71-73). Knockdown of KLF4 promotes GC cell proliferation, migration and invasion by modulating E-cadherin and modulating the Wnt/β-catenin signaling pathway, thus promoting EMT (74,75). Mechanistically, miR-135b-5p has oncogenic effects in GC cells by reducing KLF4 (76). KLF5 is upregulated in GC tissues, and its high expression is associated with poor patient prognosis. Functional studies suggest that KLF5 knockdown diminishes the proliferation of GC cells and induces cell cycle arrest at the $G_0/G_1$ phase. This effect is mediated, at least in part, through the regulation of cell cycle-related proteins, including p21 and CDK4, and thus KLF5 controls GC cell proliferation (77,78) (Fig. 1). Ji *et al* (79) found that KLF11 facilitates GC invasion and migration through its overexpression of Twist1. In a clinical study, KLF15 was found to improve GC cell proliferation through the downregulation of CDKN1A/p21 and CDKN1C/p57, and its expression levels may be a prognostic indicator for patients with GC (80). KLF16 is highly expressed in GC tissues. Knockdown of KLF16 suppresses GC cell proliferation by upregulating p21 expression and downregulating CDK4 levels, thus suggesting that KLF16 promotes cell proliferation by modulating these cell cycle regulators (81). Furthermore, high KLF16 expression plays a role in GC growth and metastasis by modulating the Notch signaling pathway (82).

However, there are members of the KLF family that serve as tumor suppressors in GC. In patient tissues and cell lines, KLF7, KLF10, KLF12 and KLF13 are relatively highly expressed while KLF1 and KLF6 have lower expression levels. Li *et al* (83) showed that silencing KLF1 inhibits the proliferation of GC cells, which was associated with decreased cell viability, decreased DNA synthesis, and $G_1$ phase cell cycle arrest, resulting in a lower percentage of cells in the S phase. KLF1 knockdown also inhibits activation of the Wnt/β-catenin pathway, which inhibits GC cell migration, invasion and the EMT process (83). Studies have shown that microRNAs (miRNAs) can regulate GC malignancy through KLF12. Specifically, miR-138-5p inhibits GC cell invasiveness by direct targeting of KLF12 (84), and overexpression of miR-200a-3p inhibits GC cell proliferation and cell cycle progression and migration by targeting KLF12, with tumor-suppressive effects (85). These results highlight the central role of KLF12 as a downstream effector of miRNAs in the regulation of GC malignancy. KLF13 has been reported to suppress GC cell proliferation, possibly by autophagic degradation of the Wnt signaling pathway protein, β-catenin, leading to decreased expression of β-catenin and downstream molecules Cyclin D1 and MYC. This mechanism causes the cell cycle to arrest at the G2/M phase (86). Contrarily, other studies indicate that KLF13 facilitates GC cell migration and invasion by activating the NF-κB/EMT signaling axis (87,88). These seemingly contradictory results are likely to reflect the influence of cellular context: The balance between proliferation and migration programs may be dependent on the particular repertoire of interacting proteins, post-translational modifications or microenvironmental cues that are present in different experimental systems or tumor subtypes. The context-dependent behavior of KLF13 underscores the complexity of the function of KLF family members in GC.

In summary, the KLF family has a key regulatory role in the tumorigenesis, progression and TME modulation of GC. By activating canonical signaling pathways, such as Wnt/β-catenin, KLFs affect malignant phenotypes including cell proliferation, invasion, metastasis and chemoresistance, all of which are associated with poor patient prognosis. Despite these insights, clinical translation is still difficult. For example, although KLF12 is a key regulator of GC malignancy as a downstream target of multiple miRNAs, studies are largely correlative and lack direct evidence that targeting KLF12 itself (26), and not its upstream miRNAs, can provide therapeutic benefit. Additionally, the functional role of KLF13 in GC is still controversial because the same molecule may exert opposite effects depending on the cellular context or experimental conditions. These observations indicate the necessity of caution in interpreting available data and the importance

Table II. Functional roles of KLF family members in gastric cancer progression.

| KLF members | Expression level | Functions | Regulatory pathways | Clinical significance | (Refs.) |
|---|---|---|---|---|---|
| KLF1 | Decreased | Tumor suppressor | Activation of Wnt/β-catenin pathway; KLF1 silencing inhibits migration, invasion and EMT | Silencing inhibits cell proliferation and DNA synthesis | (83) |
| KLF2 | Decreased | Tumor suppressor | Inhibition of PTEN/AKT signaling | Downregulation associated with reduced patient survival | (69) |
| KLF3 | Increased | Oncogene | Direct binding to WNT1 promoter activating transcription; activation of WNT/β-catenin pathway | Promotes proliferation, migration, invasion, EMT and metastasis | (70) |
| KLF4 | Decreased | Tumor suppressor | Hp promotes carcinogenesis by inhibiting KLF4; targeted by miR-135b-5p; regulation of E-cadherin and Wnt/β-catenin pathway | Downregulation promotes proliferation, migration, invasion and EMT | (71-76) |
| KLF5 | Increased | Oncogene | Regulation of p21 and CDK4, inducing G0/G1 phase arrest | High expression associated with poor prognosis | (77,78) |
| KLF6 | Decreased | Tumor suppressor | NA | Downregulation exerts tumor suppressive effect | |
| KLF7 | Increased | Oncogene | NA | Oncogenic function | |
| KLF9 | Decreased | Tumor suppressor | NA | Tumor suppressive function | |
| KLF10 | Increased | Oncogene | NA | Oncogenic function | |
| KLF11 | Increased | Oncogene | Increased Twist1 expression | Promotes invasion and migration | (79) |
| KLF12 | Increased | Oncogene | Targeted by miR-138-5p and miR-200a-3p | Downstream target of miRNAs regulating malignant behavior | (84,85) |
| KLF13 | Increased | Dual (oncogene/tumor suppressor) | Induction of autophagic degradation of β-catenin inhibiting proliferation; activation of NF-κB/EMT axis promoting migration/invasion | Complex function requiring further investigation | (86-88) |
| KLF15 | Decreased | Tumor suppressor | Upregulation of CDKN1A/p21 and CDKN1C/p57 | Predictive of patient prognosis | (80) |
| KLF16 | Increased | Oncogene | Regulation of p21 and CDK4; modulation of Notch pathway | Promotes proliferation, growth and metastasis | (81,82) |

KLF, Krüppel-like factor; Hp, Helicobacter pylori; EMT, epithelial-mesenchymal transition; miR, microRNA; EGR1, early growth response protein 1.

of systematic approaches, such as functional analyses at the single-cell level, to elucidate the specific biological roles of KLF family members in GC.

*Progression of KLFs in liver cancer.* In HCC, several members of the KLF family have been widely studied. Studies have shown that in tissues from patients with HCC and cell lines, KLF5, KLF7, KLF8, KLF13 and KLF15 are abundantly expressed, while KLF3, KLF6, KLF9 and KLF17 are low expressed. Collectively, these members of the KLF family are tumor-promoting factors in HCC (Table III).

In HCC, KLF3 has been found to be a direct target of miR-660-5p. Functional studies show that miR-660-5p enhances HCC cell proliferation, colony formation and invasive and migratory abilities by inhibiting KLF3 expression. It also inhibits apoptosis and induces EMT phenotype (89-91). KLF5 is an oncogene in HCC, and it drives cell proliferation, and tumor proliferation and metastasis (92). Mechanistically, KLF5 is responsible for inducing EMT by activating the PI3K/AKT/Snail pathway. In a set of HCC cell lines, the silencing of KLF5 leads to a notable decrease of mesenchymal markers, such as N-cadherin and vimentin, as well as the TF Snail, and an increase in the epithelial marker E-cadherin (93). These results indicate that the targeting of KLF5 may be a potential therapeutic approach for HCC. KLF7 has also been found to be an oncogenic factor in HCC, with its abnormal expression being associated with malignant progression (94). Tryptophan metabolism is a central regulatory node within the TME and is important in HCC proliferation, metastasis and invasion. KLF7 transcriptionally regulates an amino acid transporter SLC1A5, which forms the KLF7/SLC1A5 axis, promoting the uptake of tryptophan and metabolic reprogramming to maintain the malignant phenotype of HCC cells (95). These results suggest that the KLF7/SLC1A5 axis may provide a molecular target for the treatment of HCC and is a novel strategy to intervene in aberrant tryptophan metabolism. KLF8 overexpression activates Wnt/β-catenin signaling pathway target genes, such as c-Myc, Cyclin D1 and Axin1 (96). Functional studies have shown that KLF8 upregulation has a notable effect on HCC cell proliferation and invasion, inhibits apoptosis and induces EMT through modulation of the expression of epithelial and mesenchymal markers, downregulating N-cadherin, vimentin and fibronectin and upregulating E-cadherin (13,97). Clinical correlation analysis suggests that high expression of KLF8 may be a molecular marker of poor prognosis or early recurrence in surgical patients with HCC (13). Additionally, KLF9 inhibits the proliferation of HCC cells and positively regulates p53 expression (98) while low expression of KLF17 is notably associated with increased tumor invasiveness and poor patient prognosis (99). Mechanistically, KLF17 inhibits tumor growth and metastasis by regulation of the TGF-β/Smad signaling pathway (100).

Further research has shown that some members of the KLF family are tumor suppressors in HCC. In tissues from patients with HCC and cell lines, KLF6 and KLF14 are relatively highly expressed, while KLF2 and KLF4 are expressed at lower levels. Notably, KLF2 is downregulated in HCC samples, and its overexpression inhibits the growth, migration and colony-forming ability of liver cancer cells (101). Mechanistically, KLF2 exerts its tumor-suppressive effects by means of a negative feedback loop in the TGF-β/Smad signaling pathway (102). However, the long non-coding RNA, FBXL19-AS1 is upregulated in HCC and interacts with KLF2 to promote tumor cell proliferation, cell cycle progression and prevent apoptosis, thus worsening HCC progression (103). KLF4 is also a tumor suppressor in HCC with multiple regulatory functions. It reverses EMT by inhibiting the TFs Slug (104) and notably inhibits HCC cell proliferation and migration by upregulating cadherin 3 and activating the GSK-3β signaling pathway (105). Additionally, KLF4 is a major transcriptional regulator of monoglyceride lipase (MGLL), with the KLF4-MGLL axis being central to inhibiting HCC cell migration (106). In terms of metabolic regulation, KLF4 acts as a target of miR-206 and its downstream effector RICTOR, inhibiting the progression of HCC by decreasing tumor cell ATP synthesis (35). Notably, the deubiquitinase DUB3 forms a positive feedback loop with KLF4 to maintain KLF4 protein stability and cooperatively suppress HCC tumor growth and chemoresistance (107). Collectively, these mechanisms point to the tumor-suppressive activity of KLF4 and suggest that the activation of the DUB3/KLF4 pathway may be a potential therapeutic strategy against HCC progression. The expression and biological roles of KLF6 in HCC have also attracted much attention. Inhibition of KLF6 notably impairs cell proliferation and causes $G_1$-phase cell-cycle arrest, mainly by inhibition of the expression of CDK4 and cyclin D1, which results in the inhibition of retinoblastoma protein phosphorylation (108,109). KLF6 silencing also results in further upregulation of the tumor suppressor p53 and downregulation of the anti-apoptotic protein, Bcl-xL, leading to apoptosis (110). These findings suggest a key role of KLF6 in the control of cell cycle progression and apoptosis in HCC cells. Additionally, KLF6 has tumor suppressor properties, including the inhibition of the PI3K/AKT signaling pathway, which increases the sensitivity of liver cancer cells to chemotherapeutic agents. Promoter methylation of KLF6 leads to loss of expression, which is highly related to the progression of HCC. Restoration/enhancement of KLF6 expression thus represents an attractive therapeutic avenue for suppressing the malignant progression of liver cancer (111-113) (Fig. 2A).

In summary, the KLF family is involved in the development of HCC through a complex regulatory network. The double biological roles of its members, along with the interaction between metabolic reprogramming and signaling pathways, provide new insights for clinical intervention approaches. Elucidation of molecular mechanisms of KLF family members in HCC is of great scientific importance for identification of potential therapeutic targets and combination strategies targeting the KLF signaling axis. Such studies have offered an innovative theoretical basis and translational framework for the accurate diagnosis, treatment and prognosis of HCC.

*Progression of KLFs in EC*. Being an aggressive GI malignancy, EC is associated with highly invasive and metastatic potentials, which are associated with low prognosis. The systematic study of the KLF family in EC, however, is not very extensive. KLF5 is typically highly expressed in patient tissues and cell lines, but at a relatively low level in KLF12 and KLF17. These relatives play the role of tumor-promoting factors in EC (Table IV).

Table III. Functional roles of KLF family members in hepatocellular carcinoma progression.

| KLF members | Expression level | Functions | Regulatory pathways | Clinical significance | (Refs.) |
|---|---|---|---|---|---|
| KLF2 | Decreased | Tumor suppressor | Negative feedback loop in TGF-β/Smad signaling; interaction with lncRNA FBXL19-AS1 | Inhibits growth, migration and colony formation | (101-103) |
| KLF3 | Decreased | Tumor suppressor | Targeted by miR-660-5p | Downregulation promotes proliferation, invasion, migration, inhibits apoptosis, induces EMT | (89-91) |
| KLF4 | Decreased | Tumor suppressor | Inhibition of Slug reversing EMT; upregulation of CDH3 activating GSK-3β; transcriptional upregulation of MGLL; targeting miR-206/RICTOR reducing ATP synthesis; DUB3/KLF4 positive feedback loop | Multifaceted tumor suppressor; activation of DUB3/KLF4 pathway is a potential therapeutic strategy | (35,104-107) |
| KLF5 | Increased | Oncogene | Activation of PI3K/AKT/Snail pathway driving EMT | Promotes proliferation, growth and metastasis | (92,93) |
| KLF6 | Decreased | Tumor suppressor | Inhibition of CDK4 and cyclin D1, inducing G1 arrest; upregulation of p53, downregulation of Bcl-xL inducing apoptosis; inhibition of PI3K/AKT pathway enhancing chemosensitivity; promoter methylation leading to loss of expression | Restoration or enhancement of KLF6 expression may inhibit malignant progression | (108-113) |
| KLF7 | Increased | Oncogene | Transcriptional regulation of SLC1A5, driving tryptophan uptake and metabolic reprogramming; KLF7/SLC1A5 axis | Potential therapeutic target | (94,95) |
| KLF8 | Increased | Oncogene | Activation of Wnt/β-catenin target genes (c-Myc, Cyclin D1, Axin1); induction of EMT | Biomarker for early recurrence and poor prognosis | (13,96,97) |
| KLF9 | Decreased | Tumor suppressor | Positive regulation of p53 expression | Inhibits cell proliferation | (98) |
| KLF13 | Increased | Oncogene | NA | Oncogenic function | |
| KLF14 | Increased | Oncogene | NA | Oncogenic function | |
| KLF15 | Increased | Oncogene | NA | Oncogenic function | |
| KLF17 | Decreased | Tumor suppressor | Regulation of TGF-β/Smad signaling pathway | Downregulation associated with tumor invasiveness and poor prognosis | (99,100) |

KLF, Krüppel-like factor; lncRNA, long Non-Coding RNA; FBXL19-AS1, F-Box and Leucine-Rich Repeat Protein 19 Antisense RNA 1; EMT, epithelial-mesenchymal transition; Slug, SNAI2; CDH3, Cadherin 3; MGLL, monoglyceride Lipase; DUB3, deubiquitinase 3; miR, microRNA; RICTOR, rapamycin-insensitive companion of mTOR; Axin1, axis inhibition protein 1.

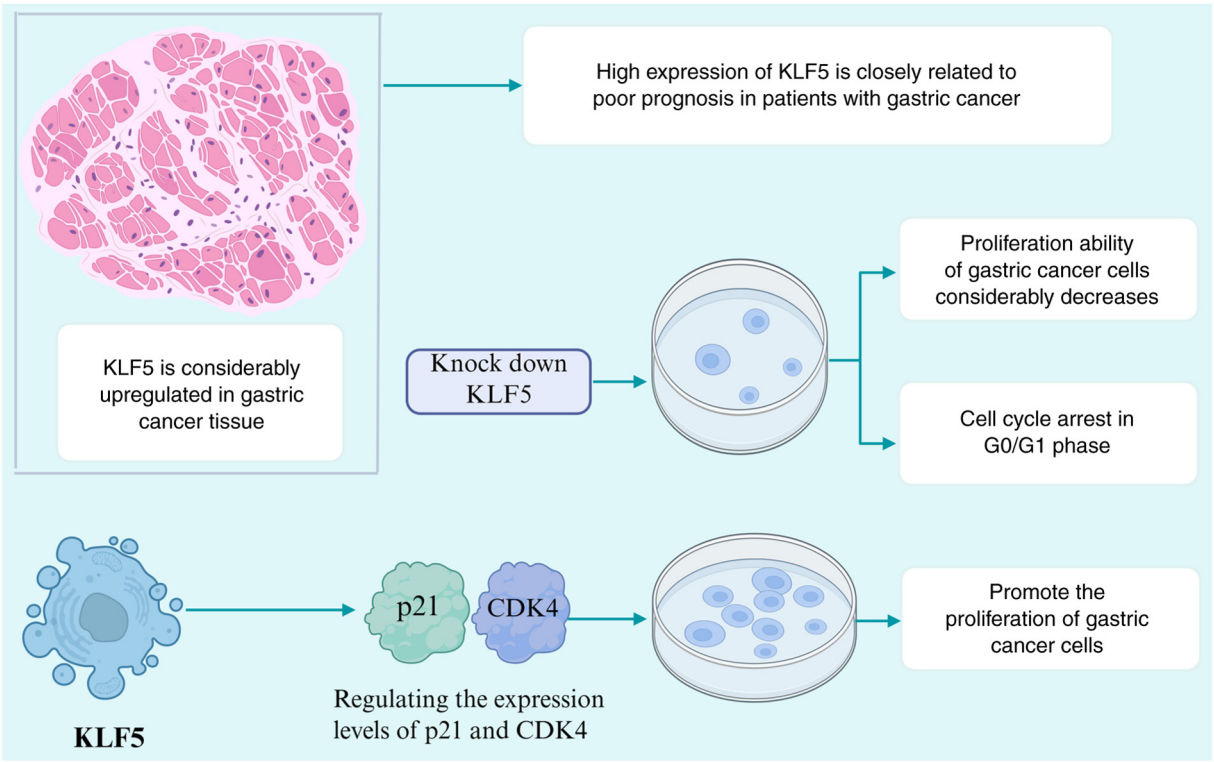


Figure 1. The expression characteristics of KLF5 in gastric cancer and its mechanism of regulating cell proliferation. KLF, Krüppel-like factor.

KLF5 is abnormally overexpressed in esophageal squamous cell carcinoma (ESCC), and the level of its expression is positively associated with the status of tumor differentiation and lymph node metastasis (114). Functional research has shown that KLF5 facilitates ESCC cell proliferation, migration and invasion, making it a primary contributor to tumor malignancy (115). KLF5 is an oncogenic signaling cascade that transcriptionally activates fibroblast growth factor-binding protein 1 and Snail family transcriptional repressor 2, and cooperatively controls extracellular matrix remodeling and the EMT process, in a mechanistic manner (115). The regulation of JNK signaling pathway by KLF5 has two effects: i) KLF5 activates the apoptotic pathway of BAX by stimulating the activation of the JNK pathway by apoptotic upstream regulators, apoptosis signal-regulating kinase 1 and mitogen-activated protein kinase 4; ii) KLF5-mediated excessive malignant proliferation is counter-regulated by JNK pathway activation; and, KLF5-mediated apoptosis is reversed by JNK inhibition and cell survival is restored (116). This mechanism shows that KLF5 actively regulates the JNK pathway to ensure TME homeostasis to balance oncogenic and pro-apoptotic activities (Fig. 3B).

Recently, it has been demonstrated that sustained suppression of KLF5 is capable of triggering an EMT phenotype without depending on the β-catenin and TGF-β signaling pathways (29,117,118). The ubiquitin proteasome system-targeted small-molecule inhibitor ML264 induces KLF5 degradation, leading to re-establishment of the epithelial cell transcriptional program and a massive increase in cell migration and invasion potential (118). The phenomenon does not only demonstrate a non-canonical regulatory process of KLF5 in ESCC-related EMT but it also gives a new understanding of cellular plasticity regulation in normal esophageal tissue repair. KLF5 translational research in EC is developing towards clinical practice. The mechanistic role of the KLF5/USP37/ programmed cell death ligand 1 (PD-L1) signaling axis in facilitating ESCC progression and immune evasion is the subject of a recently registered clinical study (119) at the First Affiliated Hospital of Baotou Medical College, Inner Mongolia University of Science and Technology (Baotou, Inner Mongolia Autonomous Region, China) (ChiCTR2500106315), which was registered in July 2025. This human tissue-based observational study is an important step in confirming the preclinical results of KLF5-mediated immune regulation and can be the basis of developing KLF5-targeted immunotherapies in the treatment of EC. According to Zhang *et al* (120), the downregulation of KLF12 enhances cisplatin resistance and metastasis in ESCC. KLF12, in a mechanistic manner, can bind to the promoter of the L1 cell adhesion molecule (L1CAM) to silence its expression, and L1CAM silencing can reverse the cisplatin-resistant and metastatic phenotype caused by KLF12 deficiency (121). Subsequent research showed that E3 ubiquitin ligase TRIM27 interacts with the N-terminal region of KLF12 and causes ubiquitination of KLF12 to block the transcriptional activity of KLF12. TRIM27 depletion increases the repression of L1CAM by KLF12, which reverses tumor cell drug resistance and metastatic potential (122). Taken together, these results indicate the fundamental regulatory importance of the KLF12/TRIM27/L1CAM signaling axis in cisplatin resistance and metastasis in ESCC. Also, a clinical study (123) indicated that KLF17 is lowly expressed in EC tissues and its inhibition increases the proliferative, migratory and invasive abilities of EC cells.

Despite the fact that the role of the KLF family in EC has not been widely studied, some of its members have been

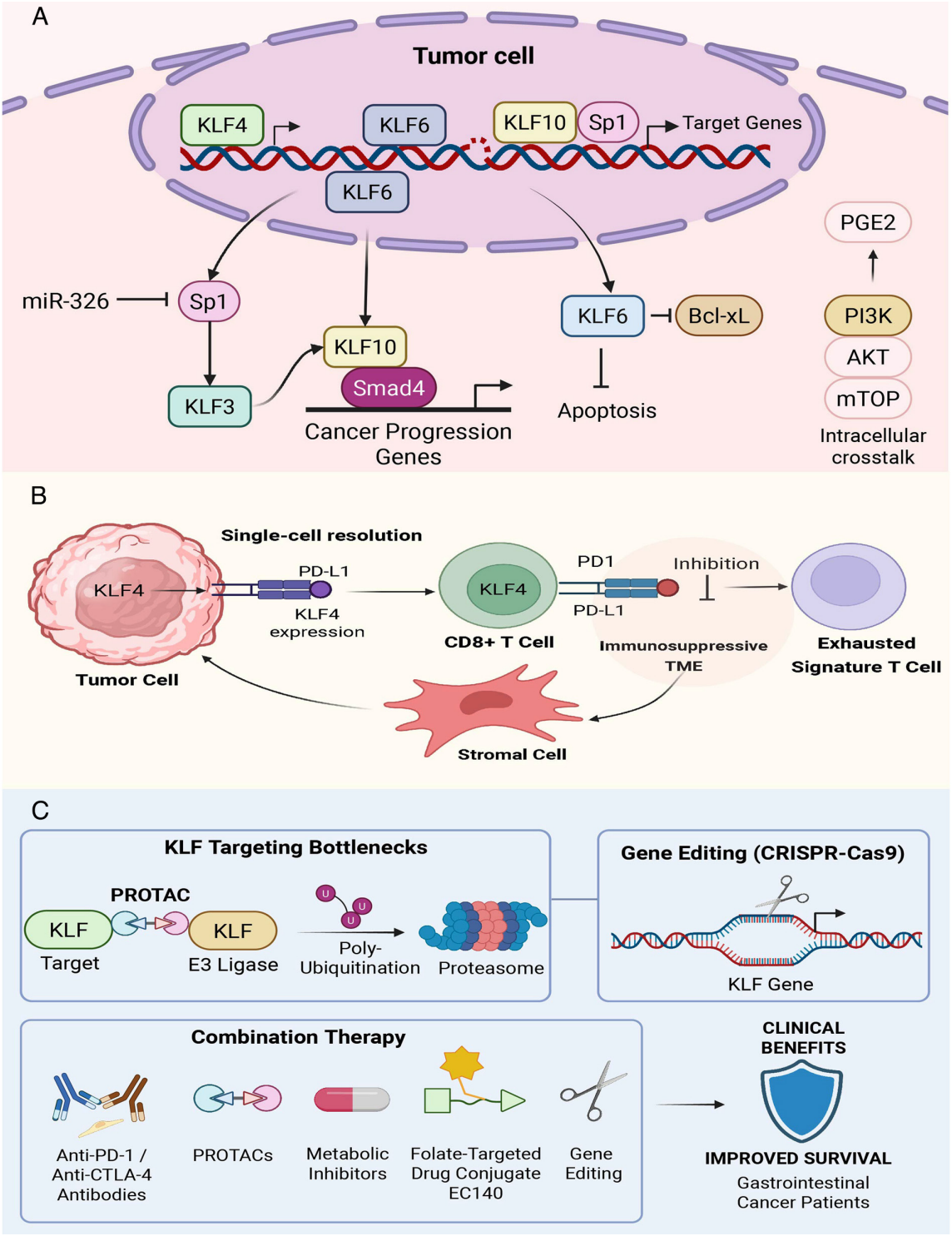


Figure 2. Mechanistic insights into KLF-mediated immune evasion and emerging therapeutic strategies in gastrointestinal cancer. (A) Intracellular signaling pathways regulated by KLFs. KLF members (for example, KLF4, KLF6 or KLF10) bind to target promoters, regulating downstream pathways (such as PI3K/AKT/mTOR) to promote cancer progression. (B) Intercellular communication in the tumor microenvironment. Interactions between tumor cells and exhausted $CD8^+$ T cells via the PD-1/PD-L1 axis lead to immune evasion. (C) Future targeted therapeutic strategies. Emerging technologies, including PROTAC-mediated protein degradation and CRISPR-Cas9 gene editing, combined with immunotherapies and metabolic interventions, aim to overcome undruggable bottlenecks and achieve clinical benefits. KLF, Krüppel-like factor; miR, microRNA; Sp1, specificity protein 1; mTOR, mechanistic target of rapamycin; PGE2, prostaglandin E2; PD-L1, programmed cell death ligand 1; PROTAC, proteolysis-targeting chimera; CTLA-4, cytotoxic T-lymphocyte-associated protein 4.

established to have tumor-suppressive roles in disease progression. The role of KLF4 in EC is controversial. The expression of KLF4 in ESCC is stage-specific and is associated with patient prognosis and tumor invasiveness (42). KLF4 acts as a tumor suppressor during the initial phases of the ESCC and downregulation of this gene triggers tumorigenesis by increasing unregulated cell proliferation and disrupting DNA repair (42,43). Conversely, during the late tumor progression,

Table IV. Functional roles of KLF family members in esophageal cancer progression.

| KLF members | Expression level | Functions | Regulatory pathways | Clinical significance | (Refs.) |
|---|---|---|---|---|---|
| KLF4 | Stage-dependent | Dual (oncogene/tumor suppressor) | Early downregulation promotes carcinogenesis; late aberrant activation accelerates metastasis; upregulation of p21 activating DNA repair pathway | Expression status may serve as a prognostic predictor | (42,43) |
| KLF5 | Increased | Oncogene | Transcriptional activation of FGF-BP1 and SNAIL2; regulation of JNK pathway (ASK1/MKK4); small molecule inhibitor ML264 induces non-canonical EMT | Positively associated with differentiation grade and lymph node metastasis | (114) |
| KLF9 | Decreased | Tumor suppressor | Interaction with TF4, inhibition of β-catenin/TF signaling and target gene Cyr61 | Inhibits growth, migration and invasion | (126,127) |
| KLF12 | Decreased | Tumor suppressor | Binding to L1CAM promoter inhibiting its expression; TRIM27 mediates KLF12 ubiquitination; KLF12/TRIM27/L1CAM axis regulates cisplatin resistance | Downregulation promotes cisplatin resistance and metastasis | (120-122) |
| KLF17 | Decreased | Tumor suppressor | NA | Downregulation enhances proliferation, migration and invasion | (123) |

KLF, Krüppel-Like Factor; FGF-BP1, fibroblast growth factor-binding protein 1; SNAIL2, snail family transcriptional repressor 2; ASK1, apoptosis signal-regulating kinase 1; MKK4, mitogen-activated protein kinase kinase 4; EMT, epithelial-mesenchymal transition; TCF4, transcription factor 4; Cyr61, cysteine-rich angiogenic inducer 61; L1CAM, L1 cell adhesion molecule; TRIM27, tripartite motif containing 27.

when the accumulation of mutations in the key oncogenes and tumor suppressor genes occurs, KLF4 can be re-expressed abnormally or its activity can be hijacked, thus facilitating tumor invasion and metastasis (38,124). This functional switching depends on the stage, which is similar to other TFs, including TGF-β, which is tumor-suppressive at early stages but pro-metastatic at late stages (38,125) (Fig. 3A).

KLF4 also has a strong interaction with the cellular microenvironment and its interacting partners. KLF4 stimulates p21-mediated cell cycle arrest and DNA repair in early-stage ESCC cells with an intact p53 signaling pathway, which supports its tumor-suppressive effect (43). Conversely, in late-stage cells where key signaling nodes are perturbed, for example, p53, KLF4 can be involved in transcriptional programs that facilitate cell survival, migration and invasion. Moreover, the activation of cofactors, post-translational modifications (for example phosphorylation and acetylation) and cross-talk with other signaling pathways (for example Wnt/β-catenin, Notch and NF-κB) can considerably modify the transcriptional output of KLF4 (42).

KLF4 regulatory mechanisms are dynamic and vary with the disease progression. Promoter hypermethylation or certain microRNAs (for example, miR-29a, miR-92a or miR-135b-5p) can repress KLF4 expression in the early-stage ESCC, leading to the loss of its tumor-suppressive activity (56,58,76). In advanced tumors, KLF4 re-expression can be stimulated by inflammatory signals or activation of oncogenic pathways in the TME through other mechanisms. KLF4 can also be modified by tumor-associated kinases or ubiquitin ligases which can change its transcriptional activity and its specificity to target genes. Such contextual plasticity is essential in designing effective targeted therapies: In early ESCC, KLF4 agonists can potentially re-establish tumor-suppressive activity, but in advanced tumors, the same strategy can potentially stimulate disease progression. Thus, the focus of future clinical trials must be on the stage-specific approaches and strict patient stratification.

In conclusion, the seemingly conflicting role of KLF4 in ESCC can be attributed to the fact that it was a tumor suppressor in early phases but a potential oncogenic driver in late phases, which depends on the tumor stage, cellular context and dynamic interactions with upstream regulatory networks. The knowledge of these context-dependent processes is key to explain discrepant results and inform KLF4-targeted therapy based on disease stage and molecular phenotypes.

KLF9 is also highly repressed in ESCC and acts as a tumor suppressor. It suppresses cell growth, migration and invasion of ESCC cells. KLF9, in its mechanistic interaction with TF4, inhibits the β-catenin/TF signaling pathway and silences target genes including Cyr61 (126,127). In general, ESCC is a violent GI neoplasm, and the metastatic nature is associated with poor prognosis. Even though the investigation of the KLF family in ESCC is comparatively new, the studies (128,129) have shown a dual regulatory effect of particular family members in the initiation and progression of tumors, which provides new insights into the mechanisms of its development and the possible treatment options. A comprehensive study of KLF expression patterns and functional regulatory networks may help shed light on the molecular mechanism of ESCC invasion and metastasis, which is important as a key theoretical basis to enhance patient survival, quality of life and overcome drug resistance. Further research efforts are needed on multi-target combination therapies and interventions targeting EMT pathways and metabolic reprogramming to increase tumor cell susceptibility to chemotherapy. In conclusion, a deeper understanding of the molecular processes of members of the KLF family will present a more exhaustive basis for accurate diagnosis and treatment of ESCC and will lead to the creation of individual therapeutic approaches.

*Progression of KLFs in PC*. As one of the most malignant tumors in the digestive tract (1), PC has increasingly become a research focus for the study of the regulatory mechanism of KLF family. In PC tissues and cell lines, KLF5, KLF7, KLF8 and KLF16 are relatively highly expressed whereas KLF9 and KLF10 are expressed at lower levels. The majority of these KLF members are tumor promoters in PC (Table V).

In patient tissues, KLF5 is highly expressed and expression levels are notably associated with prognosis. Mechanistic studies indicate that KLF5 transcriptionally activates E2F1, Cyclin D1 and Rad51 and represses p16 to drive the cell cycle from $G_1$ to S phase and promote tumor cell proliferation (130-132). A study in 2025 identified KLF5 as a transcriptional regulator of miR-1305 which inhibits the proliferation of PC cells and induces apoptosis through the KLF5-ERBB2 signaling axis, offering a promising diagnostic and therapeutic target (133). In pancreatic ductal adenocarcinoma (PDAC), KLF7 is overexpressed, and its dysregulation has an important role in promoting tumor cell proliferation and metastatic potential. Mechanistically, KLF7 is responsible for the activation of interferon-stimulated gene transcription programs as well as the maintenance of the structural integrity of the Golgi apparatus, which may carry out a role in therapeutic resistance associated with tumor growth and metastasis (134,135).

KLF8 is also overexpressed in PC tissues and cells. Functional studies have shown that KLF8 knockdown markedly blocks cell proliferation and tumor formation and induces G2/M phase cell cycle arrest. Mechanistically, KLF8 depletion causes a downregulation of CDK1/CDC2, Cyclin B1 and Cyclin D1 and an upregulation of the cell cycle inhibitors p21 and p27 (136). KLF8 is a major inducer of EMT and tumor invasiveness, and its expression levels are associated with overall survival (OS) and is an independent prognostic predictor (137,138). By contrast, KLF9 is lowly expressed in PC tissues. Clinicopathological analyses have found that low KLF9 expression is associated with poor tumor differentiation, deep vascular invasion and low OS (139). Mechanistically, KLF9 negatively regulates the Wnt/β-catenin pathway by suppressing the expression of mRNA and protein at the promoter of Frizzled-5, which suppresses PDAC tumor development (140). Overexpression of KLF9 downregulates MMP-2, MMP-9, Bcl-2 and markers of mesenchyme (N-catenin) while upregulating markers of epithelium (E-catenin), pro-apoptotic proteins (Bax, p53) and cell cycle regulators (CDK4, Cyclin D1), collectively inhibiting tumor invasion and metastasis and regulating proliferation (141).

Although the oncogenic functions of members of the KLF family in PC are well known, recent studies suggest that some members may have tumor-suppressive functions under certain microenvironments or molecular contexts (9,142).

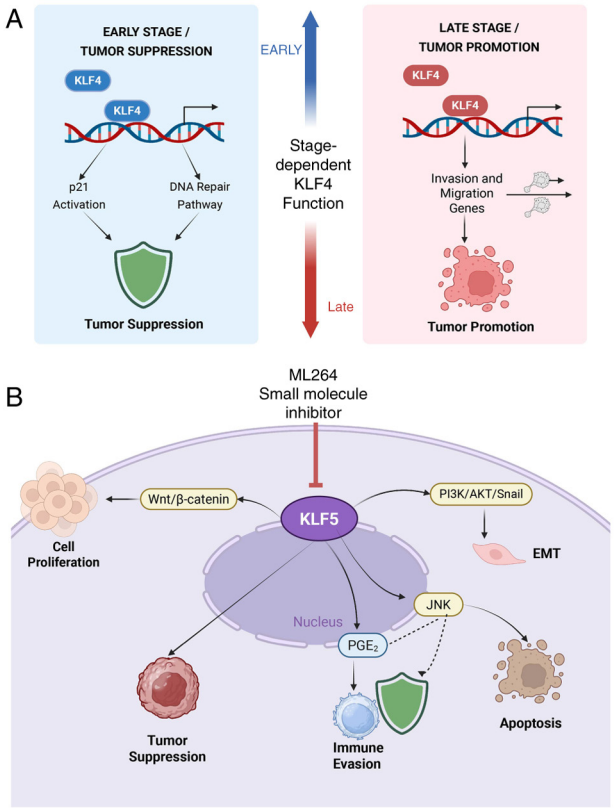


Figure 3. Schematic diagram of KLF5 functional conversion and targeted inhibition in esophageal cancer. (A) KLF5 exhibits stage dependent functional transition in esophageal cancer. (B) ML264 small molecule inhibitors target KLF5 and simultaneously inhibit multiple pro-cancer signaling pathways. KLF, Krüppel-like factor. EMT, epithelial-mesenchymal transition; KLF, Krüppel-like factor; PGE2, prostaglandin E2.

Clinical studies have demonstrated that KLF2 is overexpressed in PDAC samples and its overexpression prevents the growth, migration metastasis of PC cells (143,144). Mechanistically, KLF2 interacts with β-catenin and negatively regulates the β-catenin/TF signaling pathway (145). Further studies suggest that KLF2 knockdown affects cellular senescence and decreases p21 expression (146). KLF3 is a direct downstream target of miR-324-5p, which leads to a decrease in KLF3 expression. In PC tissues and cell lines, miR-324-5p is notably upregulated, and inhibition of this microRNA inhibits cell proliferation and induces apoptosis (147). Additionally, exosomal miR-21-5p from M2 macrophages negatively regulates KLF3 in PC stem cells and boosts tumor proliferation (148). KLF4 shows context-dependent function in pancreatic cancer. Knockdown of KLF4 triggers EMT, which greatly enhances the proliferative and metastatic potential of tumor cells. Mechanistic studies have shown that KLF4 downregulation causes an upregulation of Cav-1 and vimentin and a downregulation of E-cadherin (149,150). Conversely, KLF4 can inhibit tumor growth and metastasis by activating the p27 pathway (151), as well as by directly downregulating CD44, limiting metastatic spread (152). These findings support the development of KLF4-based targeted therapeutic strategies for advanced pancreatic cancer. KLF6 overexpression also suppresses proliferation, metastasis and EMT progression in PC cells, suppressing tumor progression through the upregulation of activating transcription factor 3 (153).

In summary, PC is an aggressive GI cancer, and the regulatory mechanism of KLF family members has attracted much research attention. KLFs have dual and context-dependent roles in pancreatic cancer, which are dependent on molecular, cellular and microenvironmental factors. An improved understanding of their mechanisms will lead to improved understanding of the pathogenesis of PC and the discovery of new targets for precision diagnostics and therapeutics, which may improve the prognosis of patients.

Future studies should be aimed at understanding the specific functions of individual KLF members in different microenvironments, their interactions and the influence of epigenetic modifications, such as methylation of the promoter, on their expression. Such studies will provide the basis for precision medicine approaches in pancreatic cancer.

## 4. Outlook

Immune checkpoint inhibitors are an innovative approach to cancer therapy, and the majority of patients with solid tumors ultimately develop resistance (154). One of the major challenges is the fact that the TME is extremely immunosuppressive and hard to reverse. Therefore, a profound insight into the molecular pathways of immune evasion by tumors, as well as the discovery of targets of actionable intervention, is essential to overcome the existing limitations of treatment. Over the last few years, KLF family members have emerged as notable controllers of the TME (128,142), which has provided new information on the possible approaches to overcoming immune resistance. There are however, several obstacles in the translation of laboratory discoveries into clinical advantages.

KLF5, as an example, facilitates immune evasion by causing the production of prostaglandin E2. KLF5 inhibitors have been shown to stimulate immunity in preclinical models, which boosts the antitumor immunity of $CD8^+$ T cells and enhances the effectiveness of anti-PD-1 treatments (155). The study, ChiCTR2500106315, which was registered in July 2025, studies ESCC and is aimed at clarifying the regulatory processes of the KLF5/USP37/PD-L1 signaling axis in human tissue samples and provides translational support to the approaches to KLF5 targeting and immune checkpoint blockade. Equally, KLF12 depletion reverses its transcriptional repression of Galectin-1 (Gal-1), which reinstates $CD8^+$ T cell infiltration and activity, indicating the KLF12/Gal-1 axis as a promising therapeutic target in overcoming immune resistance (156). However, there are multiple issues preventing translation of these findings into clinical practice: Targeting KLF5 can improve the effects of anti-PD-1 but might also impair intestinal homeostasis, resulting in systemic toxicity and the extrapolability of the KLF12/Gal-1 axis to different tumor types is unclear, and needs validation in precision animal models and early-phase clinical trials.

High PD-1 and cytotoxic T-lymphocyte-associated protein 4 expression on $CD8^+$ T cells in the TME is associated with adverse prognosis in HCC, but predictive biomarkers of immunotherapy response are scarce (157,158). It has been demonstrated that KLF4 indirectly promotes the infiltration of $CD8^+$ T cells by inhibiting the expression of PD-L1 and that it may be used in combination with PD-1 inhibitors to show synergistic antitumor effects, but the underlying molecular

Table V. Functional roles of KLF family members in pancreatic carcinoma progression.

| KLF members | Expression level | Functions | Regulatory pathways | Clinical significance | (Refs.) |
|---|---|---|---|---|---|
| KLF2 | Decreased | Tumor suppressor | Interaction with β-catenin, negative regulation of β-catenin/TF signaling; cooperation with FOXO4 upregulating p21 inducing senescence | Inhibits growth, migration and metastasis | (143-146) |
| KLF3 | Decreased | Tumor suppressor | Targeted by miR-324-5p; M2 macrophage-derived exosomal miR-21-5p negatively regulates KLF3 | Downregulation promotes proliferation | (147,148) |
| KLF4 | Decreased | Tumor suppressor | Activation of p27 pathway; direct downregulation of CD44 expression; KLF4 knockdown upregulates Cav-1 and vimentin, downregulates E-cadherin | Inhibition of cancer stem cell properties and metastasis | (149-152) |
| KLF5 | Increased | Oncogene | Transcriptional activation of E2F1, Cyclin D1, Rad51, inhibition of p16, driving G1/S transition; miR-1305/KLF5 negative feedback loop; KLF5-ERBB2 axis | High expression associated with poor prognosis; KLF5-ERBB2 axis is potential diagnostic and therapeutic target | (130-133) |
| KLF6 | Decreased | Tumor suppressor | Upregulation of ATF3 | Inhibits proliferation, metastasis and EMT | (153) |
| KLF7 | Increased | Oncogene | Activation of ISGs transcriptional program; Maintenance of Golgi apparatus integrity | Promotes growth and metastasis, mediates therapeutic resistance | (134,135) |
| KLF8 | Increased | Oncogene | Regulation of CDK1/CDC2, cyclin B1, cyclin D1, p21, p27; induction of EMT | Independent prognostic predictor | (136-138) |
| KLF9 | Decreased | Tumor suppressor | Negative regulation of Frizzled-5 inhibiting Wnt/β-catenin pathway; regulation of MMP-9, MMP-2, Bcl-2, Bax, p53, CDK4, cyclin D1 | Low expression associated with poor differentiation, vascular invasion and reduced OS | (139-141) |
| KLF10 | Decreased | Tumor suppressor | NA | Phase III clinical trial confirmed: High expression predicts clinical benefit from adjuvant chemoradiotherapy after curative resection | (14) |
| KLF16 | Increased | Oncogene | NA | Oncogenic function | |

KLF, Krüppel-like factor; Cav-1, caveolin-1; E2F1, E2F transcription factor 1; ERBB2, Erb-B2 receptor tyrosine kinase 2; ATF3, activating transcription factor 3; EMT, epithelial-mesenchymal transition; ISG, interferon-stimulated gene; OS, overall survival; NA, not available.

mechanisms remain to be verified by using multidimensional experimental models (159-161). It is worth noting that the high expression of KLF10 has been shown to be a predictive biomarker of the clinical efficacy of adjuvant chemoradiotherapy in pancreatic cancer, a novel way of personalized therapy (14) (Fig. 2B).

The aforementioned studies broaden the research scope of KLFs in tumor immune regulation in several aspects, such as molecular mechanisms, translational medicine and clinical uses to provide a theoretical foundation of immunotherapy combination strategies to GI tumors. Nevertheless, KLFs are difficult targets of conventional small-molecule inhibitors because they are nuclear, do not have classical ligand-binding domains and are in complex protein interaction networks. Technologies to overcome this undruggable barrier include protein degradation technologies, including proteolysis-targeting chimeras (PROTACs), which have the potential to overcome this barrier (162,163), but issues of tissue-specific toxicity, functional redundancy and antagonism between family members and the efficiency of nucleic acid drug delivery must be resolved (Fig. 2C).

The context-dependent nature of KLFs is of significance to precision medicine. Heterogeneous functions of the same KLF member in different patients or in different stages of the disease are also emphasized, which means that dynamic monitoring should be carried out, in addition to the evaluation of biomarkers. KLF modifications and functional outputs can be regulated by factors in the TME (inflammation, hypoxia and immune interactions). Further, the net effect is defined by functional redundancy and antagonism among KLF family members and it has to be analyzed comprehensively using systems biology.

The next generation of therapies must no longer be based on the approach of a one-size-fits-all approach but rather on particular molecular contexts that are determined by the type of tumor and genetic background and the microenvironment. Although KLF targeting has considerable potential, clinical translation has several bottlenecks: PROTACs can be used to degrade KLFs, but there are problems with tissue-specific delivery and toxicity; the majority of KLFs play key roles in normal tissues, and nucleic acid-based therapeutics continue to face stability, delivery efficiency and off-target effects. Strict patient stratification, as well as technological innovation, will be central to the development of KLF-targeted therapies in the clinic.

## 5. Conclusions

In the last decade, much progress has been made in the study of the KLF family in GI tumors (144,164). As transcriptional regulators with a zinc-finger structure, KLFs play an important role in the maintenance of GI system homeostasis and pathological remodeling by modulating fundamental biological processes such as cell proliferation, apoptosis, differentiation and EMT. Dysregulation of KLFs is associated with the development of esophageal, gastric, colorectal and pancreatic cancer, with tumor-suppressive and tumor-promoting properties. Detailed characterization of KLF expression and molecular regulatory mechanisms in different GI tumors not only clarifies their roles in tumor initiation, invasion, metastasis and treatment resistance but also lays the theoretical basis for the development of targeted KLF-based precision diagnostics and therapeutic strategies.

Despite these advances, KLF-targeted therapies are not without challenges. As nuclear-localized TFs, KLFs have traditionally been considered to be 'undruggable'. Their involvement in extensive networks of protein interactions, combined with structural similarities between family members, is a major obstacle for the development of specific inhibitors or activators. Furthermore, KLF functions are context-dependent and binary, functioning as oncogenes or tumor suppressors depending on the cellular and molecular environment. This complexity requires sophisticated therapeutic approaches to reduce potential adverse effects. Future research should focus on innovative approaches, such as PROTACs, as opposed to only targeting their DNA-binding domains.

Current research also has a number of limitations. KLF function is highly dependent on the tumor type, stage and genetic background (for example, APC, KRAS or p53 mutations), and the TME. The same KLF member may have opposing effects and, given the large heterogeneity of GI cancer types, it is still difficult to generalize findings or to develop universal treatment strategies. The majority of mechanistic studies are based on *in vitro* and *in vivo* models, which are not able to fully reflect the complexity of human disease. Moreover, several KLF-related biomarkers and therapeutic targets are still limited to retrospective studies and correlative analyses with few moving forward to prospective clinical validation.

Looking to the future, three notable transitions are required in this area: From static expression analysis to dynamic network regulation, from single molecule function studies to cooperative and antagonistic interactions between several family members and from fundamental mechanistic studies to clinical translational validation. Advanced technologies, such as single-cell sequencing, should be used to dissect the specific roles of KLF members in tumor cells, immune cells and stromal cells at single-cell resolution, with findings validated in large, well-annotated clinical cohorts. Furthermore, innovative approaches such as PROTACs and gene editing should be actively explored to overcome the challenges of targeting TFs to enable KLF-targeted strategies in combination with immunotherapy and metabolic interventions. Such efforts will help bring laboratory discoveries to actual clinical benefits, promising new therapeutic hope for patients with different types of GI cancer.

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**Availability of data and materials**

Not applicable.

**Author contributions**

JZ contributed to writing the original draft. RZ contributed to writing, review and editing and project administration. PY contributed to writing the original draft and additional writing, review and editing. YZ contributed to writing, review and editing, project administration and funding acquisition. BZ contributed to project administration, supervision, writing, review and editing, literature search, methodology and funding acquisition. Data authentication is not applicable. All authors read and approved the final manuscript

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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