Received: 15 February 2021 | Revised: 27 March 2021 | Accepted: 30 March 2021

DOI: 10.1111/cas.14910

REVIEW ARTICLE

Cancer Science WILEY

The roles and regulation of the KLF5 transcription factor in cancers

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Funding information
National Key Research and Development Program of China, Grant/Award Number: 2020YFA0112300 and 2018YFC2000400; National Natural Science Foundation of China, Grant/Award Number: 81830087

Abstract

Krüppel-like factor 5 (KLF5) is a member of the KLF family. Recent studies have suggested that KLF5 regulates the expression of a large number of new target genes and participates in diverse cellular functions, such as stemness, proliferation, apoptosis, autophagy, and migration. In response to multiple signaling pathways, various transcriptional modulation and posttranslational modifications affect the expression level and activity of KLF5. Several transgenic mouse models have revealed the physiological and pathological functions of KLF5 in different cancers. Studies of KLF5 will provide prognostic biomarkers, therapeutic targets, and potential drugs for cancers.

Abbreviations: 5FU, 5-Fluorouracil; ABCG2, ATP-binding cassette subfamily G member 2; AGGF1, Angiogenic factor with G-patch and FHA domains 1; AKT, AKT serine/threonine kinase; ALDH, Acetaldehyde dehydrogenase; ALDH3A1, Aldehyde dehydrogenase 3 family member A1; AR, Androgen receptor; ASK1, Apoptotic signal-regulating kinase 1; ATXN3L, Ataxin-3 like; BAP1, BRCA1 associated protein 1; BAX, BCL2 associated X; BECN1, Beclin1; BET, Bromodomain and extra-terminal; BRD4, Bromodomain-containing 4; BRG1, Brahma-related gene 1; CASC15, Cancer susceptibility candidate 15; CBP, CREB-binding protein; CCL5, C-C motif chemokine ligand 5; CCR5, C-C motif chemokine receptor 5; ccRCC, Clear cell renal cell carcinoma; Cdc42, Cell division cycle 42; CDK7, Cyclin dependent kinase 7; CDT1, Chromatin licensing and DNA replication Factor 1; Chk1/2, Checkpoint kinase 1/2; CINP, Cdk2-interacting protein; COX2, Cyclooxygenase 2; CPD, Cdc4 phosphodegron; CRC, Colorectal cancer; CSCs, Cancer stem cells; CUL4B, Cullin 4B; CXCR4, Cell-surface chemokine receptor 4; DDR, DNA damage repair; DEX, Dexamethasone; DII1, Delta like canonical Notch ligand 1; DNMT1, DNA methyltransferase 1; DSS, Dextran sodium sulfate; DUBs, Deubiquitinases; E2F1/3, E2F transcription factor 1/3; EFP, Estrogen-responsive finger protein; EGFR, Epidermal growth factor receptor; EGR1, Early growth response 1; EMT, Epithelial-mesenchymal transition; ERCC5, ERCC excision repair 5; ERα/β, Estrogen receptor α/β; ESCC, Esophageal squamous cell carcinoma; ESC, Embryonic stem cell; FAK, Focal adhesion kinase; FASN, Fatty acid synthase; FGF-BP1, Fibroblast growth factor binding protein 1; FoxA1, Forkhead box protein A1; FOXE1, Forkhead box E1; FOXO1, Forkhead box O1; FYN, FYN proto-oncogene kinase; *GADD45A*, Growth arrest and DNA damage-inducible 45 alpha; GATA4/6, GATA binding protein 4/6; GCN5, general control non-derepressible 5; GDF15, Growth differentiation factor 15; GlcNAc, *O*-linked *N*-acetylglucosamine; GLI1/2, GLI family zinc finger 1 /2; GLUT-1, Glucose transporter 1; GR, Glucocorticoid receptor; GSK3β, Glycogen synthase kinase 3β; GSTM1, Glutathione-*S*-transferase M1; H2AX, H2A.X variant histone; H3K27ac, Histone H3 lysine 27 acetylation; HCC, Hepatocellular carcinoma cells; HCF1, Host cell factor C1; HDAC1/2/3, Histone deacetylase 1/2/3; Hes1, Hes family bHLH transcription factor 1; HIF-1α, Hypoxia-inducible factor 1α; HNF4α, Hepatocyte nuclear factor 4α; IGF1, Insulin like growth factor 1; IL1β, Interleukin 1β; ITGB2, Integrin subunit beta2; KLF2, Krüppel-like factor 2; KLF4, Krüppel-like factor 4; KLF5, Krüppel-like factor 5; KLF8, Krüppel-like factor 8; KLFs, Krüppel-like factors; LIF, Leukemia inhibitory factor; lncRNAs, Long non-coding RNAs; LPA, Lysophosphatidic acid; MED1, Mediator complex subunit 1; mESCs, Mouse embryonic stem cells; miRNAs, MicroRNAs; MKK4/7, Mitogen-activated protein kinase 4/7; MKP-1, Mitogen-activated protein kinase phosphatase 1; mPGES1, microsomal prostaglandin E-2 synthase 1; MYC, MYC proto-oncogene; NAMPT, Nicotinamide phosphoribosyl transferase; ncRNAs, Non-coding RNAs; NDRG2, N-myc downregulated gene 2; NEAT1, Nuclear paraspeckle assembly transcript 1; NES, Nuclear export signal; NOTCH1, Notch receptor 1; NSCLC, Non–small-cell lung cancer; OGT1, *O*-linked *N*-acetylglucosamine transferase; P300, Adenovirus E1A-associated 300 kDa protein; PARP1, Poly ADP-ribose polymerase 1; PDGF, Platelet-derived growth factor; PDGFA, Platelet-derived growth factor A; PKD1, Protein kinase D1; PMA, Phorbol 12-myristate 13-acetate; PR, Progestogen receptor; PSA, Prostate-specific antigen; PTCH1, Patched 1; PTEN, Phosphate and tension homology deleted on chromosome ten; Rac1, Rac family small GTPase 1; RAD51, RAD51 recombinase; RARα, Retinoic acid receptor α; RAS, Rat sarcoma; RTK, Receptor tyrosine kinase; SCF^{FBW7}, $SCF^{F\text{-box and WD repeat domain-containing }7}$; SE, Super enhancer; SHH, Sonic hedgehog; SMAD 2/3/4, SMAD family member 2/3/4; SMURF2, SMAD ubiquitination regulatory factor 2; SNHG12, Small nucleolar RNA host gene 1; SOX2/4, SRY-Box transcription factor 2/4; SREBP-1, Sterol-regulatory-element-binding protein-1; STAT3, Signal transducer and activator of transcription 3; TAD, Transactivation domain; TAZ, Transcriptional co-activator with PDZ-binding motif; TCF3, Transcription factor 3; TEAD4, TEA domain transcription factor 4; TGF-β, Transforming growth factor-β; TNBC, Triple-negative breast cancer; TNFAIP2, Tumor necrosis factor-α (TNFα)-induced protein 2; TNFRSF11a, Tumor necrosis factor receptor superfamily member 11a; TNFα/TNFR1, Tumor necrosis factor α/ tumor necrosis factor receptor 1; TP63, Tumor protein P63; USP3, Ubiquitin-specific protease 3; VEGF, Vascular endothelial growth factor; WWP1, WW domain-containing E3 ubiquitin protein ligase 1; YAP, Yes1 associated transcriptional regulator; ZEB1/2, Zinc finger E-box binding homeobox 1/2; ZF, Zinc finger.

and 31771516; Innovative Research Team of Yunnan Province, Grant/Award Number: 2019HC005

KEYWORDS
posttranslational modification, signaling pathway, targeted therapy, transcription

1 | INTRODUCTION

Krüppel-like factors (KLFs) belong to a significant transcription factor family that is involved in multiple biological processes and diverse diseases, especially cancers.[1] Seventeen KLFs contain 3 highly conserved and tandem ZF domains at their C-terminus, which bind to DNA CACC or GC boxes and regulate the transcription of downstream target genes.[2,3] To date, several KLFs, such as Krüppel-like factor 2 (KLF2), Krüppel-like factor 4 (KLF4), Krüppel-like factor 8 (KLF8) and KLF5, have been indicated to participate in cancer development and have drawn increasing attention.[1]

KLF5 plays vital roles in disease development, especially in cancers and cardiovascular diseases. KLF5 regulates the expression of a wide range of target genes, such as *Cyclin D1*,[4] *p27*,[5] *Nanog*,[6] and Slug.[7] Over the past decade, KLF5 has been reported to participate in various biological functions, such as cell stemness, proliferation, apoptosis, autophagy, and migration. Several outstanding articles have reviewed the roles of KLF5 in cancers in recent years.[8-11]

It is well known that animal models are the best approach to study the roles of KLF5 in physiology and pathology. The study of KLF5 animal models, especially tissue specific, may provide directions for future disease treatments. KLF5 is mainly involved in embryonic development,[12] adipose tissue development,[13] prostate and mammary gland development,[7,14,15] intestinal crypt morphological maintenance,[16-18] lung morphological development,[19] and energy metabolism[13] etc. The reported mouse models are KLF5-KO, KLF5-KI, and KLF5 lineage tracking models, we have summarized these in Table 1.

In the past decade, there has been significant progress in KLF5 studies in cancers. In this review, we summarize the molecular structure, biological functions, transcriptional modulations, posttranslational modifications, signaling pathways, physiological and pathological functions of KLF5, and potential targeting strategies.

2 | MOLECULAR STRUCTURE

The *KLF5* gene is located at 13q21, and the KLF5 protein consists of 457 amino acid residues.[8] The protein structure of human KLF5 is shown in Figure 1. KLF5 has 3 highly conserved classical C2H2 ZF motifs at the C-terminus: a proline-rich transactivation domain (TAD) and a NES.[20-22] The KLF5 TAD contains a PPSY motif and a Cdc4 phosphodegron (CPD) motif (^{303}SPPSS), which recruit the E3 ubiquitin ligases WW domain-containing E3 ubiquitin protein ligase 1 (WWP1) and SCF^{FBW7}.[22,23] Recently, 2 hotspot mutations of KLF5 were identified, 1 in the CPD motif and the other in the DNA binding domain.[24] Mutations at the CPD motif of KLF5 in colorectal cancer (CRC) escape SCF^{FBW7}-mediated ubiquitination and degradation.[24] Mutations at D418 and E419 within the second zinc finger change the DNA binding properties of KLF5.[24] Interestingly, these mutations are cancer specific.[24]

3 | TRANSCRIPTIONAL TARGET GENES

As a basic transcription factor, KLF5 predominately promotes the transcription of target genes involved in various cellular functions, such as *Cyclin D1*, *platelet-derived growth factor A* (*PDGFA*), and *fibroblast growth factor binding protein 1* (*FGF-BP1*)[4,12,25] (Table 2). Accumulating evidence from our laboratory has suggested that KLF5 promotes breast cancer by regulating several key target genes, including *FGF-BP1*,[25] *microsomal prostaglandin E-2 synthase 1* (*mPGES1*),[26] *tumor necrosis factor-α* (*TNFα*)*-induced protein 2* (*TNFAIP2*),[27] *Slug*,[7] and *Cyclin D1*.[4] In addition to *mPGES1*, KLF5 was reported to induce *cyclooxygenase 2 (COX2)* expression and promote cell proliferation and migration in phosphate and tension homology deleted on chromosome ten (PTEN)-null mouse embryonic fibroblasts.[28] Consistently, KLF5 also promotes the transcription of *Cyclin E1* by binding to its polymorphic enhancer in bladder cancer.[29] KLF5 was reported to promote bladder cancer cell migration by promoting the transcription of *the FYN proto-oncogene kinase* (*FYN*) gene, which thereby activates FAK.[30] Additionally, KLF5 was shown to promote glioblastoma angiogenesis by inducing angiogenic factor with *G-patch and FHA domains 1 (AGGF1)* gene transcription in glioma-associated endothelial cells.[31] In prostate cancer, KLF5 binds to the *AR* gene promoter to increase its transcription; furthermore, KLF5 interacts with AR to increase *MYC proto-oncogene* (*MYC*), *Cyclin D1*, and *PSA* transcription.[32] KLF5 is essential for hematopoietic stem and progenitor cell bone marrow adhesion because KLF5 activates *Rab family protein Rab5* transcription.[33] KLF5 interacts with mutant p53 to promote *PLA2G16* gene transcription and pancreatic cancer cell glycolysis.[34] KLF5 increases oxidative stress by decreasing glutathione by increasing the transcription of *glutathione-S-transferase M1* (*GSTM1*) in B-cell acute lymphoblastic leukemia cells.[35] Interestingly, the KLF5 E419Q mutant gains new binding sites and activates the transcription of several target genes, including *fork head box E1* (*FOXE1*) and *nicotinamide phosphoribosyl transferase* (*NAMPT*).[24] KLF5 can upregulate the transcription of *mitogen-activated protein kinase 7* (*MKK7*), the upstream kinase of c-JNK, by binding to the proximal promoter region of the *MKK7* gene and promote the apoptosis induced by tumor necrosis factor α/tumor necrosis factor receptor 1 (TNFα/TNFR1).[36] In ESCC, KLF5, tumor protein P63 (TP63), and SRY-Box transcription factor 2 (SOX2) form a transcription complex that promotes *aldehyde dehydrogenase 3 family member A1* (*ALDH3A1*) gene transcription by binding to its SE.[37] KLF5 inhibits *Beclin1* (*BECN1*) gene transcription and

TABLE 1 KLF5-related animal models

Animal models	Organization types	Phenotypes	References
Klf5 knockout mice	Embryo	Mouse with homozygous knockout of *Klf5* died before embryonic day 8.5.	12
	Blood vessel	The medial and adventitial layers of the aortic wall of *Klf5+*$^{/-}$ mice are abnormally thinned and dilated; in response to vascular injury, the activation, proliferation, inflammation, and angiogenesis of fibroblasts and smooth muscle cells are impaired.	12
	Heart	*Klf5+*$^{/-}$ mice have reduced heart weight, reduced fibrosis, and thinner heart ventricular walls.	12
	Gastrointestinal tract	*Klf5+*$^{/-}$ mice have malformed gastrointestinal villi, and decrease the number of extracellular matrix and mesenchymal cells.	12
	Mammary gland	*Klf5* mammary gland-specific knockout mice can be observed to inhibit ductal elongation at 9 wk of age; the lobular alveolar structure is significantly reduced during pregnancy and lactation; the production of whey acidic protein (WAP) in mice during pregnancy and lactation is decrease, and there is a defect in milk secretion. Klf5 knockout decreased the proliferation, survival and stemness of mammary epithelial cells.	7
	Adipose tissue	The development of white adipose tissue in *Klf5+*$^{/-}$ mice is delayed, and lipid droplets in adipocytes are reduced. *Klf5+*$^{/-}$ mice can avoid obesity, hypercholesterolemia and impaired glucose tolerance caused by high fat.	13
	Skeleton	*Klf5* deficiency impairs cartilage degradation and calcification in the perinatal period.	194
	Lung	The fetal lung airway epithelial cells in transgenic mice with specific knockout of *Klf5* have inhibited lung maturation during the cystic development stage. Phenotypic abnormalities appear in different components of bronchiolar smooth muscle, pulmonary blood vessels, and respiratory epithelium. Mice with knocked out both alleles of *Klf5* died of respiratory distress immediately after birth. Klf5 is essential for lung function and morphogenesis.	19
	Intestine	Intestinal-specific deletion of *Klf5* using Villin-Cre showed that *Klf5* is required to maintain gut epithelial cell proliferation, differentiation, and positioning along the crypt radial axis; *Klf5* deletion in the intestinal epithelium using Shh-Cre inhibited villus morphogenesis and epithelial differentiation; depletion of *Klf5* disrupts the integrity of intestinal stem cells.	16-18
	Hematopoietic system	Knockout mice of *Klf5* have enlarged spleens and increased peripheral white blood cells; the proportion of eosinophils is significantly increased, while the proportion of neutrophils is downregulated, long-term hematopoietic progenitor cells are reduced, and the ability to reproduce is reduced.	195
	Eye	Klf5 was specifically deleted in the ectoderm-derived structure of the ocular surface of mice, resulting in eyelid defects with malformed meibomian glands, corneal abnormalities, and loss of conjunctival goblet cells; Klf5 contributed to corneal epithelial homeostasis via regulating the expression of desmosomal components.	196,197
	Prostate	Prostate-specific *Klf5* heterozygous deletion mice induced hyperplasia with thicker cell layers in the lateral prostate, anterior prostate, and dorsal prostate; Klf5 homozygous deletion caused prostate epithelial cell apoptosis instead of hyperplasia.	14
Klf5 transgenic (Tg) mice	Prostate	Knockin of the *Klf5*^{K358R} gene in mouse model, the prostate has changed, showing a lighter, smaller and denser tissue morphology; prostate cells were reduced, the acinar area was smaller, and increased differentiation of basal cells into luminal cells.	15
	Skin	*Klf5* transgenic mice showed craniofacial defects, extracerebral malformations, persistent abdominal herniation, and ectodermal dysplasia; overexpression of *Klf5* in adult mice resulted in hair follicle occlusion, hyperkeratosis and epidermal erosion.	198
	Esophagus	Esophageal epithelial cells specifically overexpress Klf5 in ED-L2/*Klf5* mouse suprabasal cells without proliferation, but have increased proliferation of basal cells.	199

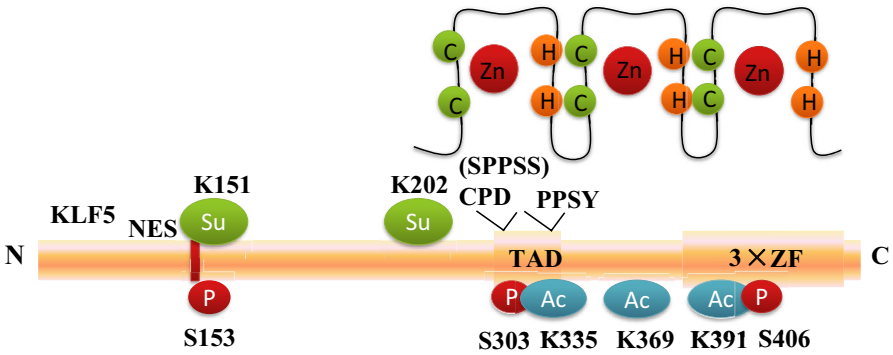

FIGURE 1 The human KLF5 protein structure. The *KLF5* gene is located at 13q21, and the KLF5 protein consists of 457 amino acid residues. KLF5 has 3 highly conserved classical C2H2 ZF motifs at the C-terminus: a proline-rich transactivation domain (TAD) and a NES. The KLF5 TAD contains a PPSY motif and a CPD motif (SPPSS), which recruit the E3s WWP1 and SCF^{FBW7}. KLF5 is regulated by multiple post-transcriptional modifications, including ubiquitination (Ub), phosphorylation (P at S153, S303, S406), acetylation (Ac at K335, K369, K391), and SUMOylation (Su at K151 and K202)

autophagy in prostate cancer cells.[38] KLF5 activates *tumor necrosis factor receptor superfamily member 11a* (*TNFRSF11a*) gene transcription by binding to the *TNFRSF11a* gene promoter in cervical cancer.[39] In non–small-cell lung cancer (NSCLC), KLF5 promotes the expression of *growth differentiation factor 15 (GDF15)* and cell proliferation induced by C5a.[40] Moreover, KLF5 activates the transcription of *E2F transcription factor 1* (*E2F1*) and *RAD51 recombinase* (*Rad51*) in pancreatic cancer and promotes cell proliferation.[41]

In addition to protein-encoding genes, KLF5 also regulates the transcription of several long non-coding RNAs (lncRNAs). LncRNAs are RNA with a length greater than 200 nt. KLF5 and transcription factor 3 (TCF3) activate the transcription of LINC00094 by binding to its SE, thereby promoting the growth of ESCC cells.[42] KLF5 recruits adenovirus E1A-associated 300 kDa protein (p300) to induce lncRNA RP1 transcription, and RP1 can, in turn, inhibit $p27^{kip1}$ protein translation to drive breast cancer tumorigenesis.[43] Additionally, KLF5 induces cancer susceptibility candidate 15 (CASC15) to promote breast cancer cell proliferation and migration.[44] KLF5 and MYC induce LINC00346 to promote gastric cancer.[45] The LINC00346 is amplified and overexpressed in gastric cancer. High expression of LINC00346 is correlated with poor pathological stage, large tumor volume, and poor prognosis.[45] LINC00346 functions as a molecular sponge for miR-34a-5p and antagonizes its ability to inhibit gastric cancer.[45] Additionally, KLF5 induces nuclear paraspeckle assembly transcript 1 (NEAT1), which recruits Brahma-related gene 1 (BRG1) to silence growth arrest and DNA damage-inducible 45 alpha (GADD45A) gene transcription in gastric cancer.[46] KLF5 promotes CRC cell invasion and metastasis by upregulating lncRNA small nucleolar RNA host gene 1 (SNHG12).[47]

MicroRNAs (miRNAs) are a group of short (generally 21 to 24 nucleotides in length), non-coding RNA (ncRNAs) molecules that fine tune gene expression levels. miRNAs play a role in RNA interference, destroying mRNA, suppressing gene expression and controlling translation of target mRNAs, thereby regulating cancer initiation and development. In clear cell renal cell carcinoma (ccRCC), KLF5 positively regulates the transcription of miR-27a, thereby targeting the E3 ubiquitin ligase FBW7 to promote cell migration and invasion.[48] In the context of p53 loss, KLF5 promotes miR-192 transcription, which inhibits the expression of zinc finger E-Box binding homeobox 2 (ZEB2) and EMT in liver cancer cells.[49] Additionally, KLF5 induces the transcription of miR-200 and inhibits the EMT process of epithelial cells.[50] Furthermore, KLF5 promotes miR-124, miR-145 and miR-183 transcription, therefore inhibiting pituitary adenoma cell migration and invasion.[51]

In addition to upregulating target gene transcription, KLF5 can also inhibit the transcription of a few target genes, such as *p21*,[52] *p27*[5], and *p16*.[41] Additionally, KLF5 and histone deacetylase 1 (HDAC1) cooperate to inhibit the transcription of *insulin like growth factor 1 (IGF1)* in prostate cancer cells.[53] Recently, KLF5 was shown to suppress the transcription of *forkhead box protein A1* (*FoxA1*), thereby promoting the morphogenesis of intestinal villi.[17] KLF5 also inhibits the transcription of *ATP-binding cassette subfamily G member 2 (ABCG2)* and sensitizes lung cancer cells to doxorubicin.[54]

4 | INTERACTING PROTEINS

Various KLF5-interacting proteins were identified by immunoprecipitation and mass spectrometry. As shown in Table 3. KLF5 can form a transcription complex with transcription-related factors or histone modifiers and regulate the transcription of target genes.

We reported that KLF5 interacts with the transcription factors host cell factor C1 (HCF1)[55] and TEA domain transcription factor 4 (TEAD4)[5] to regulate *FGF-BP1* and *p27* gene transcription in TNBC. Additionally, there is a physical interaction between KLF5 and AR to maintain the transcriptional activity of AR.[32] Moreover, KLF5 cooperates with the transcription factors GATA binding protein 4/6 (GATA4/6) to regulate the transcription of downstream oncogenes (ie, *hepatocyte nuclear factor 4α*, *HNF4α*) in gastric cancer.[56] Jiang et al found that KLF5 interacts with TP63 and SOX2 to regulate target gene transcription in ESCC.[37] KLF5 binds to ERα in breast cancer and inhibits the transcriptional activity of estrogen receptor

TABLE 2 New identified KLF5 target genes in cancers

Types	Target genes	Functions	Cancers	References
Protein-encoding genes	TNFAIP2	Promote cell migration and invasion	Breast cancer	27
	mPGES1	Promote the production of PGE2 and cell proliferation	Breast cancer	26
	Slug	Promote stemness	Breast cancer	7
	GDF15	Promote cell proliferation	Non–small-cell lung cancer	40
	GSTM1	Increase oxidative stress by reducing glutathione	B-cell acute lymphoblastic leukemia	35
	TNFRSF11a	Promote cell proliferation, migration, and invasion	Cervical cancer	39
	FYN	Promote cell migration	Bladder cancer	30
	Cyclin E1	Promote cell cycle	Bladder cancer	29
	AGGF1	Promote angiogenesis	Glioblastoma	31
	HNF4α	Promote cell proliferation	Gastric cancer	56
	MYC	Promote cell proliferation	Prostate cancer	32
	BECN1	Promote autophagy	Prostate cancer	38
	MKK7	Promote apoptosis induced by TNFα/TNFR1	Prostate cancer	36
	ALDH3A1	Promote cell proliferation and tumor growth	Esophageal squamous cell carcinoma	37
	PLA2G16	Promote glycolysis	Pancreatic cancer	34
	E2F1, Rad51	Promote cell proliferation	Pancreatic cancer	41
	ABCG2	Reduce the chemotherapy resistance to anthracyclines	Lung cancer	54
	IGF1	Inhibit the STAT3 signaling pathway and tumor metastasis	Prostate cancer	53
LncRNA	LINC00094	Promote cell proliferation	Esophageal squamous cell carcinoma	42
	NEAT1	Promote cell proliferation, and inhibit apoptosis	Gastric cancer	46
	LINC00346	Promotes cell growth, migration and invasion	Gastric cancer	45
	CASC15	Promotes cell proliferation, invasion, and tumor growth	Breast cancer	44
	RP1	Promote tumorigenesis	Breast cancer	43
	SNHG12	Promote invasion and metastasis	Colorectal cancer	47
miRNA	miR-27a	Promote cell migration and invasion in response to cholesterol	Clear cell renal cell carcinoma	48
	miR-200	Inhibit EMT	Epithelial cells	50
	miR-145, miR-124, miR-183	Inhibit cell migration and invasion	Pituitary adenoma	51
	miR-192	Inhibit EMT in the context of p53 loss or mutation	Liver cancer	49

α (ERα).[57] In prostate cancer, estrogen receptor β (ERβ) cooperates with KLF5 to promote *forkhead box O1 (FOXO1)* transcription and suppress tumor growth.[58] Nuclear early growth response 1 (EGR1) interacts with KLF5 to inhibit the transcription of miR-124, miR-145, and miR-183 and promote the migration and invasion of pituitary adenomas.[51] In response to transforming growth factor-β (TGF-β), KLF5 forms a transcription complex with SMAD family member 2/3/4 (SMAD2/3/4) to activate the transcription of p15 and inhibit the transcription of *c-Myc*.[59,60] Under hypoxia, KLF5 interacts with hypoxia-inducible factor 1α (HIF-1α) to promote the transcription of *Cyclin B1* and *Survivin* in lung cancer.[61]

KLF5 also binds to enzymes that mediate posttranslational modifications. It has been reported that several E3 ligases, including WWP1,[62] estrogen-responsive finger protein (EFP),[63] FBW7,[22] and SMAD ubiquitination regulatory factor 2 (SMURF2),[64] interact with KLF5 and promote KLF5 ubiquitination and degradation. Because ubiquitination is reversible, 3 deubiquitinases (DUBs), BRCA1 associated protein-1 (BAP1),[55] Ataxin-3 like (ATXN3L),[65] and Ubiquitin-specific protease 3 (USP3),[66] were identified to mediate the deubiquitination of KLF5. BAP1 has been reported to form a complex with HCF1 and *O*-Linked *N*-acetylglucosamine transferase (OGT1).[55] OGT1 is an *O*-linked *N*-acetylglucosamine (GlcNAc) transferase, however whether KLF5 is modified with GlcNAc is unknown.[55] Glycogen synthase kinase 3β (GSK3β) interacts with KLF5 to phosphorylate KLF5 at S303, which promotes FBW7-mediated KLF5 ubiquitination and degradation.[22] KLF5 and histone

TABLE 3 New identified KLF5 interacting proteins

Classification	KLF5 interacting proteins
Transcription factors	EGR1,[51] GATA4/6,[56] Miz-1,[60] MYC,[134] TEAD4,[5] SMAD4,[60] ERα/β,[57,200] TP63,[37] SOX2,[37] AR,[32] HIF-1α,[61] HCF1[55]
Enzymes	HDAC3,[38] SMURF2,[64] FBW7,[22] BAP1,[55] USP3,[66] ATXN3L,[65] GCN5,[40] GSK3β,[22] EFP,[63] OGT1[55]
Others	CNIP,[67] TAZ,[68] YAP[68]

acetyltransferase general control non-derepressible 5 (GCN5) form a transcription complex to activate *GDF15* gene transcription in NSCLC cells.[40] Additionally, KLF5 was shown to interact with histone deacetylase 3 (HDAC3) to inhibit the transcription of *BECN1*.[38]

Cdk2-interacting protein (CINP) was identified as a new KLF5 interacting protein in bladder cancer.[67] CINP knockdown attenuated the transcription of KLF5 target genes, including *Cyclin D1* and *Caspase 7*, and therefore inhibited cell cycle progression and tumorigenesis.[67] Transcriptional co-activator with PDZ-binding motif (TAZ) and Yes1 associated transcriptional regulator (YAP), 2 key transcription activators of the Hippo pathway, can competitively antagonize the binding of WWP1 and KLF5 and increase KLF5 protein stability.[68]

5 | TRANSCRIPTIONAL AND POST-TRANSCRIPTIONAL MODULATIONS OF KLF5

5.1 | Promoter methylation inhibits KLF5 transcription

DNA hypermethylation at gene promoters is a common mechanism that causes transcriptional repression. Accumulating data indicate that KLF5 is regulated by DNA methylation. KLF5 intron 1 is hypermethylated in acute myeloid leukemia, and methylation is associated with poor overall survival.[69] KLF5 expression is also inhibited in ccRCC cells by DNA methyltransferase 1 (DNMT1)-induced hypermethylation at exon 4.[70] The expression of KLF5 can be recovered by knockdown of DNMT1 or the methylation inhibitor 5-Aza-CdR.[70]

5.2 | Super enhancer

SE consists of clusters of transcriptional enhancers, which are highly enriched for histone H3 lysine 27 acetylation (H3K27ac), bromodomain-containing 4 (BRD4), mediator complex subunit 1 (MED1) and other transcriptional coactivators.[71,72] KLF5 transcription was reported to be regulated by SE in various cancers.[24] KLF5 SE was amplified in head and neck squamous cell carcinoma, lung squamous cell carcinoma, gastric adenocarcinoma, CRC, cervical squamous cell carcinoma, bladder cancer, and esophageal cancer.[24] In tumor cells with SE amplification, the average activation expression of KLF5 was upregulated by 39%.[24] Next, we reported that SE maintains high expression levels of KLF5 in HCC1806 and HCC1937 breast cancer cell lines.[73] The BRD4 inhibitors JQ-1 and compound 870 and the cyclin dependent kinase 7 (CDK7) inhibitor THZ1 strongly inhibited the transcriptional expression of KLF5 and basal-like breast cancer cell growth.[73]

5.3 | miRNAs inhibit KLF5 expression

KLF5 was reported to be targeted by multiple miRNAs, such as miR-217,[74] miR-153,[75] miR-145-5p,[76] miR-152-3p,[77] miR-5195-3p,[78] miR-590-5p,[79] miR-4711-5p,[80] miR-214-5p,[81] miR-21,[82] miR-211,[31] miR-320,[83] and miR-375,[84] in various cancers.

Mifepristone induced the tumor suppressor miR-153 to suppress KLF5 expression and CSCs in TNBC.[75] Interestingly, miR-153 also targets HIF-1α[85] and angiopoietin 1[86] in response to hypoxia. miR-217 targeted KLF5 and suppressed TNBC cell growth, migration, and invasion.[74] The tumor suppressor miR-145-5p targeted KLF5 and decreased the proliferation of gastric cancer[76] and cervical carcinoma cells.[87,88] The tumor suppressor miR-152 also targets KLF5 in cervical cancer.[89] miR-5195-3p inhibited bladder cancer cell proliferation and invasion by targeting KLF5.[78] miR-590-5p targeted KLF5 and inhibited cell proliferation, migration and tumor growth of bladder cancer.[79] Consistently, miR-4711-5p suppressed colon cancer cell stemness and cell cycle progression in part by downregulating KLF5.[80] miR-214-5p exerted a tumor suppressor function by targeting KLF5 in HCC.[81] Crocin induced the expression of miR-320 to target KLF5 and inhibited the EMT, migration, and invasion of gastric cancer cells.[83] miR-375 reduces the expression of KLF5 in oral squamous cell carcinoma.[84]

KLF5 was reported to play a context-dependent role in different cancers. In prostate cancer, highly expressed miR-21 targeted KLF5 and promoted cancer cell proliferation, survival, migration, and invasion.[82] miR-21 also plays a similar role in HCC[90] and acute myeloid leukemia.[91] miR-27a targeted FBW7 and indirectly increased KLF5 expression in ccRCC.[48]

5.4 | LncRNA

CASC15 promoted KLF5 expression and breast cancer cell proliferation, invasion, and tumor growth by inhibiting miR-153-3p.[44] MCM3AP-AS1 increased KLF5 expression in glioma-associated endothelial cells by inhibiting miR-211.[31] In endometrial cancer, UCA1 upregulates the expression of KLF5 by sponging both miR-1-3p and miR-143-3p.[92] In addition, PVT1 was found to bind to KLF5 and

increase KLF5 protein stability by recruiting BAP1.[93] LINC00337 promoted the cancer stem cell-like properties of cervical cancer cells through the miR-145/KLF5 axis.[88] LINC00908 promoted the expression of KLF5 by absorbing miR-143-3p, thereby promoting the proliferation and survival of CRC cells.[94]

6 | POSTTRANSLATIONAL MODIFICATIONS

6.1 | Phosphorylation

KLF5 has been shown to be phosphorylated by protein kinase C (PKC) at S153, which upregulates its transactivation activities by enhancing the interaction between KLF5 and CBP.[95] KLF5 S406 phosphorylation by extracellular signal regulated kinase 1/2 (ERK1/2) enhanced the interaction between KLF5 and C-JUN[96] or retinoic acid receptor α (RARα).[97] KLF5 phosphorylation at S303 by GSK3β recruits FBW7 to promote KLF5 ubiquitination and degradation by the proteasome.[22]

6.2 | Acetylation

KLF5 acetylation at K369 by p300 promoted the transactivation activity of KLF5 and induced p15 transcription in response to TGF-β.[60] Recently, GCN5 was reported to acetylate KLF5 at K335 and K391 and increase the transcription of the downstream target gene *GDF15* and the proliferation of NSCLC cells.[40] It is well known that acetylation is reversible. KLF5 can be deacetylated by histone deacetylase 1/2 (HDAC1/2) and SET, which inhibit the function of KLF5.[98,99] A recent study suggested that KLF5 acetylation may regulate KLF5 protein stability.[99] Additionally, acetylated KLF5 is essential to maintain basal progenitor cells and prostate differentiation.[15] Recently, KLF5 was shown to interact with HDAC3 to inhibit the transcription of *BECN1*.[38]

6.3 | Ubiquitination

KLF5 has been demonstrated to be ubiquitinated.[100] KLF5 can be ubiquitinated by E3 ligases, such as WWP1,[62] FBW7,[22] SMURF2,[64] and EFP.[63] Interestingly, YAP and TAZ, 2 well known WW domains containing coactivators in the Hippo pathway, competitively bind to the KLF5 PY motif and protect KLF5 from WWP1-mediated ubiquitinated degradation.[68,101,102] Curcumin appears to target KLF5 for degradation by downregulating YAP/TAZ in bladder cancer cells.[68]

It is well known that ubiquitination is also reversible. In recent years, 3 KLF5 deubiquitinating enzymes, BAP1, ATXN3L, and USP3, have been identified through siRNA library screening.[55,65,66] BAP1 was shown to promote breast tumor growth and metastasis by stabilizing KLF5.[55] Furthermore, KLF5 forms a complex with BAP1/HCF-1/OGT1 to regulate the transcription of *FGF-BP1* and *p27* and cell cycle progression.[55] In melanoma, the high expression of BAP1 also indicates a poor prognosis for patients, which promotes tumor progression by hindering KLF5 ubiquitination.[103] Although ATXN3L was identified as another KLF5 DUB, the endogenous ATXN3L protein could not be detected because of its low expression or antibody sensitivity.[65] Most recently, USP3 was validated to reduce KLF5 polyubiquitination and increase KLF5 protein stability, therefore promoting breast cancer cell proliferation and tumor growth.[66] Most importantly, the expression levels of USP3 and KLF5 in breast tumors are positively correlated.[66] How these E3s and DUBs are coordinated to regulate KLF5 protein stability and activity in response to signaling requires further investigation.

7 | CELLULAR FUNCTIONS

KLF5 is broadly expressed during embryogenesis and in adult tissues. Accumulating evidence suggests that KLF5 is expressed in several tissues, including the colon,[104] intestine,[18] pancreas,[104] stomach,[105] placenta,[106] prostate,[15] testis,[104] breast,[7] bladder,[107] lung,[19] and skeletal muscle.[104] KLF5 has been well documented to regulate multiple cellular processes, including the cell cycle and proliferation, apoptosis and autophagy, migration and invasion, and stemness and differentiation.

7.1 | Proliferation and cell cycle progression

Several lines of new evidence support the idea that KLF5 promotes the cell cycle and proliferation. In a mouse model of intestinal-specific deletion of Klf5, it was found that Klf5 is necessary for gut epithelial cell proliferation.[16] Progesterone and PR promote breast cell proliferation by inducing KLF5 transcription, which in turn upregulates the expression of several genes, including *Cyclin A*, *chromatin licensing* and *DNA replication factor 1* (*CDT1*), and *E2F transcription factor 3* (*E2F3*).[108] Consistently, Klf5 knockout in mouse mammary glands showed defects after pregnancy because epithelial cell proliferation was significantly decreased, as examined by Ki67 IHC staining.[7] In addition to *FGF-BP1* and *integrin subunit beta 2* (*ITGB2*),[101] we demonstrated that KLF5 also promoted breast cancer cell proliferation through *mPGES1*[26] and *TNFAIP2*.[27] In pancreatic cancer cells, KLF5 promotes the transcription of *E2F1*, *Cyclin D1* and *Rad51* while inhibiting the expression of *p16*.[41] KLF5 is also required for androgen/AR-dependent prostate cancer cell proliferation.[32]

7.2 | Stemness and differentiation

KLF5 plays important roles in the self-renewal of ESCs, tissue-specific stem cells, and CSCs. Klf5 is induced by leukemia inhibitory factor (LIF)/signal transducer and activator of transcription 3 (STAT3) in mouse ESCs to maintain the undifferentiated state.[109] In mammary glands, KLF5 promotes *Slug* gene transcription to maintain stemness.[7] Depletion of Klf5 in mouse mammary glands

significantly decreased $CD24^{+}/CD49f^{high}$ normal breast stem cells.[7] Mammosphere formation and breast regeneration efficiency were suppressed in the absence of Klf5.[7] Knockdown of KLF5 or Slug also reduced the number of acetaldehyde dehydrogenase positive ($ALDH^{+}$) stem cells in 184B5 and MCF10A breast epithelial cell lines.[7] Consistently, mifepristone, metformin, and miR153 suppress breast CSCs by inhibiting KLF5 expression.[6,75] Additionally, Klf5 is essential for maintaining the progenitor cells of prostate basal cells.[15]

Several studies have shown that KLF5 plays an important role in the maturation of gut cells.[16] Klf5 depletion destroyed the colonic crypt structure.[16] Klf5 is essential for initiating morphogenesis of the early endoderm into a compartmentalized intestinal epithelium comprised of villi and terminally differentiated cells.[17] miR-4711-5p suppressed colon cancer cell stemness by downregulating KLF5.[80] KLF5 depletion also caused the differentiation of gastric cancer cells.[76]

7.3 | Apoptosis and autophagy

Accumulating evidence suggests that KLF5 is a pro-survival protein. In pancreatic ductal adenomas, Klf5 blocked Sox4-induced apoptosis.[110] In breast cancer, we found that KLF5 increases mitogen-activated protein kinase phosphatase 1 (MKP-1) protein stability to inhibit apoptosis.[111] Dexamethasone (DEX) increases docetaxel and cisplatin resistance by upregulating KLF5 in TNBC.[112] Consistently, KLF5 downregulation promoted cisplatin-induced apoptosis by inhibiting the phosphorylation of the DNA damage checkpoint protein checkpoint kinase 1/2(Chk1/2) in NSCLC.[113] KLF5 depletion markedly induced apoptosis of anaplastic thyroid carcinoma cells and increased doxorubicin sensitivity, and likely to be through inhibiting the JNK signaling pathway.[114]

In contrast, ectopic KLF5 expression was reported to promote apoptosis in ESCC cells[115] and in LNCaP prostate cancer cells in the presence of phorbol 12-myristate 13-acetate (PMA) by activating the JNK signaling pathway.[116] Interestingly, KLF5 inhibited autophagy in castration-resistant prostate cancer cells by suppressing the transcription of *BECN1*.[38] KLF5 knockdown decreased the sensitivity of prostate cancer cells to docetaxel.[38] In A2058 melanoma cells, KLF5 knockdown increased autophagosomes and autolysosomes.[103] Therefore, KLF5 plays a context-dependent role in regulating cell death and drug resistance.

7.4 | Migration and invasion

Large numbers of studies suggest that KLF5 promotes cell migration and invasion. KLF5 increased TNBC cell adhesion, migration, and invasion by inducing the transcription of *TNFAIP2*, which in turn activated Rac family small GTPase 1 (Rac1) and cell division cycle 42 (Cdc42).[27] In agreement with this, miR-217 inhibits TNBC cell migration and invasion by targeting KLF5.[74] Additionally, depletion of Klf5 in 4T1 mouse breast cancer cells significantly suppressed lung metastasis.[55] KLF5 promoted cervical cancer migration and invasion by inducing *TNFRSF11a* expression.[39] KLF5 promoted cell migration via the FYN/p-FAK axis in bladder cancer cells.[30] Cholesterol accelerated ccRCC cell migration and invasion by inducing KLF5.[48] Consistently, miR-4711-5p suppressed colon cancer cell migration and invasion by downregulating KLF5.[80] miR-590-5p suppressed osteosarcoma cell migration and invasion by targeting KLF5.[79] KLF5 knockdown reduced laryngeal carcinoma Hep-2 cell migration and invasion and EMT by inhibiting the NF-κB pathway.[117] Similarly, KLF5 was reported to promote thyroid cancer metastasis by activating the NF-κB pathway.[118] KLF5 activated LINC00346 transcription and promoted gastric cancer cell migration and invasion.[45] Consistently, crocin inhibited EMT, migration, and invasion of gastric cancer cells partially through increasing the expression of miR-320, which targets KLF5.[83] Studies have found that overexpression of BAP1 in esophageal cancer cells upregulates the expression of KLF5 and its downstream genes *FGF-BP1* and *Cyclin D1*, and promotes the proliferation and migration of ECA109 esophageal cancer cells.[119]

In sharp contrast, KLF5 knockdown in A549 lung cancer cells induced EMT by downregulating the expression of E-cadherin and upregulating the expression of Vimentin protein.[120] Consistently, KLF5 is required to maintain epithelial characteristics and prevent EMT induction in epithelial cells by inducing the expression of miR-200.[50] TTK kinase induced the expression of ZEB1 and EMT in TNBC by inhibiting KLF5-induced miR-200 expression.[121] In the absence of p53, KLF5 inhibits EMT in liver cancer cells through the miR-192/ZEB2 axis.[49] miR-21 promoted prostate cancer cell migration and invasion by directly targeting KLF5.[82] Similar results were observed in hepatocellular carcinoma.[90] In ESCC, KLF5 loss inhibited notch receptor 1 (NOTCH1) expression and induced invasion when p53 was inactivated.[122] These findings suggest that KLF5 has a context-dependent role in regulating cell migration and invasion.

8 | KLF5 INVOLVED ONCOGENIC SIGNALING PATHWAYS

KLF5 plays important roles in the regulation of multiple cancer-related signaling pathways (Figure 2).

8.1 | Wnt

The Wnt signaling pathway plays a vital role in various cancers, especially intestinal and CRC. McConnell et al first reported that KLF5 haploinsufficiency inhibited intestinal adenoma formation in Apc^{Min} mice by 96%, with decreased expression of Wnt target genes, including *c-Myc* and *Cyclin D1*.[123] Consistently, KLF5 interacted with β-catenin to promote β-catenin nuclear localization.[123] A subsequent study demonstrated that deletion of Klf5 in the gut epithelium

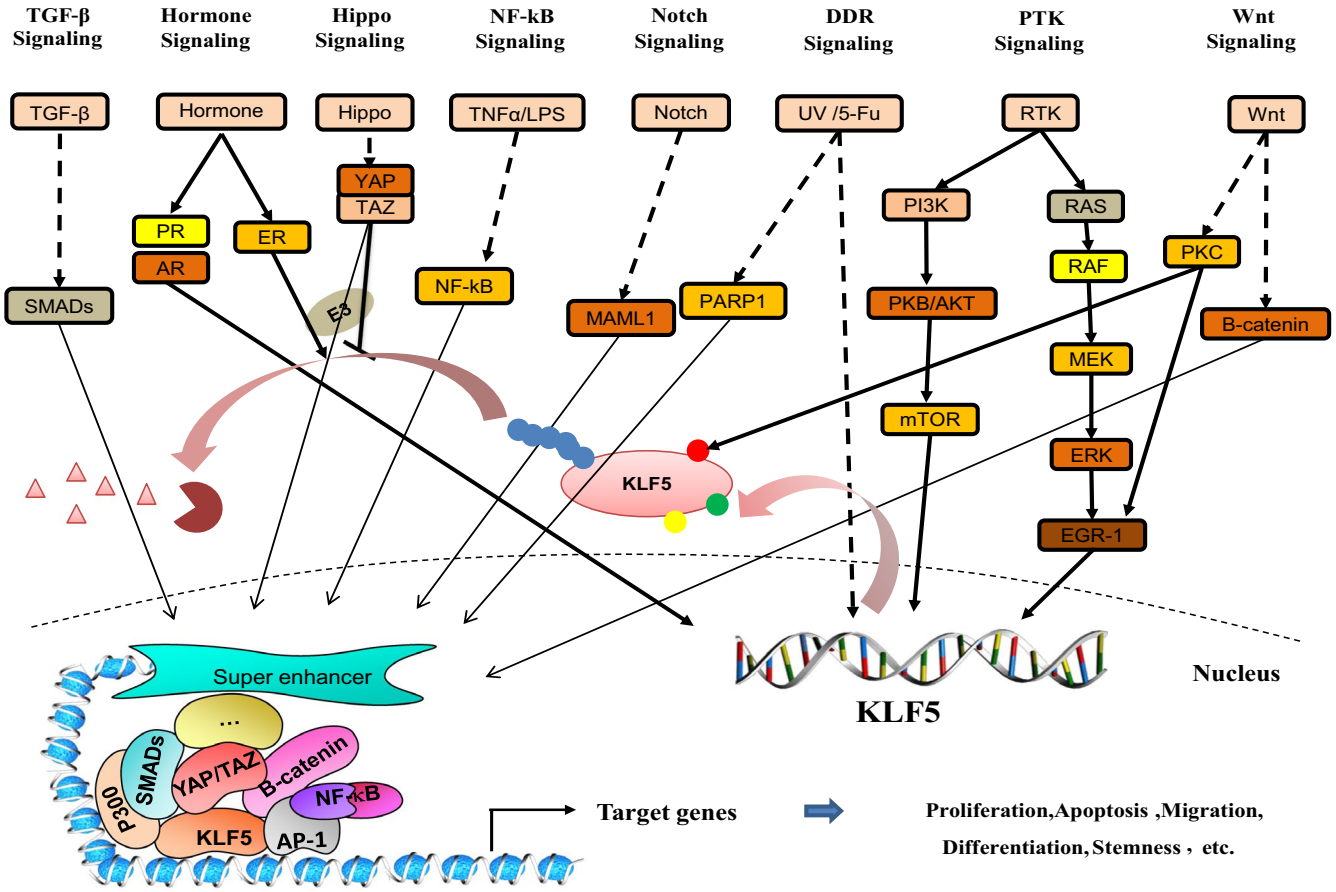

FIGURE 2 KLF5 is involved in diverse oncogenic signaling pathways. The protein expression and function of KLF5 involve multiple signal pathways, including Wnt, RTK, hormone, TGF-β, Hippo, NOTCH, NF-κB and Hedgehog signaling pathways. It can form a transcription complex with a variety of transcription factors to regulate the expression of target genes

decreased epithelial proliferation, differentiation, and cell positioning along the crypt radial axis because of the disruption of canonical Wnt signaling.[16] Nakaya et al further confirmed that inducible deletion of *Klf5* in Lgr5$^+$ mouse intestinal stem cells suppressed cell proliferation, survival and production of lethal adenomas and carcinomas induced by an oncogenic mutant of β-catenin.[18] This conclusion was confirmed by another independent study. Klf5 knockout in Lgr5$^+$ intestinal stem cells inactivated numerous canonical WNT-responsive and NOTCH-responsive genes and caused regeneration defects.[124,125] In CRC progenitor cells, KLF5 and YAP1 form a complex to induce the transcription of the *Ascl2* gene, a Wnt signaling target, to maintain self-renewability.[126] Taken together, these findings suggest a crucial role of KLF5 in the Wnt signaling pathway and CRC.

8.2 | RTK

RTK activates the rat sarcoma/mitogen-activated protein kinase (RAS/MAPK), phosphatidylinositol 3-kinase/AKT serine/threonine kinase/mechanistic target of rapamycin kinase (PI3K/AKT/mTOR), and STAT3 pathways. Accumulating evidence suggests that RAS/MAPK/PI3K can increase KLF5 transcription to promote cell proliferation.[127,128] Pharmacological inhibition of MEK and PI3K kinases reduced KLF5 protein levels in mouse pancreatic cancer cells.[129] We showed that KLF5 activates ERK in breast cancer by inducing the expression of FGF-BP1.[25,111] Activated ERK phosphorylates and stabilizes the MKP-1 protein, which decreases MAPK phosphorylation as a negative feedback loop.[111] Interestingly, Klf5 suppressed ERK activity in mESCs by inducing the transcription of *Spred1*, a negative regulator of ERK signaling.[130]

Some studies suggest that KLF5 promotes cancer by activating the PI3K/AKT signaling pathway. For example, KLF5 knockdown inhibited the activation of the PI3K/AKT/mTOR pathway and HIF-1α-dependent glycolysis, therefore overcoming hypoxia-induced cisplatin resistance in NSCLC cells.[131] The latest research shows that knocking down BAP1 in melanoma cells also reduced the phosphorylation of PI3K, AKT and mTOR activated by KLF5.[103] Additionally, KLF5 was reported to promote EMT of HCC by activating the PI3K/AKT/Snail signaling pathway.[132] Furthermore, KLF5 increased the activities of both the PI3K/AKT and ERK1/2 signaling pathways, possibly by upregulating the expression of AGGF1 in glioma-associated endothelial cells.[31] Consistently, miR-493-5p inhibited the proliferation and metastasis of osteosarcoma cells by downregulating KLF5 and inactivating the PI3K/AKT signaling pathway.[133] Resveratrol inhibited the PI3K/protein kinase D1 (PKD1)/AKT pathway and increased KLF5 phosphorylation, which decreased its interaction with

c-Myc in HEK293 cells.[134] However, the opposite conclusion was reached in prostate cancer. Klf5 and PTEN depletion additively increased AKT activity, the expression of HIF-1α, VEGF, and PDGF, and angiogenesis, although the mechanism by which KLF5 inhibits the PI3K/AKT pathway is unclear.[135] An independent study supported this finding. miR-21 promoted prostate cancer by directly targeting KLF5, which downregulates the expression of GSK3β and the phosphorylation of AKT.[82]

Additionally, KLF5 was reported to activate STAT3. He et al demonstrated that Klf5 knockout decreased Ras-induced pancreatic tumorigenesis by reducing the activation of STAT3 due to the increase in the expression of *N*-myc downregulated gene 2 (NDRG2).[129] ML264, a small molecular inhibitor of KLF5, also inhibited the activation of STAT3 in osteosarcoma.[136] However, KLF5 was reported to inhibit STAT3 activity and prostate cancer metastasis by suppressing *IGF1* transcription.[53]

8.3 | Hormone

In 2013, Liu, R et al summarized the relationships among steroid hormonal signaling (progesterone, estrogen and androgen) and KLF5 in breast cancer.[10] In brief, KLF5 was induced by progesterone in PR-positive breast cancer cells and promoted cell proliferation and dedifferentiation.[108] Consistently, KLF5 expression is significantly increased in mouse mammary glands after pregnancy, and KLF5 is essential to maintain breast stemness.[7] Mifepristone, a PR antagonist, not only blocked progesterone-induced KLF5 expression in PR-positive breast cancer cells[10,108] but also inhibited the expression of KLF5 in TNBC by inducing miR-153.[75]

Similarly, androgen also induced *KLF5* transcription through AR in prostate cancer cells and KLF5-mediated androgen-induced cell-surface chemokine receptor 4 (CXCR4) expression and migration.[137] This finding was confirmed by an independent study in which androgen induced *KLF5* transcription and KLF5 interacted with an interaction with sterol-regulatory-element-binding protein-1 (SREBP-1) to induce *fatty acid synthase* (*FASN*) gene transcription and in LNCaP prostate cancer cells.[138] In agreement with these results, *KLF5* is also an androgen-responsive gene in human breast carcinomas.[139] Recently, KLF5 was shown to interact with AR to regulate the expression of AR target genes in prostate cancer cells.[32] Additionally, acetylation of KLF5 at K369 is essential for androgen-mediated organoid organization and prostate regeneration.[15]

Glucocorticoids, such as DEX and hydrocortisone, can also induce KLF5 expression through GR and confer docetaxel and cisplatin resistance in TNBC cell lines.[112] This finding was supported by an independent study in which DEX-bound GR accelerated adipogenesis by directly promoting the expression of KLF5.[140] Interestingly, glucocorticoids also induced the expression of several KLF5 interacting partners, such as TEAD4[141] and YAP,[142] to promote breast cancer growth and metastasis. It is likely that activated GR interacts with the YAP/TEAD4/KLF5 complex to promote cancer cell proliferation, survival, and metastasis.

In contrast, estrogen suppresses KLF5 expression in ERα-positive breast cancer cells through multiple mechanisms, and KLF5 also suppresses ERα-mediated gene transcription.[10] It was also shown that 17β-estradiol suppressed KLF5-mediated *FOXO1* and *PDGFA* transcription through ERβ in prostate cancer cells.[58]

8.4 | TGF-β

The TGF-β/SMAD pathway plays a dual role in tumorigenesis and development. TGF-β inhibits epithelial cell proliferation in the early stage of cancer development but promotes metastasis in the late stage of cancer progression. In response to TGF-β, KLF5 is acetylated by p300, binds to SMADs, and regulates the transcription of *p15* and c-*Myc*.[60,143] Recently, Ras was shown to inhibit TGF-β-mediated KLF5 acetylation, block the assembly of the p300-KLF5-SMAD complex, and regulate the expression of *p15* and c-*Myc*.[59]

8.5 | Hippo

The Hippo pathway regulates cell stemness, proliferation, survival, migration, and organ size.[144] YAP and TAZ are 2 key transcriptional coactivators in the Hippo pathway. Our studies showed that both YAP and TAZ increased KLF5 protein stability by preventing WWP1-mediated ubiquitination and degradation.[68,101,102] Consistently, curcumin downregulated the expression of KLF5 by targeting YAP/TAZ and inhibited bladder cancer cell growth.[68] Additionally, TEAD4, a key transcription factor and partner of YAP/TAZ, was found to interact with KLF5 and inhibit *p27* gene transcription in breast cancer.[5] In agreement with this, TEAD4, similar to KLF5, promoted breast cancer stemness, cell growth, survival, metastasis, and chemoresistance.[5,141] Furthermore, glucocorticoids also induced GR-dependent TEAD4 transcription, nuclear accumulation, and transcription complex formation.[141] It is reasonable to suspect that KLF5, TEAD4, and GR form a transcription complex to execute the above oncogenic functions in breast cancer.

8.6 | NOTCH

KLF5 may be a tumor suppressor in ESCC. KLF5 and p53 maintain the expression of NOTCH1, which suppresses primary human keratinocyte transformation. Loss of both p53 and KLF5 led to the formation of invasive tumors.[122] In the mouse prostate, Klf5 deacetylation activates NOTCH signaling, Hes family bHLH transcription factor 1 (Hes1), Myc, Jagged 1 and delta like canonical NOTCH ligand 1 (Dll1)), which promotes luminal cell proliferation.[15] DAPT, a NOTCH signaling inhibitor, blocked the abnormal phenotype induced by $Klf5^{K358R}$ knockin.[15] Klf5 knockout in $Lgr5^{+}$ intestinal stem cells led to loss of stem cell identification and premature differentiation because of inactivation of NOTCH and WNT target genes.[125]

Interestingly, KLF5, NOTCH, and MYC are substrates of the tumor suppressor SCF^{FBW7}.[145]

8.7 | NF-κB

NF-κB signaling is activated in response to inflammatory stimuli, such as TNFα, interleukin 1β (IL1β), and lipopolysaccharide (LPS). Early studies showed that LPS induced KLF5 expression and that KLF5 was necessary for NF-κB activation.[146,147] TNFα was reported to induce KLF5 by activating p38 in cervical cancer cells.[39] Several studies have suggested that KLF5 activates NF-κB signaling. For example, KLF5 increased the phosphorylation of IKKβ, IκBα and p65 nuclear translocation in thyroid cancer cells.[118] KLF5 silencing significantly decreased Hep-2 laryngeal cancer cell proliferation, survival, and migration by reducing the phosphorylation of IκBα and p65.[117] KLF5 also regulates several target genes related to the NF-κB signaling pathway. We demonstrated that KLF5 and NF-κB may coordinately induce *TNFAIP2* gene transcription in breast cancer cells.[27,148] KLF5 was shown to induce the transcription of *TNFRSF11a*, which promotes cervical cancer cell proliferation and invasion.[39]

8.8 | Hedgehog

KLF5 also promotes sonic hedgehog (SHH) signaling. KLF5 was highly expressed in esophageal adenocarcinoma, and KLF5 knockdown significantly decreased SHH signaling and cancer cell proliferation and migration.[149] *GLI family zinc finger 1 (GLI1)*, a typical SHH pathway target gene, was significantly downregulated by KLF5 knockdown, however SHH and patched 1 (PTCH1) expression levels were upregulated.[149] Bell et al generated conditional Klf5 knockout mice using SHH-Cre and found that Klf5 depletion resulted in the inhibition of villus morphogenesis and intestinal epithelial differentiation.[17] Consistently, Klf5-KO increased the expression of PTCH1 and GLI family zinc finger 2 (GLI2).[17] The mechanism by which KLF5 participates in the SHH signaling pathway remains to be elucidated.

8.9 | DNA damage repair

5-Fluorouracil (5-FU)-induced DNA damage activated KLF5 transcription via a p53-independent mechanism in HCT116 colon cancer cells. KLF5, in turn, induced the expression of Pim1 to promote cell survival.[150] Consistently, irradiation also induced Klf5 expression in mouse intestinal epithelial cells.[151] KLF5 modulates DDR via p21-mediated growth arrest and BCL2 associated X (BAX)-mediated apoptosis in response to UV irradiation in TE2 esophageal cancer cells.[152] Klf5 intestinal-specific heterozygote-deficient mice had more severe intestinal damage after radiation damage than WT mice.[151] The mechanism was associated with reduced expression of DDR genes, such as *ERCC excision repair 5* (*ERCC5*) and *cullin 4B* (*CUL4B*).[151] Additionally, KLF5 was reported to interact with poly ADP-ribose polymerase 1 (PARP1), an enzyme associated with DDR and apoptosis.[153] Importantly, knockdown of KLF5 sensitized NSCLC cells to cisplatin.[113] KLF5 depletion inhibited the DDR by reducing the activation of Chk1/2 and H2A.X variant histone (H2AX), allowing cells to enter mitosis with damaged DNA.[113] KLF5 knockdown also sensitized TNBC cells to cisplatin and docetaxel.[112]

8.10 | Hypoxia

KLF5 is involved in hypoxia-induced cancer behaviors, such as vascular remodeling,[154] cell proliferation,[154] apoptosis,[61] and drug resistance.[131] HIF-1α is often rapidly activated under hypoxia.[155] In pancreatic cancer, KLF5 is upregulated by hypoxia, and KLF5 interacts with HIF-1α to induce transcription of some target genes, such as *glucose transporter 1 (GLUT-1)*.[156] In CRC cells, lysophosphatidic acid (LPA) induces KLF5 expression, which in turn transactivates *HIF-1α* gene transcription.[157] Consistently, hypoxia promotes the survival of NSCLC cells by inducing the expression of HIF-1α in a KLF5-dependent manner.[61] Gong et al also found that hypoxia upregulated the expression of KLF5 in NSCLC cells and that hypoxia-induced cisplatin resistance was reversed by KLF5 knockdown because KLF5 knockdown inhibited hypoxia-induced HIF-1α expression, PI3K/AKT/mTOR pathway activation, and glycolysis.[131] Crocin inhibits gastric cancer cell migration, invasion and EMT by activating the miR320/KLF5/HIF-1α axis.[83] In contrast, KLF5 deletion promotes the accumulation of HIF-1α and angiogenesis in PTEN-deficient prostate cancer.[135]

9 | FUNCTIONS OF KLF5 IN VARIOUS CANCERS

The expression of KLF5 is abnormal in a variety of solid tumors, such as breast cancer, prostate cancer, colon cancer, NSCLC, and ESCC. The function of KLF5 is context dependent, although it promotes tumorigenesis in most cancers.

9.1 | Breast cancer

Accumulating evidence suggests that KLF5 promotes breast cancer cell stemness, proliferation, survival, adhesion, and migration. In breast cancer, KLF5 promotes cancer cell proliferation and the cell cycle by inducing transcription of *FGF-BP1*,[25] *mPGES1*,[26] *TNFAIP2*,[27] and *Cyclin D1*[4] and inhibiting transcription of *p27*[5] and *p21*.[26] KLF5 maintains cell stemness by inducing the transcription of *Slug*[7] and *Nanog*.[6] KLF5 is essential for progesterone to induce cell proliferation and dedifferentiation.[108] Consistently, breast-specific Klf5 knockout mice significantly reduced the proliferation, survival, and stemness of breast epithelial cells and inhibited PyMT-induced tumorigenesis.[7] Klf5 is essential for the formation of milk bubble structures during pregnancy and lactation.[7] Interestingly, KLF5 is also induced by

androgen 5α-dihydrotestosterone and promotes MCF7 cell proliferation.[139] Glucocorticoids also induce KLF5 expression through GR and confer docetaxel and cisplatin resistance to TNBC cells.[112,141]

PVT1 directly interacts with KLF5 and recruits BAP1 to stabilize the KLF5 protein in breast cancer.[93] CASC15 functions as a competitive endogenous RNA for miR-153-3p, which targets KLF5.[44] Interestingly, CASC15 is also a direct target gene of KLF5; therefore, a positive feedback loop is formed to accelerate breast tumor progression.[44] Several drugs or compounds, such as mifepristone[75] and its derivatives,[158,159] metformin,[6] and mithramycin A,[160] have been shown to inhibit the expression of KLF5 in TNBC. In addition, the SE inhibitors JQ1, compound 870, and THZ1 potently inhibited the expression of KLF5 in TNBC.[73]

9.2 | Prostate cancer

Some studies have suggested that KLF5 promotes prostate cancer. KLF5 siRNA delivered by a nanoparticle system inhibited PC-3 xenograft growth and angiogenesis.[161] Androgen induces KLF5 and CXCR4 expression and promotes prostate cancer cell migration in vitro.[137] This conclusion is supported by a recent study, in which acetylated KLF5 promoted bone metastasis by activating CXCR4.[162] In two androgen-responsive prostate cancer cell lines, C4-2B and LNCaP, the expression of KLF5 was upregulated by androgen/AR.[32] At the same time, KLF5 interacts with AR to coordinately increase the expression of AR target genes, including *Myc*, *Cyclin D1* and *PSA*, which promote cell proliferation and differentiation.[32] Estrogen (17β-estradiol) promoted prostate tumor angiogenesis through the ERβ/KLF5 pathway.[58]

However, a line of evidence also supports that KLF5 is a tumor suppressor in prostate cancer. The *KLF5* gene is located at chromosome 13q.21 and is frequently deleted in prostate cells.[163] A low expression level of KLF5 was correlated with poor prognosis in prostate cancer patients.[38] Klf5 deletion promoted PTEN deletion-initiated luminal-type mouse prostate tumors.[164] Klf5 inhibited angiogenesis in PTEN-deficient prostate cancer by attenuating AKT activation and HIF-1α accumulation.[135] TNFα induced the expression of KLF5 in LNCaP cells and increased the levels of phosphorylation of JNK and apoptosis in response to PMA.[116] Consistently, KLF5 upregulated the transcription of *MKK7*, the upstream kinase of JNK, and promoted TNFα-induced apoptosis in LNCaP cells.[36] miR-21 is highly expressed in prostate cancer.[82] It can directly target KLF5, upregulate GSK3β expression and AKT phosphorylation, and promote prostate cancer cell proliferation, survival, migration, and invasion.[82] Loss and downregulation of KLF5 increased autophagy, thereby decreasing the sensitivity of prostate cancer cells C4-2 and CWR22RV1 to docetaxel.[38]

Therefore, the role of KLF5 in prostate cancer seems controversial. Acetylated KLF5 exhibits antitumor activity; in contrast, deacetylated KLF5 plays a tumor-promoting effect, which is related to the TGF-β signaling pathway.[165] KLF5 acetylation in prostate basal cells is essential to maintain the characteristics of basal progenitor cells by inhibiting the NOTCH pathway.[15] KLF5 downregulation promoted the invasion of prostate cancer by increasing the expression of IGF1, which in turn activated the STAT3 signaling pathway.[53] A circular RNA CircCRKL is downregulated in the prostate and can inhibit miR-141, upregulate the expression of KLF5, and inhibit prostate cancer.[166]

9.3 | Bladder cancer

KLF5 plays an important role in the normal development of mouse bladder tissue.[107] Our early study indicated that KLF5 promotes bladder cancer cell proliferation.[4] KLF5 can bind to a *Cyclin E1* gene enhancer to activate its transcription and increase susceptibility to bladder cancer.[29] In addition, KLF5 promotes bladder cancer cell migration by increasing the expression of FYN.[30] Furthermore, KLF5 promotes angiogenesis in bladder cancer by directly increasing *vascular endothelial growth factor A (VEGFA)* transcription.[127] Consistently, miR-5195-3p targets KLF5 to inhibit the expression of Cyclin D1 and VEGFA and to suppress the proliferation and invasion of bladder cancer cells.[78] Curcumin can inhibit bladder tumor growth by targeting the YAP/TAZ/KLF5/CyclinD1 axis.[68]

9.4 | Renal cell carcinoma

KLF5 is expressed in kidney and its collecting system. ccRCC is a common subtype of renal cell carcinoma in which KLF5 is highly expressed.[48] KLF5 was shown to increase the expression of miR-27a, which targets FBW7 and prevents FBW7-mediated KLF5 ubiquitination and degradation, promoting renal cancer cell migration and invasion.[48] In contrast, DNMT1-mediated KLF5 promoter hypermethylation inhibits KLF5 expression.[70] KLF5 was shown to inhibit ccRCC xenograft tumor growth and metastasis.[70] The deubiquitinase BAP1 was reported to stabilize KLF5.[55] Interestingly, the *BAP1* gene is mutated in ~15% of ccRCC, which also defines a new subtype of renal cell carcinoma.[167] Whether *BAP1* mutations cause renal cell carcinoma by promoting KLF5 degradation should be investigated.

9.5 | Intestinal and colorectal cancer

Overall, KLF5 is an oncogenic transcription factor in intestinal and CRC. In *Klf5*$^{+/-}$ mice, DSS induced more severe colitis, suggesting that KLF5 is required for intestinal epithelial repair.[168] Intestinal-specific deletion of *Klf5* using Villin-Cre showed that *Klf5* is required to maintain gut epithelial cell proliferation, differentiation, and positioning along the crypt radial axis.[16] Consistently, *Klf5* deletion in the intestinal epithelium using Shh-Cre inhibited villus morphogenesis and epithelial differentiation.[17] Furthermore, depletion of *Klf5* in Lgr5^{+} stem cells disrupts the integrity and oncogenicity of intestinal stem cells.[18] *Klf5* haploinsufficiency rescued the intestinal tumor formation induced by APC$^{Min/+}$ because KLF5 promotes the

nuclear translocation of β-catenin and upregulates the expression of *CyclinD1* and *Myc*.[123] Similarly, *Klf5* haploinsufficiency also decreased intestinal tumor formation in $APC^{Min/+}$/KRASV12 mice.[169] *Klf5* is also essential for intestinal epithelial cell proliferation and transformation by oncogenic $KRAS^{G12D}$.[169,170]

Zhang et al reported that the second CPD domain of KLF5 and the WD40 domain of FBW7 were frequently mutated, which reduced the degradation of KLF5 protein in CRC.[24] The KLF5 P301S mutation also increased the stability and transcriptional activity of KLF5 in CRC.[171] The tumor suppressors miR-143 and miR-145 can downregulate the expression of KLF5 in CRC.[172] LINC00908 is highly expressed in CRC and promotes cell proliferation and survival through the miR-143-3p/KLF5 axis.[94] LPA induced HIF-1α through KLF5 in colon cancer cell lines.[157] Recently, KLF5 was reported to induce lncRNA SNHG12 expression and to promote invasion and metastasis of CRC.[47] KLF5 also induces the transcription of the intestinal differentiation marker gene alkaline phosphatase.[173] ML264 was identified as a KLF5 inhibitor that effectively inhibited the expression of KLF5 and the growth of CRC xenograft tumors.[128] ML264 appears to inhibit the expression of KLF5 by inhibiting its upstream transcription factor EGR1, although the exact mechanism is unknown.[128]

9.6 | Esophageal squamous cell cancer

Esophageal cancer is a common malignant tumor, and its 5-y survival rate is less than 20%. Squamous cell carcinoma (51.6%) or adenocarcinoma (41.9%) accounts for more than 90% of esophageal cancers.[174] The function of KLF5 in ESCC is also controversial. KLF5 is expressed in normal esophageal epithelial cells, but its expression is downregulated or absent in ESCC.[115] In abnormally proliferating esophageal squamous epithelial cells, KLF5 promotes *NOTCH1* transcription in the context of p53 mutation or loss.[122] KLF5 and NOTCH1 loss is a critical event in squamous cell transformation and invasion. Additionally, KLF5 induces the transcription of *apoptotic signal-regulating kinase 1 (ASK1)* and *MKK4*, which activate the JNK pathway and promote apoptosis.[115]

In contrast, KLF5 interacts with TCF3 to induce LINC00094 transcription, thereby promoting the growth of ESCC.[42] In ECA109 cells, BAP1 can promote cell proliferation and migration by upregulating KLF5.[119] Additionally, KLF5, TP63, and SOX2 form a transcription complex to synergistically regulate the expression of target genes, including *ALDH3A1*, which is highly expressed in ESCC, and ALDH3A1 knockdown inhibits colony formation, cell viability and tumor growth in vivo.[37] This study also reported that the combination of the HDAC inhibitor romidepsin and the BET inhibitor ARV-771 can synergistically inhibit ESCC.[37]

9.7 | Gastric cancer

The *KLF5*, *GATA4*, and *GATA6* genes are independently amplified, and the 3 proteins form a transcription complex to promote the transcription of *Hnf4α* and tumorigenesis of gastric cancer.[56] Crocin can induce miR320 to target both KLF5 and HIF-1α to inhibit EMT in gastric cancer cells.[83] Interestingly, miR153 also targets both KLF5 [75] and HIF-1α.[85] Furthermore, miR-145-5p targets KLF5 and promotes gastric cancer cell differentiation.[76] In addition, KLF5 and MYC induce the transcription of LINC00346 to promote gastric cancer tumorigenesis.[45] KLF5 can activate the transcription of lncRNA NEAT1, which recruits BRG1 to silence the transcription of *GADD45A* and promotes gastric cancer cell proliferation and survival.[46] Notably, an early study reported that KLF5 is downregulated in gastric cancer and that KLF5 expression is positively correlated with early, small, and no lymph node metastasis tumors.[175] Zhang et al showed that the expression of KLF5 has no relationship with the prognosis of gastric cancer patients.[176] Interestingly, KLF5 is highly expressed in the tumor-associated fibroblasts of gastric cancer patients, and its expression is positively correlated with tumor grade, invasion depth, size, metastasis, and poor prognosis.[177] KLF5 knockdown in cancer-associated fibroblasts not only inhibited the growth of tumor cells but also inhibited their migration and invasion by inhibiting the C-C motif chemokine ligand 5/C-C motif chemokine receptor 5 (CCL5/CCR5) axis.[177]

9.8 | Hepatocellular carcinoma

It has been reported that KLF5 is significantly overexpressed in HCC specimens, and high KLF5 expression predicts a poor prognosis for HCC patients.[132] KLF5 promotes HCC growth and metastasis by activating PI3K/AKT/Snail signaling.[132] Consistently, the tumor suppressor miR-145-5p inhibits HCC cell proliferation and migration by targeting KLF5.[178] In contrast, miR-21 promotes the migration and invasion of HuH7 cells by targeting KLF5.[90] In HCC, the function of KLF5 may depend on the p53 status.[49] When WT p53 is present in HepG2 cells, KLF5 does not regulate cell migration.[49] When p53 is inactivated in Hep3B cells, KLF5 inhibits ZEB2 expression and EMT by promoting miR-192.[49] The defined role of KLF5 in HCC requires more studies.

9.9 | Pancreatic cancer

Pancreatic cancer is one of the most aggressive tumors. KLF5 expression is a poor prognostic marker for pancreatic cancer patients.[41] KLF5 promoted G1/S pancreatic cancer cell cycle progression by inducing the expression of E2F1, Cyclin D1 and Rad51 while inhibiting the expression of p16.[41] In pancreatic cancer, KLF5 is induced by IL-1β through p38 and hypoxia through HIF-1α.[156] In pancreatic cancer with p53 mutation, KLF5 induced PLA2G16 expression to promote glycolysis.[34]

KLF5 and SMAD4 inhibited the infiltration of T cells in the tumor immune microenvironment and promoted the infiltration of myeloid cells in pancreatic cancer.[179]

9.10 | Lung cancer

Klf5 is essential for mouse lung development.[19] KLF5 may also have a dual role in lung cancer. KLF5 was shown to promote lung cancer cell proliferation and tumorigenesis through upregulation of Sox4 expression.[180] Recently, KLF5 was reported to be highly expressed in NSCLC, and its expression was significantly higher than that of adjacent tissues, indicating a poor prognosis.[113] KLF5 depletion can overcome cisplatin resistance in NSCLC.[113] Under hypoxic conditions, the expression of KLF5 and HIF-1α was induced, and KLF5 interacted with HIF-1α to promote the survival of NSCLC cells.[61] Moreover, KLF5 knockdown inhibited hypoxia-induced HIF-1α expression, the PI3K/AKT/mTOR pathway, glycolysis, and cisplatin resistance in NSCLC cells.[131] In A549 cells, KLF5 interacted with GCN5 to induce the expression of GDF15 and promoted cell proliferation and tumor growth.[40] However, it was reported that Klf5 was not necessary in the mouse K-RasG12D lung tumorigenesis model.[54] In this study, KLF5 expression was positively correlated with better disease-specific survival of patients with NSCLC.[54]

9.11 | Leukemia

KLF5 interacted with p53 to induce *survivin* gene transcription and increase the survival of acute lymphoblastic leukemia cells.[181] However, KLF5 was downregulated in acute myeloid leukemia blast cells because of promoter methylation.[69,182,183] Low expression of KLF5 was associated with poor overall survival in acute myeloid leukemia patients.[183] In acute myeloid leukemia, miR-21 targeted KLF5 and promoted the proliferation of acute myeloid leukemia cells in vitro.[91] The expression of KLF5 was also downregulated in BCR-ABL1$^+$ B-ALL leukemia.[35] In B-cell acute lymphoblastic leukemia cells, overexpression of KLF5 can induce imatinib-resistant cell apoptosis by increasing oxidative stress.[35]

9.12 | Ovarian cancer

KLF5 was highly expressed in SKOV3 ovarian cancer cells and was positively correlated with high levels of survivin.[184] Knockdown of KLF5 sensitized SKOV3 cells to cisplatin or paclitaxel treatment.[184]

9.13 | Cervical cancer

KLF5 is an oncogene in cervical cancer. Among 17 KLF members, only *KLF5* mRNA was highly expressed in cervical cancer.[185] The KLF5/TNFRSF11a axis promoted the proliferation, migration and invasion of cervical cancer cells.[39] TNFα induced the expression of KLF5 in cervical cancer by activating the p38 signaling pathway.[39] miR-152 and miR-145-5p inhibited cervical cancer cell proliferation by directly inhibiting the expression of KLF5.[87,89] Consistently, LINC00337 maintained tumor stem cell-like characteristics by downregulating miR-145 and increasing the expression of KLF5.[88]

9.14 | Head and neck cancer

The *KLF5* gene is frequently amplified in salivary adenomas.[186] Liu et al found for the first time that KLF5 can inhibit the proliferation, survival, and migration of Hep-2 laryngeal cancer cells.[117] Knockdown of KLF5 inhibited EMT by suppressing the NF-κB signaling pathway.[117]

9.15 | Melanoma

In melanoma, KLF5 promoted tumor growth.[103] Clinical data showed that KLF5 was highly expressed in melanoma patients, and the *WWP1* gene was also downregulated.[103] It was observed in A2058 melanoma cells that KLF5 knockdown decreased cell proliferation, migration, and invasion, but increased autophagy.[103] The transplanted tumor experiments in mice also further verified the cancer-promoting effect of KLF5 in melanoma.[103] Previous studies have found that KLF5 is downregulated in Ras mutant melanoma cell lines.[187] The function of KLF5 in melanoma needs further exploration.

9.16 | Other cancers

In glioblastoma, KLF5 activated the transcription of the *AGGF1* gene to promote angiogenesis.[31] In pituitary adenoma cells, KLF5 upregulated the expression levels of miR-124, miR-145, and miR-148 and inhibited cell migration and invasion.[51] In addition, KLF5 is downregulated in nasopharyngeal carcinoma and Ras mutant melanoma cell lines.[188]

10 | TARGETED THERAPY

Given the important role of KLF5 in tumorigenesis and development, an increasing number of scientists have tried to target this transcription factor for cancer therapy. It is well known that transcription factors are undruggable to date because of their nuclear localization and the lack of small molecular binding pockets. Therefore, more attention has been given to targeting KLF5 upstream positive regulators and downstream effectors. A recent review comprehensively summarized the compounds regulating the expression of KLF5.[11] Here, we listed a few examples of the latest progress, and as shown in Table 4. Recently, several old drugs were reported to inhibit the expression of KLF5. First, mifepristone inhibits KLF5 expression by inducing miR-153 to suppress TNBC cell proliferation, survival and CSCs.[75] Two mifepristone-derived compounds, FZU-00,003 and FZU-00,004, showed higher efficiency.[158,159] Second, metformin

TABLE 4 KLF5 targeted compounds

Compounds	Functional mechanism	References
CID51003603(ML264)	Inhibit the expression of EGR1 and KLF5	128,190
CID5951923, CID46931043, CID46931037	Inhibit the expression of EGR1 and KLF5	189
Metformin	Promote KLF5 phosphorylation and degradation	6
Mifepristone	Induce miR-153 to inhibit KLF5 protein translation	75
Mithramycin A	Inhibit the binding of Sp1 to the KLF5 promoter	160
Curcumin	Inhibit YAP/TAZ	68
Crocin	Induce miR-320	83
JQ-1 and compound 870	BRD4 inhibitors	73
THZ1	CDK7 inhibitor	73
Sodium butyrate	Histone deacetylase inhibitor	173

suppressed PKA activity, promoted GSK3β-mediated KLF5 phosphorylation and degradation and decreased TNBC stem cells.[6] Additionally, mithramycin A inhibited TNBC by inhibiting the binding of Sp1 to the *KLF5* promoter and the binding of KLF5 to the *FGF-BP1* promoter.[160] Furthermore, curcumin promoted KLF5 degradation in bladder cancer by inhibiting the transcription of YAP/TAZ.[68] Crocin inhibited KLF5 expression by inducing miR-320 expression in gastric cancer cells.[83] The deacetylase inhibitor sodium butyrate also inhibited KLF5 expression in colon cancer cells.[173]

Beyond old drugs, we found that the CDK7 inhibitor THZ1 and BRD4 inhibitor JQ-1 can efficiently downregulate the transcription of KLF5 and inhibit TNBC cell growth in vitro.[73] JQ-1-derived compound 870 showed better efficacy.[73] Using ultrahigh-throughput screening, CID5951923 and ML264 (CID51003603) were identified to inhibit the expression of KLF5 and the proliferation of CRC cells.[128,189] We confirmed that ML264 also inhibited KFL5 expression in breast cancer cells.[190] Interestingly, the ML264-derived compound YD277 lost this capability, although it triggered ER stress in breast cancers.[190]

11 | CONCLUSION

In general, KLF5 is a critical transcription factor that controls the transcription of multiple downstream target genes. KLF5 can regulate cell stemness and differentiation, proliferation, apoptosis, and autophagy and participate in a variety of cell physiology and pathological processes such as organ development, tissue regeneration, angiogenesis, and disease development. KLF5 is involved in the initiation and development of diverse cancers in a context-dependent manner. KLF5 promotes several cancers, such as breast cancer, CRC, bladder cancer, and cervical cancer. However, KLF5 may have dual functions in prostate cancer, gastric cancer, lung cancer, and so on. KLF5 undergoes a variety of posttranslational modifications, such as phosphorylation, acetylation, and ubiquitination. KLF5 is regulated by various signaling pathways, including RTK, Hippo, Wnt, etc. Some small molecules have been identified to inhibit KLF5 expression through different mechanisms.

12 | PERSPECTIVES

Given the important roles of KLF5 in cancer initiation and development, we should further understand KLF5 biology, including its physiological and pathological functions, downstream effectors, interacting partners, and upstream regulatory mechanism. Eventually, small molecular modulators should be developed to target this key transcription factor for cancer treatment. In this regard, Klf5 transgenic animal models will be very useful in the future.[191]

KLF5 participates in a variety of physiological processes by regulating a variety of downstream target genes. Recent studies have found that KLF5 is involved in glycolysis and lipid metabolism. For example, KLF5 promotes glycolysis, inhibits mitochondrial respiration, and promotes pancreatic tumor growth by upregulating the expression of PLA2G16.[34] KLF5 can interact with SREBP-1 to regulate the expression of FASN, thereby promoting the proliferation of prostate cancer cells.[138] Additionally, KLF5 plays a vital role in inflammation and tumor immunity. Several inflammatory factors, including TNFα[39] and IL1β,[156] induce KLF5 expression. A recent study reported that KLF5 and SMAD4 inhibited the infiltration of T cells in the tumor immune microenvironment and promoted the infiltration of myeloid cells in pancreatic cancer by upregulating the expression of EGFR.[179] Therefore, the combined immunotherapy of EGFR and reshaping of the immune microenvironment may be a promising targeted therapy strategy.[179] Identification of KLF5 target genes, including non-coding RNAs, that participate in metabolism and affect the immune microenvironment will provide a better idea how to clarify the role of KLF5 in tumor development. High-throughput analysis methods, such as ChIP-seq, Hi-C-seq, RNA-seq, and ATAC-seq, will be useful to identify the functional mechanism and KLF5 direct target genes from the whole genome landscape.

It is important to identify KLF5 interaction proteins and transcriptional complex components. As a transcription factor, KLF5 does not function alone. For example, KLF5-TP63-SOX2, KLF5-GATA4-GATA6, and KLF5-SMAD4-Miz-1-p300 transcriptional complexes have been reported in different cancers.[37,56,60] KLF5 is induced by androgen through AR, and then KLF5 cooperates with AR to promote the transcription of AR downstream target genes and promote cell proliferation.[32] Epigenetic enzymes, such as p300, HDACs, and BAP1, have been reported to participate in gene transcription in addition to modifying the KLF5 protein. It would be interesting to understand how these enzymes function in gene transcription.

Disruption of the KLF5 transcriptional complex may be a promising approach to inhibit its oncogenic functions.

It is crucial to understand the upstream regulatory mechanisms of KLF5 in cancers to design effective targeting strategies. At the genomic level, gene copy number variations and promoter methylation have been shown to regulate *KLF5* expression. Some KLF5 upstream transcription factors and cofactors, including Sp1,[160] AR,[32] PR,[108] GR,[112] and EGR1,[128] have been reported in different cancers.

KLF5 mRNA should be regulated by miRNA, lncRNA, alternative splicing, and even RNA modifications. Finally, KLF5 proteins undergo different posttranslational modifications, including the well known phosphorylation, acetylation, ubiquitination, and SUMOylation. New posttranslational modifications of KLF5 will need further investigation.

It is difficult to target a transcription factor. Alternatively, new downstream effectors may be targeted. For example, KLF5 induces the expression of FGF-BP1, a secretory protein activating FGF signaling. An anti-FGF-BP1 antibody was developed to inhibit growth.[192,193] Ma et al showed that blocking the KLF5 target IGF1 with antibodies inhibited the STAT3/ matrix metalloproteinase 9 (MMP9) signaling pathway, thereby reducing the invasion of prostate cancer.[53]

Taken together, understanding the functions and functional and regulatory mechanisms of KLF5 will help us to better develop more effective targeted therapies for cancer treatment.

ACKNOWLEDGMENTS

This work was supported by the National Key Research and Development Program of China (2020YFA0112300 and 2018YFC2000400 to C. Chen), National Natural Science Foundation of China (81830087 and 31771516 to C. Chen),and project of Innovative Research Team of Yunnan Province (2019HC005).

DISCLOSURE

Authors have no conflict of interest.

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How to cite this article: Luo Y, Chen C. The roles and regulation of the KLF5 transcription factor in cancers. *Cancer Sci*. 2021;112:2097–2117. https://doi.org/10.1111/cas.14910