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 genetic 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.
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.\(^4\)

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, post-translational 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 Cd4 phosphate (CPD) motif\(^23\)(SPSSP), 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).\(^6,12,25\) 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 E2 synthase 1 (mPGES1),\(^26\) tumor necrosis factor-α (TNFa)-induced protein 2 (TNFAIP2),\(^27\) Slug,\(^2\) 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 translation 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.\(^5\)
| 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    | 12         |
|                            |                    | abnormally thinned and dilated; in response to vascular injury, the         |            |
|                            |                    | activation, proliferation, inflammation, and angiogenesis of fibroblasts and |            |
|                            |                    | smooth muscle cells are impaired.                                           |            |
| Heart                      | Klf5+/− mice       | have reduced heart weight, reduced fibrosis, and thinner heart               | 12         |
|                            |                    | ventricular walls.                                                          |            |
| Gastrointestinal tract     | Klf5+/− mice       | have malformed gastrointestinal villi, and decrease the number of          | 12         |
|                            |                    | extracellular matrix and mesenchymal cells.                                |            |
| Mammary gland              | Klf5 mammary       | gland-specific knockout mice can be observed to inhibit ductal elongation  | 7          |
|                            |                    | 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.                                  |            |
| Adipose tissue             | The development    | of white adipose tissue in Klf5+/− mice is delayed, and lipid droplets in   | 13         |
|                            | of adipocytes      | adipocytes are reduced. Klf5+/− mice can avoid obesity,                     |            |
|                            |                    | hypercholesterolemia and impaired glucose tolerance caused by high fat.    |            |
| 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  | 19         |
|                            |                    | have inhibited lung maturation during the cystic development stage.        |            |
|                            |                    | Phenotypic abnormalities appear in different components of bronchial        |            |
|                            |                    | 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.                                                             |            |
| Intestine                  | Intestinal-specific | deletion of Klf5 using Villin-Cre showed that Klf5 is required to maintain  | 16-18      |
|                            | deletion of Klf5   | gut epithelial cell proliferation, differentiation, and positioning         |            |
|                            | using Villin-Cre    | 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.          |            |
| Hematopoietic system       | Knockout mice of   | Klf5 have enlarged spleens and increased peripheral white blood cells; the | 195        |
|                            | Klf5               | 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.     |            |
| Eye                        | Klf5 was specifically | deleted in the ectoderm-derived structure of the ocular surface of mice,   | 196,197    |
|                            | deleted in the     | resulting in eyelid defects with malformed melobian glands, corneal        |            |
|                            | ectoderm-derived   | abnormalities, and loss of conjunctival goblet cells; Klf5 contributed to  |            |
|                            | structure of the   | corneal epithelial homeostasis via regulating the expression of desmosomal |            |
|                            | ocular surface of   | components.                                                                 |            |
|                            | mice, resulting in  | eyelid defects with malformed melobian glands, corneal abnormalities, and  |            |
|                            | eyelid defects     | loss of conjunctival goblet cells; Klf5 contributed to corneal epithelial  |            |
|                            | with malformed     | homeostasis via regulating the expression of desmosomal components.        |            |
| Prostate                   | Prostate-specific  | Klf5 heterozygous deletion mice induced hyperplasia with thicker cell layers| 14         |
|                            | Klf5               | in the lateral prostate, anterior prostate, and dorsal prostate; Klf5        |            |
|                            |                    | homozygous deletion caused prostate epithelial cell apoptosis instead of    |            |
|                            |                    | hyperplasia.                                                               |            |
| Klf5 transgenic (Tg) mice  | Prostate           | Knockin of the Klf5^{K358R} gene in mouse model, the prostate has changed,   | 15         |
|                            |                    | 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.                                         |            |
| Skin                       | Klf5 transgenic    | mice showed craniofacial defects, extracerebral malformations, persistent  | 198        |
|                            | mice               | abdominal herniation, and ectodermal dysplasia; overexpression of Klf5 in  |            |
|                            |                    | adult mice resulted in hair follicle occlusion, hyperkeratosis and         |            |
|                            |                    | epidermal erosion.                                                         |            |
| Esophagus                  | Esophageal epithelial cells specifically overexpress Klf5 in ED-L2/Klf5    | mouse suprabasal cells without proliferation, but have increased            | 199        |
|                            |                    | mouse suprabasal cells without proliferation, but have increased            |            |
|                            |                    | proliferation of basal cells.                                              |            |
autophagy in prostate cancer cells. KLF5 activates tumor necrosis factor receptor superfamily member 11a (TNFRSF11a) gene transcription by binding to the TNFRSF11a gene promoter in cervical cancer. In non–small-cell lung cancer (NSCLC), KLF5 promotes the expression of growth differentiation factor 15 (GDF15) and cell proliferation induced by C5a. Moreover, KLF5 activates the transcription of E2F transcription factor 1 (E2F1) and RAD51 recombinase (Rad51) in pancreatic cancer and promotes cell proliferation.

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 factors GATA binding protein 4/6 (GATA4/6) to regulate the transcription of downstream oncogenes Zn Zn Zn C C C

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).

KLF5 binds to E2F, which inhibits the expression of zinc finger E-Box binding homeobox 2 (ZEB2) and EMT in liver cancer cells. Additionally, KLF5 promotes miR-192 transcription, which inhibits the expression of zinc finger E-Box binding homeobox 2 (ZEB2) and EMT in liver cancer cells. Additionally, KLF5 activates the transcription of miR-124, miR-145 and miR-183 transcription, therefore inhibiting pituitary adenoma cell migration and invasion.

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

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) and TEA domain transcription factor 4 (TEAD4) 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. Moreover, KLF5 cooperates with the transcription factors GATA binding protein 4/6 (GATA4/6) to regulate the transcription of downstream oncogenes (i.e., hepatocyte nuclear factor 4α, HNF4α) in gastric cancer. Jiang et al found that KLF5 interacts with TP63 and SOX2 to regulate target gene transcription in ESCC. KLF5 binds to ERs in breast cancer and inhibits the transcriptional activity of estrogen receptor
In prostate cancer, estrogen receptor α (ERα) interacts with KLF5 to promote forkhead box O1 (FOXO1) transcription and suppress tumor growth.58 Nuclear early growth response 1 (EGR1) binds to enzymes that mediate posttranslational modifications. It has been reported that several E3 ligases, including WWP1,62 estrogen-responsive finger protein (EFP),63 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), 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 (OGT).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

| 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/TNFFR1                  | 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         |
| CASCl5                    | 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         |

**TABLE 2**-New identified KLF5 target genes in cancers

- α (ERα) interacts 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 and SMAD ubiquitination regulatory factor 2 (SMURF2),64 interact with KLF5 and promote KLF5 ubiquitination and degradation.
acetyltransferase general control non-derepressible 5 (GCN5) form a transcription complex to activate GDF15 gene transcription in NSCLC cells. Additionally, KLF5 was shown to interact with histone deacetylase 3 (HDAC3) to inhibit the transcription of BECN1. 

Cdk2-interacting protein (CINP) was identified as a new KLF5 interacting protein in bladder cancer. CINP knockdown attenuated the transcription of KLF5 target genes, including Cyclin D1 and Caspase 7, and therefore inhibited cell cycle progression and tumorigenesis. 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.

## 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. KLF5 expression is also inhibited in ccRCC cells by DNA methyltransferase 1 (DNMT1)-induced hypermethylation at exon 4. The expression of KLF5 can be recovered by knockdown of DNMT1 or the methylation inhibitor 5-Aza-Cdr.

### 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. KLF5 transcription was reported to be regulated by SE in various cancers. 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. In tumor cells with SE amplification, the average activation expression of KLF5 was upregulated by 39%. Next, we reported that SE maintains high expression levels of KLF5 in HCC1806 and HCC1937 breast cancer cell lines. 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.

### 5.3 | miRNAs inhibit KLF5 expression

KLF5 was reported to be targeted by multiple miRNAs, such as miR-217, miR-153, miR-145-5p, miR-152-3p, miR-519-3p, miR-590-5p, miR-4711-5p, miR-214-5p, miR-21-5p, miR-211, miR-320, and miR-375 in various cancers. Mifepristone induced the tumor suppressor miR-153 to suppress KLF5 expression and CSCs in TNBC. Interestingly, miR-153 also targets HIF-1α and angiopoietin 1 in response to hypoxia. miR-217 targeted KLF5 and suppressed TNBC cell growth, migration, and invasion. The tumor suppressor miR-145-5p targeted KLF5 and decreased the proliferation of gastric cancer and cervical carcinoma cells. The tumor suppressor miR-152 also targets KLF5 in cervical cancer. miR-519-3p inhibited bladder cancer cell proliferation and invasion by targeting KLF5, and miR-590-5p targeted KLF5 and inhibited cell proliferation, migration and tumor growth of bladder cancer. Consistently, miR-4711-5p suppressed colon cancer cell stemness and cell cycle progression in part by downregulating KLF5. miR-214-5p exerted a tumor suppressor function by targeting KLF5 in HCC. Crocin induced the expression of miR-320 to target KLF5 and inhibited the EMT, migration, and invasion of gastric cancer cells. miR-375 reduces the expression of KLF5 in oral squamous cell carcinoma.

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. miR-21 also plays a similar role in HCC and acute myeloid leukemia. miR-27a targeted FBW7 and indirectly increased KLF5 expression in ccRCC.

### 5.4 | LncRNA

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

### TABLE 3 New identified KLF5 interacting proteins

| Classification | KLF5 interacting proteins |
|----------------|---------------------------|
| Transcription factors | EGR1, GATA4/6, Miz-1, MYC, TEAD4, SMAD4, ERα/β, TP63, SOX2, AR, HIF-1α, HCF1 |
| Enzymes | HDAC3, SMURF2, FBW7, BAP1, USP3, ATXN3L, GCN5, GST3, EF, OGT1 |
| Others | CNP, TAZ, YAP |

Additionally, KLF5 was shown to interact with histone deacetylase 3 (HDAC3) to inhibit the transcription of BECN1. KLF5 was reported to be regulated by SE in various cancers. In prostate cancer, highly expressed miR-21 targeted KLF5 and promoted cancer cell proliferation, survival, migration, and invasion. miR-21 also plays a similar role in HCC and acute myeloid leukemia. miR-27a targeted FBW7 and indirectly increased KLF5 expression in ccRCC. Mifepristone induced the tumor suppressor miR-153 to suppress KLF5 expression and CSCs in TNBC. Interestingly, miR-153 also targets HIF-1α and angiopoietin 1 in response to hypoxia. miR-217 targeted KLF5 and suppressed TNBC cell growth, migration, and invasion. The tumor suppressor miR-145-5p targeted KLF5 and decreased the proliferation of gastric cancer and cervical carcinoma cells. The tumor suppressor miR-152 also targets KLF5 in cervical cancer. miR-519-3p inhibited bladder cancer cell proliferation and invasion by targeting KLF5, and miR-590-5p targeted KLF5 and inhibited cell proliferation, migration and tumor growth of bladder cancer. Consistently, miR-4711-5p suppressed colon cancer cell stemness and cell cycle progression in part by downregulating KLF5. miR-214-5p exerted a tumor suppressor function by targeting KLF5 in HCC. Crocin induced the expression of miR-320 to target KLF5 and inhibited the EMT, migration, and invasion of gastric cancer cells. miR-375 reduces the expression of KLF5 in oral squamous cell carcinoma.

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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.18 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.55 KLF5 S406 phosphorylation by extracellular signal regulated kinase 1/2 (ERK1/2) enhanced the interaction between KLF5 and C-JUN96 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 KLF5.9899 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.10 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 WWPP1-mediated ubiquitinated degradation.68101102 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.555666 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,19 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 mPGES126 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. Mammosphere formation and breast regeneration efficiency were suppressed in the absence of Klf5. Knockdown of KLF5 or Slug also reduced the number of acetaldehyde dehydrogenase positive (ALDH+) stem cells in 184B5 and MCF10A breast epithelial cell lines. Consistently, mifepristone, metformin, and miR153 suppressed breast CSCs by inhibiting KLF5 expression. Additionally, Klf5 is essential for maintaining the progenitor cells of prostate basal cells.

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

7.3 | Apoptosis and autophagy

Accumulating evidence suggests that KLF5 is a pro-survival protein. In pancreatic ductal adenomas, Klf5 blocked Sox4-induced apoptosis. In breast cancer, we found that KLF5 increases mitogen-activated protein kinase phosphatase 1 (MKP-1) protein stability to inhibit apoptosis. Dexamethasone (DEX) increases docetaxel and cisplatin resistance by upregulating KLF5 in TNBC. 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. KLF5 depletion markedly induced apoptosis of anaplastic thyroid carcinoma cells and increased doxorubicin sensitivity, and likely to be through inhibiting the JNK signaling pathway.

In contrast, ectopic KLF5 expression was reported to promote apoptosis in ESCC cells and in LNCaP prostate cancer cells in the presence of phorbol 12-myristate 13-acetate (PMA) by activating the JNK signaling pathway. Interestingly, KLF5 induced autophagy in castration-resistant prostate cancer cells by suppressing the transcription of BECN1. KLF5 knockdown decreased the sensitivity of prostate cancer cells to docetaxel. In A2058 melanoma cells, KLF5 knockdown increased autophagosomes and autolysosomes. 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). In agreement with this, miR-217 inhibits TNBC cell migration and invasion by targeting KLF5. Additionally, depletion of Klf5 in 4T1 mouse breast cancer cells significantly suppressed lung metastasis. KLF5 promoted cervical cancer migration and invasion by inducing TNFRSF11a expression. KLF5 promoted cell migration via the FYN/p-FAK axis in bladder cancer cells. Cholesterol accelerated ccRCC cell migration and invasion by inducing KLF5. Consistently, miR-4711-5p suppressed colon cancer cell migration and invasion by downregulating KLF5. miR-590-5p suppressed osteosarcoma cell migration and invasion by targeting KLF5. KLF5 knockdown reduced laryngeal carcinoma Hep-2 cell migration and invasion and EMT by inhibiting the NF-κB pathway. Similarly, KLF5 was reported to promote thyroid cancer metastasis by activating the NF-κB pathway. KLF5 activated LINC00346 transcription and promoted gastric cancer cell migration and invasion. Consistently, crocin inhibited EMT, migration, and invasion of gastric cancer cells partially through increasing the expression of miR-320, which targets KLF5. 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.

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. Consistently, KLF5 is required to maintain epithelial characteristics and prevent EMT induction in epithelial cells by inducing the expression of miR-200. TTK kinase induced the expression of ZEB1 and EMT in TNBC by inhibiting KLF5-induced miR-200 expression. In the absence of p53, KLF5 inhibits EMT in liver cancer cells through the miR-192/ZEB2 axis. miR-21 promoted prostate cancer cell migration and invasion by directly targeting KLF5. Similar results were observed in hepatocellular carcinoma. In ESCC, KLF5 loss inhibited notch receptor 1 (NOTCH1) expression and induced invasion when p53 was inactivated. 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 ApcMin mice by 96%, with decreased expression of Wnt target genes, including c-Myc and Cyclin D1. Consistently, KLF5 interacted with β-catenin to promote β-catenin nuclear localization. A subsequent study demonstrated that deletion of Klf5 in the gut epithelium
decreased epithelial proliferation, differentiation, and cell positioning along the crypt radial axis because of the disruption of canonical Wnt signaling. 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. 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. 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. 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. Pharmacological inhibition of MEK and PI3K kinases reduced KLF5 protein levels in mouse pancreatic cancer cells. We showed that KLF5 activates ERK in breast cancer by inducing the expression of FGF-BP1. Activated ERK phosphorylates and stabilizes the MKP-1 protein, which decreases MAPK phosphorylation as a negative feedback loop. Interestingly, Klf5 suppressed ERK activity in mESCs by inducing the transcription of Sprd1, a negative regulator of ERK signaling.

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. The latest research shows that knocking down BAP1 in melanoma cells also reduced the phosphorylation of PI3K, AKT and mTOR activated by KLF5. Additionally, KLF5 was reported to promote EMT of HCC by activating the PI3K/AKT/Snail signaling pathway. Furthermore, KLF5 increased the activities of both the PI3K/AKT and ERK1/2 signaling pathways, possibly by upregulating the expression of AEGF1 in glioma-associated endothelial cells. Consistently, miR-493-5p inhibited the proliferation and metastasis of osteosarcoma cells by downregulating KLF5 and inactivating the PI3K/AKT signaling pathway. Resveratrol inhibited the PI3K/protein kinase D1 (PKD1)/AKT pathway and increased KLF5 phosphorylation, which decreased its interaction with...
c-Myc in HEK293 cells. 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. 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. 

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), ML264, a small molecular inhibitor of KLF5, also inhibited the activation of STAT3 in osteosarcoma. However, KLF5 was reported to inhibit STAT3 activity and prostate cancer metastasis by suppressing IGF1 transcription. 

### 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. In brief, KLF5 was induced by progesterone in PR-positive breast cancer cells and promoted cell proliferation and dedifferentiation. Consistently, KLF5 expression is significantly increased in mouse mammary glands after pregnancy, and KLF5 is essential to maintain breast stemness. Mifepristone, a PR antagonist, not only blocked progesterone-induced KLF5 expression in PR-positive breast cancer cells but also inhibited the expression of KLF5 in TNBC by inducing miR-153.

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. 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. In agreement with these results, KLF5 is also an androgen-responsive gene in human breast carcinomas. Recently, KLF5 was shown to interact with AR to regulate the expression of AR target genes in prostate cancer cells. Additionally, acetylation of KLF5 at K369 is essential for androgen-mediated organoid organization and prostate regeneration.

Glucocorticoids, such as DEX and hydrocortisone, can also induce KLF5 expression through GR and confer docetaxel and cisplatin resistance in TNBC cell lines. This finding was supported by an independent study in which DEX-bound GR accelerated adipogenesis by directly promoting the expression of KLF5. Interestingly, glucocorticoids also induced the expression of several KLF5 interacting partners, such as TEAD4 and YAP, 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. It was also shown that 17β-estradiol suppressed KLF5-mediated FOXO1 and PDGFA transcription through ERβ in prostate cancer cells.

### 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. 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.

### 8.5 Hippo

The Hippo pathway regulates cell stemness, proliferation, survival, migration, and organ size. 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. Consistently, curcumin downregulated the expression of KLF5 by targeting YAP/TAZ and inhibited bladder cancer cell growth. 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. In agreement with this, TEAD4, similar to KLF5, promoted breast cancer stemness, cell growth, survival, metastasis, and chemoresistance. Furthermore, glucocorticoids also induced GR-dependent TEAD4 transcription, nuclear accumulation, and transcription complex formation. 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. 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. DAPT, a NOTCH signaling inhibitor, blocked the abnormal phenotype induced by Klf5 knockdown. 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.
Interestingly, KLF5, NOTCH, and MYC are substrates of the tumor suppressor SCFβTr7.145

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, IkBα 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 IkBα 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 TNFα-dependent 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 deletion resulted in the inhibition of villus morphogenesis and intestinal epithelial differentiation.15 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.112 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 mPGES1,16 TNFAIP2,27 and Cyclin D1 and inhibiting transcription of p2726 and p21.26 KLF5 maintains cell stemness by inducing the transcription of Slug2 and Nanog.4 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. Glucocorticoids also induce KLF5 expression through GR and confer docetaxel and cisplatin resistance to TNBC cells. PVT1 directly interacts with KLF5 and recruits BAP1 to stabilize the KLF5 protein in breast cancer. CASC15 functions as a competitive endogenous RNA for miR-153-3p, which targets KLF5. Interestingly, CASC15 is also a direct target gene of KLF5; therefore, a positive feedback loop is formed to accelerate breast tumor progression. Several drugs or compounds, such as mifepristone and its derivatives, metformin, and mithramycin A, 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.

### 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. Androgen induces KLF5 and CXCR4 expression and promotes prostate cancer cell migration in vitro. This conclusion is supported by a recent study, in which acetylated KLF5 promoted bone metastasis by activating CXCR4. In two androgen-responsive prostate cancer cell lines, C4-2B and LNCaP, the expression of KLF5 was upregulated by androgen/AR. 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. Estrogen (17β-estradiol) promoted prostate tumor angiogenesis through the ERβ/KLF5 pathway.

However, a line of evidence also supports that KLF5 is a tumor suppressor in prostate cancer. The KLF5 gene is located at chromosome 13q21 and is frequently deleted in prostate cells. A low expression level of KLF5 was correlated with poor prognosis in prostate cancer patients. Klf5 deletion promoted PTEN deletion-initiated luminal-type mouse prostate tumors. KLF5 inhibited angiogenesis in PTEN-deficient prostate cancer by attenuating AKT activation and HIF-1α accumulation. TNFα induced the expression of KLF5 in LNCaP cells and increased the levels of phosphorylation of JNK and apoptosis in response to PMA. Consistently, KLF5 upregulated the transcription of MKK7, the upstream kinase of JNK, and promoted TNFα-induced apoptosis in LNCaP cells.

### 9.3 Bladder cancer

KLF5 plays an important role in the normal development of mouse bladder tissue. Our early study indicated that KLF5 promotes bladder cancer cell proliferation. KLF5 can bind to a Cyclin E1 gene enhancer to activate its transcription and increase susceptibility to bladder cancer. In addition, KLF5 promotes bladder cancer cell migration by increasing the expression of FYN. Furthermore, KLF5 promotes angiogenesis in bladder cancer by directly increasing vascular endothelial growth factor A (VEGFA) transcription. 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.

### 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. 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. In contrast, DNMT1-mediated KLF5 promoter hypermethylation inhibits KLF5 expression. KLF5 was shown to inhibit ccRCC xenograft tumor growth and metastasis. The deubiquitinase BAP1 was reported to stabilize KLF5. Interestingly, the BAP1 gene is mutated in ~15% of ccRCC, which also defines a new subtype of renal cell carcinoma. 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. 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. Consistently, Klf5 deletion in the intestinal epithelium using Shh-Cre inhibited villus morphogenesis and epithelial differentiation. Furthermore, depletion of Klf5 in Lgr5+ stem cells disrupts the integrity and oncogenicity of intestinal stem cells. Klf5 haploinsufficiency rescued the intestinal tumor formation induced by APCMin/+ because KLF5 promotes the
nuclear translocation of β-catenin and upregulates the expression of CyclinD1 and Myc.\textsuperscript{123} Similarly, KLF5 haploinsufficiency also decreased intestinal tumor formation in APC\textsuperscript{Min}+/KRASV12 mice.\textsuperscript{169} KLF5 is also essential for intestinal epithelial cell proliferation and transformation by oncocgenic KRAS\textsuperscript{G12D} \textsuperscript{196,170}.

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.\textsuperscript{24} The KLF5 P301S mutation also increased the stability and transcriptional activity of KLF5 in CRC.\textsuperscript{171} The tumor suppressors miR-143 and miR-145 can downregulate the expression of KLF5 in CRC.\textsuperscript{157} LINCO0908 is highly expressed in CRC and promotes cell proliferation and survival through the miR-143-3p/KLF5 axis.\textsuperscript{94} LPA induced HIF-1α through KLF5 in colon cancer cell lines.\textsuperscript{157} Recently, KLF5 was reported to induce IncRNA SNHG12 expression and to promote invasion and metastasis of CRC.\textsuperscript{47} KLF5 also induces the transcription of the intestinal differentiation marker gene alkaline phosphatase.\textsuperscript{173} ML264 was identified as a KLF5 inhibitor that effectively inhibited the expression of KLF5 and the growth of CRC xenograft tumors.\textsuperscript{128} ML264 appears to inhibit the expression of KLF5 by inhibiting its upstream transcription factor EGR1, although the exact mechanism is unknown.\textsuperscript{128}

### 9.6 Esophageal squamous cell cancer

Esophageal cancer is a common malignant tumor, and its 5-7 survival rate is less than 20%. Squamous cell carcinoma (51.6%) or adenocarcinoma (41.9%) accounts for more than 90% of esophageal cancers.\textsuperscript{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.\textsuperscript{115} In abnormally proliferating esophageal squamous epithelial cells, KLF5 promotes NOTCH1 transcription in the context of p53 mutation or loss.\textsuperscript{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.\textsuperscript{115}

In contrast, KLF5 interacts with TCF3 to induce LINCO0909 transcription, thereby promoting the growth of ESCC.\textsuperscript{42} In ECA109 cells, BAP1 can promote cell proliferation and migration by upregulating KLF5.\textsuperscript{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.\textsuperscript{37} This study also reported that the combination of the HDAC inhibitor romidepsin and the BET inhibitor ARV-771 can synergistically inhibit ESCC.\textsuperscript{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.\textsuperscript{56} Crocin can induce miR320 to target both KLF5 and HIF-1α to inhibit EMT in gastric cancer cells.\textsuperscript{83} Interestingly, miR153 also targets both KLF5 \textsuperscript{75} and HIF-1α.\textsuperscript{85} Furthermore, miR-145-5p targets KLF5 and promotes gastric cancer cell differentiation.\textsuperscript{76} In addition, KLF5 and MYC induce the transcription of LINCO0346 to promote gastric cancer tumorigenesis.\textsuperscript{45} KLF5 can activate the transcription of IncRNA NEAT1, which recruits BRG1 to silence the transcription of GADD45A and promotes gastric cancer cell proliferation and survival.\textsuperscript{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.\textsuperscript{175} Zhang et al showed that the expression of KLF5 has no relationship with the prognosis of gastric cancer patients.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{132} KLF5 promotes HCC growth and metastasis by activating PI3K/AKT/Snail signaling.\textsuperscript{132} Consistently, the tumor suppressor miR-145-5p inhibits HCC cell proliferation and migration by targeting KLF5.\textsuperscript{178} In contrast, miR-21 promotes the migration and invasion of HuH7 cells by targeting KLF5.\textsuperscript{190} In HCC, the function of KLF5 may depend on the p53 status.\textsuperscript{49} When WT p53 is present in HepG2 cells, KLF5 does not regulate cell migration.\textsuperscript{49} When p53 is inactivated in Hep3B cells, KLF5 inhibits ZEB2 expression and EMT by promoting miR-192.\textsuperscript{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.\textsuperscript{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.\textsuperscript{41} In pancreatic cancer, KLF5 is induced by IL-1β through p38 and hypoxia through HIF-1α.\textsuperscript{156} In pancreatic cancer with p53 mutation, KLF5 induced PLA2G16 expression to promote glycolysis.\textsuperscript{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.\textsuperscript{179}
9.10 | Lung cancer

Klf5 is essential for mouse lung development.\textsuperscript{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.\textsuperscript{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.\textsuperscript{112} KLF5 depletion can overcome cisplatin resistance in NSCLC.\textsuperscript{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.\textsuperscript{51} Moreover, KLF5 knockdown inhibited hypoxia-induced HIF-1α expression, the PI3K/AKT/mTOR pathway, glycolysis, and cisplatin resistance in NSCLC cells.\textsuperscript{131} In A549 cells, KLF5 interacted with GCN5 to induce the expression of GDF15 and promoted cell proliferation and tumor growth.\textsuperscript{69} However, it was reported that Klf5 was not necessary in the mouse K-RasG12D lung tumorigenesis model.\textsuperscript{54} In this study, KLF5 expression was positively correlated with better disease-specific survival of patients with NSCLC.\textsuperscript{54}

9.11 | Leukemia

KLF5 interacted with p53 to induce survivin gene transcription and increase the survival of acute lymphoblastic leukemia cells.\textsuperscript{181} However, KLF5 was downregulated in acute myeloid leukemia blast cells because of promoter methylation.\textsuperscript{59,182,183} Low expression of KLF5 was associated with poor overall survival in acute myeloid leukemia patients.\textsuperscript{183} In acute myeloid leukemia, miR-21 targeted KLF5 and promoted the proliferation of acute myeloid leukemia cells in vitro.\textsuperscript{91} The expression of KLF5 was also downregulated in BCR-ABL\textsuperscript{+} B-ALL leukemia.\textsuperscript{92} In B-cell acute lymphoblastic leukemia cells, overexpression of KLF5 can induce imatinib-resistant cell apoptosis by increasing oxidative stress.\textsuperscript{35}

9.12 | Ovarian cancer

KLF5 was highly expressed in SKOV3 ovarian cancer cells and was positively correlated with high levels of survivin.\textsuperscript{184} Knockdown of KLF5 sensitized SKOV3 cells to cisplatin or paclitaxel treatment.\textsuperscript{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.\textsuperscript{185} The KLF5/TNFRSF11a axis promoted the proliferation, migration and invasion of cervical cancer cells.\textsuperscript{59} TNFα induced the expression of KLF5 in cervical cancer by activating the p38 signaling pathway.\textsuperscript{39} miR-152 and miR-145-5p inhibited cervical cancer cell proliferation by directly inhibiting the expression of KLF5.\textsuperscript{87,89} Consistently, LINCO0337 maintained tumor stem cell-like characteristics by downregulating miR-145 and increasing the expression of KLF5.\textsuperscript{88}

9.14 | Head and neck cancer

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

9.15 | Melanoma

In melanoma, KLF5 promoted tumor growth.\textsuperscript{103} Clinical data showed that KLF5 was highly expressed in melanoma patients, and the WWP1 gene was also downregulated.\textsuperscript{103} It was observed in A2058 melanoma cells that KLF5 knockdown decreased cell proliferation, migration, and invasion, but increased autophagy.\textsuperscript{103} The transplanted tumor experiments in mice also further verified the cancer-promoting effect of KLF5 in melanoma.\textsuperscript{103} Previous studies have found that KLF5 is downregulated in Ras mutant melanoma cell lines.\textsuperscript{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.\textsuperscript{31} In pituitary adenoma cells, KLF5 upregulated the expression levels of miR-124, miR-145, and miR-148 and inhibited cell migration and invasion.\textsuperscript{51} In addition, KLF5 is downregulated in nasopharyngeal carcinoma and Ras mutant melanoma cell lines.\textsuperscript{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.\textsuperscript{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.\textsuperscript{75} Two mifepristone-derived compounds, FZU-00,003 and FZU-00,004, showed higher efficiency.\textsuperscript{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.⁵ 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.⁷² JQ-1-derived compound 870 showed better efficacy.⁷² 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 KLF5 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 TNFa³⁹ 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.⁵⁷,⁶⁰ 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, AR, PR, GR, and EGR1, 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. 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.

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REFERENCES
1. McConnell BB, Yang VW. Mammalian Kruppel-like factors in health and diseases. Physiol Rev. 2010;90:1337-1381.
2. Kaczyński J, Cook T, Urrutia R. Sp1- and Kruppel-like transcription factors. Genome Biol. 2003;4:206.
3. Dang DT, Pevsner J, Yang VW. The biology of the mammalian Kruppel-like family of transcription factors. Int J Biochem Cell Biol. 2000;32:1103-1121.
4. Chen C, Benjamin MS, Sun X, et al. KLF5 promotes cell proliferation and tumorigenesis through gene regulation and the TSU-Pr1 human bladder cancer cell line. Int J Cancer. 2006;118:1346-1355.
5. Wang C, Nie Z, Zhou Z, et al. The interplay between TEAD4 and KLF5 promotes breast cancer partially through inhibiting the transcription of p27Kip1. Oncotarget. 2015;6:17685-17697.
6. Shi P, Liu W, Tala, et al. Metformin suppresses triple-negative breast cancer stem cells by targeting KLF5 for degradation. Cell Discov. 2017:3:17010.
7. Liu R, Shi P, Zhou Z, et al. Krüppel-like factor 5 is essential for mammary gland development and tumorigenesis. J Pathol. 2018;246:497-507.
8. Dong JT, Chen C. Essential role of KLF5 transcription factor in cell proliferation and differentiation and its implications for human diseases. Cell Mol Life Sci. 2009;66:2691-2706.
9. Diakiw SM, D’Andrea RJ, Brown AL. The double life of KLF5: Opposing roles in regulation of gene-expression, cellular function, and transformation. IUBMB Life. 2013;65:999-1011.
10. Liu R, Dong JT, Chen C. Role of KLF5 in hormonal signaling and breast cancer development. Vitam Horm. 2013;93:213-225.
11. Gao Y, Ding Y, Chen H, Chen H, Zhou J. Targeting Krüppel-like factor 5 (KLF5) for cancer therapy. Curr Top Med Chem. 2015;15:699-713.
12. Shindo T, Manabe I, Fukushima Y, et al. Krüppel-like zinc-finger transcription factor KLF5/BTEB2 is a target for angiotensin II signaling and an essential regulator of cardiovascular remodeling. Nat Med. 2002;8:856-863.
13. Oishi Y, Manabe I, Tobe K, et al. Krüppel-like transcription factor KLF5 is a key regulator of adipocyte differentiation. Cell Metab. 2005;1:27-39.
14. Xing C, Fu X, Sun X, Guo P, Li M, Dong JT. Different expression patterns and functions of acetylated and unacetylated Klf5 in the proliferation and differentiation of prostatic epithelial cells. PLoS One. 2013;8:e65538.
15. Zhang B, C.X, Tao R, et al. KLF5 acetylation regulates luminal differentiation of basal progenitors in prostate development and regeneration. Nat Commun. 2020;11:997.
16. McConnell B, Kim S, Yu K, et al. Krüppel-like factor 5 is important for maintenance of crypt architecture and barrier function in mouse intestine. Gastroenterology. 2011;141:1302-1313, 1313.e1301-1306.
17. Bell SM, Zhang L, Xu Y, et al. Kruppel-like factor 5 controls villus formation and initiation of cytidifferentiation in the embryonic intestinal epithelium. Dev Biol. 2013;375:128-139.
18. Nakaya T, Ogawa S, Manabe I, et al. KLF5 regulates the integrity and oncogenicity of intestinal stem cells. Can Res. 2014;74:2882-2891.
19. Wan H, Luo F, Wert SE, et al. Krüppel-like factor 5 is required for perinatal lung morphogenesis and function. Development. 2008;135:2563-2572.
20. Du JX, Bialkowska AB, McConnell BB, Yang VW. SUMOylation regulates nuclear localization of Krüppel-like factor 5. J Biol Chem. 2008;283:31991-32002.
21. Shao M, Ge GZ, Liu WJ, et al. Characterization and phylogenetic analysis of Krüppel-like transcription factor (KLF) gene family in tree shrews (Tupaia belangericheniis). Oncotarget. 2017;8:16325-16339.
22. Zhao D, Zheng HQ, Zhou Z, Chen C. The Fbw7 tumor suppressor targets KLF5 for ubiquitin-mediated degradation and suppresses breast cell proliferation. Can Res. 2010;70:4728-4738.
23. Zhi X, Chen C. WWP1: a versatile ubiquitin E3 ligase in signaling and diseases. Cell Mol Life Sci. 2012;69:1425-1434.
24. Zhang X, Choi PS, Francis JM, et al. Somatic superenhancer duplications and hotspot mutations lead to oncogenic activation of the KLF5 transcription factor. Cancer Discov. 2018;8:108-125.
25. Zheng HQ, Zhou Z, Huang J, Chaudhury L, Dong JT, Chen C. Kruppel-like factor 5 promotes breast cell proliferation partially through upregulating the transcription of fibroblast growth factor binding protein 1. Oncogene. 2009;28:3702-3713.
26. Xia H, Wang C, Chen W, et al. Krüppel-like factor 5 transcription factor promotes microsomal prostaglandin E2 synthase 1 gene transcription in breast cancer. J Biol Chem. 2013;288:26731-26740.
27. Jia L, Zhou Z, Liang H, et al. KLF5 promotes breast cancer proliferation, migration and invasion in part by upregulating the transcription of TNFAIP2. Oncogene. 2016;35:2040-2051.
28. Zhang L, Wu Y, Wu J, et al. KLF5-mediated COX2 upregulation contributes to tumorigenesis driven by PTEN deficiency. Cell Signal. 2020;75:10976.

29. Pattison JM, Posternak V, Cole MD. Transcription factor KLF5 binds a cyclin E1 promyelocytic intronic enhancer to confer increased bladder cancer risk. Mol Cancer Res. 2016;14:1078-1086.

30. Du C, Gao Y, Xu S, et al. KLF5 promotes cell migration by up-regulating FYN in bladder cancer cells. FEBS Lett. 2016;590:408-418.

31. Yang C, Zheng J, Xue Y, et al. The effect of MCM3AP-AS1/miR-211/KLF5/AGGF1 axis regulating glioblastoma angiogenesis. Front Mol Neurosci. 2017;10:437.

32. Li J, Zhang B, Liu M, et al. KLF5 is crucial for androgen-ar signaling to transactivate genes and promote cell proliferation in prostate cancer cells. Cancers. 2020;12:748.

33. Ishikawa ET, Chang KH, Nayak R, et al. Klf5 controls bone marrow homing of stem cells and progenitors through Rab5-mediated beta 1/beta 2-integrin trafficking. Nat Commun. 2013;4:1660.

34. Xia W, Bai H, Deng Y, Yang Y. PLA2G16 is a mutant p53/KLF5 transcriptional target and promotes glycolysis of pancreatic cancer. Cell Signal. 2019;107:100065.

35. Yang C, Zheng J, Xue Y, et al. The effect of MCM3AP-AS1/miR-211/KLF5/AGGF1 axis regulating glioblastoma angiogenesis. Front Mol Neurosci. 2017;10:437.

36. Shi QI, Gao Y, Xu S, et al. Krüppel-like factor 5 promotes apoptosis triggered by tumor necrosis factor α in LNCaP prostate cancer cells via up-regulation of mitogen-activated protein kinase kinase 7. Urol Oncol. 2016;34(58):58.e11-58.e18.

37. Jiang Y-Y, Jiang Y, Li C-Q, et al. TP63, SOX2, and KLF5 establish a core regulatory circuitry that controls epigenetic and transcription patterns in esophageal squamous cell carcinoma cells. Gastroenterology. 2020;159:1311-1327.e1319.

38. Jia J, Zhang H-B, Shi QI, et al. KLF5 downregulation desensitizes castration-resistant prostate cancer cells to docetaxel by increasing BECN1 expression and inducing cell autophagy. Thera nosics. 2019;5:5464-5477.

39. Ma D, Chang L-Y, Zhao S, et al. KLF5 promotes cervical cancer proliferation, migration and invasion in a manner partly dependent on TNFRSF11a expression. Sci Rep. 2017;7:15683.

40. Zhao C, Li Y, Qiu W, et al. Csa induces A549 cell proliferation of non-small cell lung cancer via GDF15 gene activation mediated by GCNS-dependent KLF5 acetylation. Oncogene. 2018;37:4821-4837.

41. Li Y, Kong R, Chen H, et al. Overexpression of KLF5 is associated with poor survival and G1/S progression in pancreatic cancer. Aging. 2019;11:5035-5057.

42. Wang Q-Y, Peng L, Chen Y, et al. Characterization of super-enhancer-associated functional IncRNAs acting as ceRNAs in ESCC. Mol Oncol. 2020;14(9):2203-2220.

43. Jia X, Shi L, Wang X, et al. KLF5 regulated IncRNA RP1 promotes the growth and metastasis of breast cancer via repressing p27kip1 translation. Cell Death Dis. 2019;10:373.

44. Yu L, Xu Q, Yu W, Duan J, Dai G. LncRNA cancer susceptibility candidate 15 accelerates the breast cancer cells progression via miR-153-3p/KLF5 positive feedback loop. Biochem Biophys Res Comm. 2018;506:819-825.

45. Xu T-P, Ma P, Wang W-Y, et al. KLF5 and MYC modulated LINC00346 contributes to gastric cancer progression through acting as a competing endogenous RNA and indicates poor outcome. Cell Death Differ. 2019;26:2179-2193.

46. Ma P, Pan Y, Yang F, et al. KLF5-Modulated IncRNA NEAT1 contributes to tumorigenesis by acting as a scaffold for BRG1 to silence GADD45A in gastric cancer. Mol Ther Nucleic Acids. 2020;22:382-395.

47. Liao QI, Chen L, Zhang N, et al. Network analysis of KLF5 targets showing the potential oncogenic role of SNHG12 in colorectal cancer. Cancer Cell Int. 2020;20:439.
67. Wu Q, Fu C, Li M, et al. CINP is a novel cofactor of KLF5 required for its role in the promotion of cell proliferation, survival and tumor growth. *Int J Cancer*. 2019;144:582-594.

68. Gao Y, Shi Q, Xu S, et al. Curcumin promotes KLF5 proteasome degradation through downregulating YAP/TAZ in bladder cancer cells. *Int J Mol Sci*. 2014;15:15173-15187.

69. Diakiw SM, Kok CH, To LB, Lewis ID, Brown AL, D’Andrea RJ. The granulocyte-associated transcription factor Kruppel-like factor 5 is silenced by hypermethylation in acute myeloid leukemia. *Leuk Res*. 2012;36:110-116.

70. Fu R-J, He W, Wang X-B, et al. DNM1L-maintained hypermethylation of Kruppel-like factor 5 involves in the progression of clear cell renal cell carcinoma. *Cell Death Dis*. 2017;8:e2952.

71. Shi W, Yang J, Li S, et al. Potential involvement of miR-375 in the premalignant progression of oral squamous cell carcinoma. *Cell Death Dis*. 2019;12:e01733.

72. Hnisz D, Abraham B, Lee T, et al. Super-enhancers in the control of cell identity and disease. *Cell*. 2013;155:934-947.

73. Chen C-H, Yang N, Zhang Y, et al. Inhibition of super enhancer downregulates the expression of KLF5 in basal-like breast cancers. *Int J Biol Sci*. 2019;15:1733-1742.

74. Zhou W, Song F, Wu Q, et al. miR-217 inhibits triple-negative breast cancer cell growth, migration, and invasion through targeting KLF5. *PloS One*. 2017;12:e017635.

75. Liu R, Shi P, Nie Z, et al. Mifepristone suppresses basal triple-negative breast cancer stem cells by down-regulating KLF5 expression. *Theranostics*. 2016;6:533-544.

76. Zhou T, Chen S, Mao X. miR-145-5p affects the differentiation of gastric cancer by targeting KLF5 directly. *J Cell Physiol*. 2019;234:7634-7644.

77. Luo S, Ding S, Liao J, et al. Excessive miR-152-3p results in increased BAFF expression in SLE B-cells by inhibiting the KLF5 expression. *Front Immunol*. 2019;10:1127.

78. Jiang Z, Zhang Y, Cao R, et al. miR-5195-3p inhibits proliferation and invasion of human bladder cancer cells by targeting KLF5. *Oncol Lett*. 2019;17:115-121.

79. Cao H, Pan G, Tang S, et al. miR-145-5p regulates the proliferation, migration and invasion in cervical carcinoma by targeting KLF5. *Oncol Targets Ther*. 2020;13:2369-2376.

80. Han Q, Wu W, Cui Y. LINCO0337 regulates KLF5 and maintains stem-cell like traits of cervical cancer cells by modulating miR-145. *Front Oncol*. 2020;10:1433.

81. Zhang H, Lu Y, Wang S, Sheng X, Zhang S. MicroRNA-152 acts as a tumor suppressor microRNA by inhibiting Krüppel-Like Factor 5 in human cervical cancer. *Oncol Res*. 2019;27:335-340.

82. Wang J, Chu Y, Xu M, Zhang X, Zhou Y, Xu M. miR-21 promotes cell migration and invasion of hepatocellular carcinoma by targeting KLF5. *Oncol Lett*. 2019;17:2221-2227.

83. Li C, Yan H, Yin J, et al. MicroRNA-21 promotes proliferation in acute myeloid leukemia by targeting Kruppel-like factor 5. *Oncol Lett*. 2019;18:3367-3372.

84. Liu T, Wang X, Zhai J, Wang Q, Zhang B. Long noncoding RNA UCA1 facilitates endometrial cancer development by regulating KLF5 and RXFP1 gene expressions. *Cancer Biol Ther*. 2020. https://doi.org/10.1089/cbr.2019.3278.

85. Tang J, Li Y, Song Y, et al. LncRNA PVT1 regulates triple-negative breast cancer through KLF5/beta-catenin signaling. *Oncogene*. 2018;37:4723-4734.

86. Shan T-D, Tian Z-B, Li Q, et al. Long intergenic noncoding RNA 00908 promotes proliferation and inhibits apoptosis of colorectal cancer cells by regulating KLF5 expression. *J Cell Physiol*. 2021;236:889-899.

87. Zhang Z, Teng CT. Phosphorylation of Kruppel-like factor 5 (KLF5/IKLF) at the CBP interaction region enhances its transactivation function. *Nucleic Acids Res*. 2003;31:2196-2208.

88. He M, Han M, Zheng B, Shu YN, Wen JK. Angiotensin II stimulates KLF5 phosphorylation and its interaction with c-Jun leading to suppression of p21 expression in vascular smooth muscle cells. *J Biochem*. 2009;146:683-691.

89. Zhang XH, Zhang B, Sheng X, Zhang S. MicroRNA-152 acts as a tumor suppressor microRNA by inhibiting Krüppel-Like Factor 5 in human cervical cancer. *Oncol Res*. 2012;36:110-116.

90. Tang J, Li Y, Sang Y, et al. Long noncoding RNA UCA1 facilitates endometrial cancer development by regulating KLF5 and RXFP1 gene expressions. *Cancer Biol Ther*. 2019;20:1149-1161.

91. Jia X, Chen H, Ren Y, et al. BAP1 antagonizes WWP1-mediated KLF5 degradation and promotes breast cell proliferation via targeting KLF5. *Oncol Res*. 2019;15:1733-1742.

92. Liu T, Wang X, Zhai J, Wang Q, Zhang B. Long noncoding RNA UCA1 facilitates endometrial cancer development by regulating KLF5 and RXFP1 gene expressions. *Cancer Biol Ther*. 2019;20:1149-1161.

93. Zhang J, Zhang Z, Wang X, Liu S, Teng CT. Isolation and characterization of a gene encoding human Kruppel-like factor 5 (IKLF): binding site and promoter regions. *J Biochem*. 1993;21:1527-1532.

94. Zhi X, Zhao D, Zhou Z, Liu R, Chen C. YAP promotes breast cell proliferation and survival partially through stabilizing the KLF5 transcription factor. *Am J Pathol*. 2012;180:2452-2461.

95. Tao R, Zhang B, Li Y, et al. HDAC-mediated deacetylation of KLF5 associates with its proteasomal degradation. *Biochem Biophys Res Comm*. 2018;500:777-782.

96. Chen C, Sun X, Ran Q, et al. Ubiquitin-proteasome degradation of KLF5 transcription factor in cancer and untransformed epithelial cells. *Oncogene*. 2005;24:3319-3327.

97. Shi H, Zhang Z, Wang X, Liu S, Teng CT. Isolation and characterization of a gene encoding human Kruppel-like factor 5 (IKLF): binding site and promoter regions. *J Biochem*. 1993;21:1527-1532.

98. Han Q, Wu W, Cui Y. LINCO0337 regulates KLF5 and maintains stem-cell like traits of cervical cancer cells by modulating miR-145. *Front Oncol*. 2020;10:1433.
Bell SM, Zhang L, Mendell A, et al. Kruppel-like factor 5 is required for formation and differentiation of the bladder urothelium. Dev Biol. 2011;358:79-90.

Liu R, Zhou Z, Zhao D, Chen C. The induction of KLF5 transcription factor by progesterone contributes to progesterone-induced breast cancer cell proliferation and dedifferentiation. Mol Endocrinol. 2011;25:1137-1144.

Bourillot PY, Savatier P. Krüppel-like transcription factors and control of pluripotency. BMC Biol. 2010;8:125.

David CJ, Huang YH, Chen M, et al. TGF-beta tumor suppression through a lethal EMT. Cell. 2016;164:1015-1030.

Liu R, Zheng HQ, Zou Z, Dong JT, Chen C. KLF5 promotes breast cell survival partially through fibroblast growth factor-binding protein 1-pERK-mediated dual specificity MAPK-1 protein phosphorylation and stabilization. J Biol Chem. 2009;284:16791-16798.

Li Z, Dong J, Zou TN, et al. Dexamethasone induces docetaxel and cisplatin resistance-partially through up-regulating Kruppel-like factor 5 in triple-negative breast cancer. Oncotarget. 2017;8:11555-11565.

Zhang H, Shao F, Guo W, Gao Y, He J. Knockdown of KLF5 promotes cisplatin-induced cell apoptosis via regulating DNA damage checkpoint proteins in non-small cell lung cancer. Thorac Cancer. 2019;10:1069-1077.

Wang Z, Qiu X, Zhang H, Li W. KLF5 influences cell biological function and chemotherapy sensitivity through the JNK signaling pathway in anaplastic thyroid carcinoma. J Biochem Mol Toxicol. 2020;34:e22469.

Tarapore RS, Yang Y, Katz JP. Restoring KLF5 in esophageal squamous cell cancer cells activates the JNK pathway leading to apoptosis and reduced cell survival. Neoplasia. 2013;15:472-480.

Shi Qi, Jia J, Hui KE, et al. KLF5 promotes apoptosis induced by phorbol ester as an effector of the autocrine factor TNFα in LNCaP prostate cancer cells. Oncol Lett. 2017;14:1847-1854.

Liu FF, Dong L, Yang X, Li DJ, Shen YY, Liu ZL. KLF5 silence attenuates proliferation and epithelial-mesenchymal transition induction in Hep-2 cells through NF-κB signaling pathway. Eur Rev Med Pharmacol Sci. 2019;23:3867-3875.

Ma Y, Wang Q, Liu F, et al. KLF5 promotes the tumorigenesis and metastatic potential of thyroid cancer cells through the NF-kappaB signaling pathway. Oncol Rep. 2018;40:2608-2618.

Wang F, Luo M, Qu H, Cheng Y. BAP1 promotes viability and migration of ECA109 cells through KLF5/CyclinD1/FGF-BP1. FEBS Open Bio. 2021. https://doi.org/10.1002/2211-5463.13105.

Shimamura T, Imoto S, Shimada Y, et al. A novel network profiling analysis reveals system changes in epithelial-mesenchymal transition. PLoS One. 2011;6:e20804.

King JL, Zhang B, Li Y, et al. TTK promotes mesenchymal signaling via multiple mechanisms in triple negative breast cancer. Oncogenesis. 2018;7:69.

Yang Y, Nakagawa H, Tetreault MP, et al. Loss of transcription factor KLF5 in the context of p53 ablation drives invasive progression of human squamous cell cancer. Cancer Res. 2011;71:6475-6484.

McConnell BB, Bialkowska AB, Nandan MO, Ghaele AM, Gordon FJ, Yang VW. Haploinsufficiency of Krüppel-like factor 5 rescues the tumor-initiating effect of the Apc(Min) mutation in the intestine. Cancer Res. 2009;69:4125-4133.

Kim C-K, Saxena M, Maharjan K, et al. Krüppel-like Factor 5 regulates stemness, lineage specification, and regeneration of intestinal epithelial stem cells. Cell Mol Gastroenterol Hepatol. 2020;9:587-609.

Goswami S, Gao N. KLF5 governs stemness in the adult intestinal stem cell niche. Cell Mol Gastroenterol Hepatol. 2020;9:705-706.

Wei X, Ye J, Shang Y, et al. Ascl2 activation by YAP1/KLF5 ensures the self-renewability of colon cancer progenitor cells. Oncotarget. 2017;8:109301-109318.

Gao Y, Wu K, Chen Y, et al. Beyond proliferation: KLF5 promotes angiogenesis of bladder cancer through directly regulating VEGFA transcription. Oncotarget. 2015;6:43791-43805.

Ruiz de Sabando A, Wang C, He Y, et al. ML264, a novel small-molecule compound that potently inhibits growth of colorectal cancer. Mol Cancer Ther. 2016;15:72-83.

He P, Yang JW, Yang VW, Bialkowska AB. Krüppel-like Factor 5, increased in pancreatic ductal adenocarcinoma, promotes proliferation, acinar-to-ductal metaplasia, pancreatic intraepithelial neoplasia, and tumor growth in mice. Gastroenterology. 2018;154:1494-1508.e1413.

Azami T, Matsumoto K, Jeon H, et al. Klf5 suppresses ERK signaling in mouse pluripotent stem cells. PLoS One. 2018;13:e0207321.

Gong T, Cui L, Wang H, Wang H, Han N. Knockdown of KLF5 suppresses hypoxia-induced resistance to cisplatin in NSCLC cells by regulating HIF-1α-dependent glycolysis through inactivation of the PI3K/Akt/mTOR pathway. J Transl Med. 2018;16:164.

An T, Dong T, Zhou H, et al. The transcription factor Kruppel-like factor 5 promotes cell growth and metastasis via activating PI3K/AKT/Snail signaling in hepatocellular carcinoma. Biochim Biophys Acta. 2019;508:159-168.

Zhang Z, Luo G, Yu C, Yu G, Jiang R, Shi X. MicroRNA-493-5p inhibits proliferation and metastasis of osteosarcoma cells by targeting Krüppel-like factor 5. J Cell Physiol. 2019;234:13525-13533.

Yang H, Chen Q, Sun F, et al. Down-regulation of the klf5-c-Myc interaction due to klf5 phosphorylation mediates resveratrol repressing the cavin-1 transcription through the PI3K/PDK1/Akt pathway. PLoS One. 2017;12:e0189156.

Ci X, Xing C, Zhang B, et al. KLF5 inhibits angiogenesis in PTEN-deficient prostate cancer by attenuating AKT activation and subsequent HIF1alpha accumulation. Mol Cancer. 2015;14:91.

Huang H, Han Y, Chen Z, et al. ML264 inhibits osteosarcoma growth and metastasis via inhibition of JAK2/STAT3 and WNT/beta-catenin signalling pathways. J Cell Mol Med. 2020;24:5652-5664.

Friso DE, Sherk AB, Wittmann BM, et al. Induction of Kruppel-like factor 5 expression by androgens results in increased CXCR4-dependent migration of prostate cancer cells in vitro. Mol Endocrinol. 2009;23:1385-1396.

Lee MY, Moon JS, Park SW, Koh YK, Ahn YH, Kim KS. KLF5 enhances SREBP-1 action in androgen-dependent induction of fatty acid synthase in prostate cancer cells. Biochem J. 2009;417:313-322.

Takagi K, Miki Y, Onodera Y, et al. Kruppel-like factor 5 in human breast carcinoma: a potent prognostic factor induced by androgens. Endocr Relat Cancer. 2012;19:741-750.

Park YK, Ge K. Glucocorticoid receptor accelerates, but is dispensable for, adipsogenesis. Mol Cell Biol. 2017;37:e00260.

He L, Yuan L, Sun Y, et al. Glucocorticoid receptor signaling activates TEAD4 to promote breast cancer progression. Can Res. 2019;79:4399-4411.

Sorrentino G, Ruggeri N, Zannini A, et al. Glucocorticoid receptor signalling activating YAP in breast cancer. Nat Commun. 2017;8:14073.

Guo P, Dong XY, Zhao K, Sun X, Li Q, Dong JT. Opposing effects of KLF5 on the transcription of MYC in epithelial proliferation in the context of transforming growth factor beta. J Biol Chem. 2009;284:28243-28252.

Shi P, Feng J, Chen C. Hippo pathway in mammary gland development and breast cancer. Acta Biochim Biophys Sin. 2015;47:53-59.

Yumimoto K, Nakayama KI. Recent insight into the role of FBXW7 in the tumor-suppressor function. Semin Cancer Biol. 2020;67:1-15.

Chanchevalap S, Nandan MO, McConnell BB, et al. Krüppel-like factor 5 is an important mediator for lipopolysaccharide-induced proinflammatory response in intestinal epithelial cells. Nucleic Acids Res. 2006;34:1216-1223.
2116

147. Chen HL, Chong IW, Lee YC, et al. Kruppel-Like Factor 5 mediates proinflammatory cytokine expression in lipopolysaccharide-induced acute lung injury through upregulation of nuclear factor-kappa b phosphorylation in vitro and in vivo. Mediat Inflamm. 2014;2014:281984.

148. Jia L, Shi Y, Wen Y, Li W, Feng J, Chen C. The roles of TNFAIP2 in cancers and infectious diseases. J Cell Mol Med. 2018;22:5188-5195.

149. Ng CK, Ma K, Cheng Y, Miyashita T, Harmon JW, Meltzer SJ. Chen HL, Chong IW, Lee YC, et al. Kruppel- Like Factor 5 mediates proinflammatory cytokine expression in lipopolysaccharide-induced acute lung injury through upregulation of nuclear factor-kappa b phosphorylation in vitro and in vivo. Mediat Inflamm. 2014;2014:281984.

150. Zhao Y, Hamza MS, Leong HS, et al. Kruppel- like factor 5 mediates sonic hedgehog signaling and neoplasia in Barrett’s esophagus and esophageal adenocarcinoma. Transl Oncol. 2019;12:1432-1441.

151. Zhao Y, Hamza MS, Leong HS, et al. Kruppel- like factor 5 mediates sonic hedgehog signaling and neoplasia in Barrett’s esophagus and esophageal adenocarcinoma. Transl Oncol. 2019;12:1432-1441.

152. Yang Y, Goldstein BG, Chao HH, Katz JP. KLF4 and KLF5 regulate p53-independent apoptosis through Pim1 survival kinase in cancer cells. Oncogene. 2008;27:1-8.

153. Li M, Gu Y, Ma Y-C, et al. Krüppel-like factor 5 promotes epithelial proliferation and DNA damage repair in the intestine of irradiated mice. Int J Biol Sci. 2015;11:1458-1468.

154. Yang Y, Goldstein BG, Chao HH, Katz JP. KLF4 and KLF5 regulate apoptosis, proliferation and invasion in esophageal cancer cells. Cancer Biol Ther. 2005;4:1216-1221.

155. Suzuki T, Nishi T, Nagino T, et al. Functional interaction between the transcription factor Kruppel-like factor 5 and poly(ADP-ribose) polymerase-1 in cardiovascular apoptosis. J Biol Chem. 2007;282:9895-9901.

156. Mori A, Moser C, Lang SA, et al. Up-regulation of Kruppel- Like Factor 5 in pancreatic cancer is promoted by interleukin-1 beta signaling and hypoxia-inducible factor-1 alpha. Mol Cancer Res. 2009;7:1390-1398.

157. Lee SJ, No YR, Dang DT, et al. Regulation of hypoxia-inducible factor 1alpha (HIF-1alpha) by lysophosphatidic acid is dependent on interplay between p53 and Kruppel-like factor 5. J Biol Chem. 2013;28:25244-25253.

158. Liu R, Chen H, Zhao P, et al. Mifepristone derivative FZU-0003 suppresses triple-negative breast cancer cell growth partially via miR-153-KLF5 axis. Int J Biol Sci. 2020;16:611-619.

159. Lin Y, Liu R, Zhao P, et al. Discovery of novel mifepristone derivates via suppressing KLF5 expression for the treatment of triple-negative breast cancer. Eur J Med Chem. 2018;146:354-367.

160. Liu R, Zhi X, Zhou Z, et al. Mithramycin A suppresses basal triple-negative breast cancer cell survival partially via down-regulating Kruppel-like factor 5 transcription by Sp1. Sci Rep. 2018;8:1138.

161. Pagliuca A, Valvo C, Fabrizi E, et al. Analysis of the combined action of miR-143 and miR-145 on oncogenic pathways in colorectal cancer cells reveals a coordinate program of gene repression. Oncogene. 2013;32:4806-4813.

162. Zhang B, Li Y, Wu Q, et al. Interruption of KLF5 acetylation contributes to tumor immune microenvironment in pancreatic cancer. Discov Med. 2019;25:4705-4715.

163. Zhang B, Li Y, Wu Q, et al. Interruption of KLF5 acetylation contributes to tumor immune microenvironment in pancreatic cancer. Discov Med. 2019;25:4705-4715.

164. Dong Z, Yang L, Lai D. KLF5 strengthens drug resistance of ovarian cancer stem-like cells by regulating survivin expression. Cell Prolif. 2013;46:425-435.
185. Marrero-Rodriguez D, Taniguchi-Ponciano K, Jimenez-Vega F, et al. Kruppel-like factor 5 as potential molecular marker in cervical cancer and the KLF family profile expression. Tumour Biol. 2014;35:11399-11407.

186. Giefing M, Wierzbicka M, Rydzanicz M, Cegla R, Kujawski M, Szyfter K. Chromosomal gains and losses indicate oncogene and tumor suppressor gene candidates in salivary gland tumors. Neoplasma. 2008;55:55-60.

187. Bloethner S, Chen BW, Hemminki K, et al. Effect of common B-RAF and N-RAS mutations on global gene expression in melanoma cell lines. Carcinogenesis. 2005;26:1224-1232.

188. Fang W, Li X, Jiang Q, et al. Transcriptional patterns, biomarkers and pathways characterizing nasopharyngeal carcinoma of Southern China. J Transl Med. 2008;6:32.

189. Bialkowski AB, Crisp M, Bannister T, et al. Identification of small-molecule inhibitors of the colorectal cancer oncogene Kruppel-like factor 5 expression by ultrahigh-throughput screening. Mol Cancer Ther. 2011;10:2043-2051.

190. Chen Z, Wu Q, Ding YE, et al. YD277 suppresses triple-negative breast cancer partially through activating the endoplasmic reticulum stress pathway. Theranostics. 2017;7:2339-2349.

191. Zeng L, Li W, Chen CS. Breast cancer animal models and applications. Zool Res. 2020;41:477-494.

192. Tassi E, Wellstein A. Tumor angiogenesis: initiation and targeting - therapeutic targeting of an FGF-binding protein, an angiogenic switch molecule, and indicator of early stages of gastrointestinal adenocarcinomas. Cancer Res Treat. 2006;38:189-197.

193. Tassi E, Henke RT, Bowden ET, et al. Expression of a fibroblast growth factor-binding protein during the development of adenocarcinoma of the pancreas and colon. Cancer Res. 2006;66:1191-1198.

194. Shinoda Y, Ogata N, Higashikawa A, et al. Kruppel-like factor 5 causes cartilage degradation through transactivation of matrix metalloproteinase 9. J Biol Chem. 2008;283:24682-24689.

195. Shahrin NH, Diakiw S, Dent LA, Brown AL, D’Andrea RJ. Conditional knockout mice demonstrate function of Klf5 as a myeloid transcription factor. Blood. 2016;128:55-59.

196. Kenchegowda D, Swamynathan S, Gupta D, Wan H, Whitsett J, Swamynathan SK. Conditional disruption of mouse Klf5 results in defective eyelids with malformed meibomian glands, abnormal cornea and loss of conjunctival goblet cells. Dev Biol. 2011;356:5-18.

197. Kenchegowda D, Harvey SA, Swamynathan S, Lathrop KL, Swamynathan SK. Critical role of Klf5 in regulating gene expression during post-eyedlid opening maturation of mouse corneas. PLoS One. 2012;7:e44771.

198. Sur I, Rozell B, Jaks V, Bergström A, Toftgård R. Epidermal and craniofacial defects in mice overexpressing Klf5 in the basal layer of the epidermis. J Cell Sci. 2006;119:3593-3601.

199. Goldstein BG, Chao HH, Yang Y, Yermolina YA, Tobias JW, Katz JP. Overexpression of Kruppel-like factor 5 in esophageal epithelia in vivo leads to increased proliferation in basal but not suprabasal cells. Am J Physiol Gastrointest Liver Physiol. 2007;292:G1784-1792.

200. Nakajima Y, Akaogi K, Suzuki T, et al. Estrogen regulates tumor growth through a nonclassical pathway that includes the transcription factors ERβ and KLF5. Sci Signal. 2011;4:ra22.