Acta Biochim Biophys Sin 2023, 55(5): 713–725
https://doi.org/10.3724/abbs.2023061
Advance Access Publication Date: 24 May 2023
Review

Review

Molecular function of Krüppel-like factor 7 in biology

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Received 11 September 2022 Accepted 23 December 2022

Abstract

Krüppel-like factor 7 (*KLF7*), also named ubiquitous *KLF* (*UKLF*) based on its ubiquitous expression in adult human tissues, is a conserved gene in animals. There are few reports on KLF7 among KLFs; however, an increasing number of reports are demonstrating that KLF7 plays an important role in development and diseases. Genetic studies have shown that the DNA polymorphisms of *KLF7* are associated with obesity, type 2 diabetes mellitus (T2DM), lachrymal/salivary gland lesions, and mental development in some populations of humans, and the DNA methylation of *KLF7* is associated with the development of diffuse gastric cancer. In addition, biological function studies have shown that KLF7 regulates the development of the nervous system, adipose tissue, muscle tissue and corneal epithelium as well as the preservation of pluripotent stem cells. Additionally, disease-related studies have shown that KLF7 is involved in the development or progression of T2DM, hematologic diseases, lung cancer, gastric cancer, squamous cell carcinoma of the head and neck, pancreatic ductal adenocarcinoma, glioma, advanced high-grade serous ovarian cancer and osteosarcoma. This review provides research progress on the genetic association, molecular properties and biological function of KLF7, and it may shed light on the understanding of the molecular function of KLF7 in biology and the molecular mechanisms of some diseases.

Key words Krüppel-like factor 7 (*KLF7*), genetic association, molecular properties, biological function

Introduction

Krüppel-like factors (KLFs) are a subfamily of zinc-finger transcription factors characterized by three conserved tandem C_2H_2 zinc fingers at C-terminal regions that typically function as DNA-binding domains [1]. In addition, their N-terminal structures are poorly conserved among KLFs and usually act as transcriptional regulatory domains [2]. To date, 17 KLFs have been identified in humans and animals, and they are involved in multiple physiological and pathological processes. KLFs can serve as transcriptional activators, repressors or both by interacting with GC-rich consensus in target genes, including 5′-CACCC-3′ DNA sequences [3].

The 17 KLFs comprise three phylogenetic groups [3]. Group 1 contains KLF3, KLF8 and KLF12, and they share a PVDLT motif that mediates their interactions with C-terminal binding protein (CtBP) and usually serve as transcriptional repressors [3]. Group 2 contains KLF1, 2, and 4–7, which usually act as transcriptional activators [3]. Group 3 contains KLF9–11, 13, 14, and 16, and they share a conserved α-helical motif AA/VXXL that mediates their binding to Sin3A and their activities as transcriptional repressors [3]. KLF15 and KLF17 do not cluster among these three phylogenetic groups, as their protein interaction domains have yet to be determined [3]. The functions of KLFs are in some cases overlapping and in others widely divergent.

KLF7 was first cloned in human vascular endothelial cells by polymerase chain reaction (PCR) using degenerated oligonucleotides corresponding to the DNA-binding domain of KLF1 in 1998, and it was also named ubiquitous *KLF* (*UKLF*) based on structural considerations and its ubiquitous expression in adult tissues of human beings [4]. *KLF7* is a highly conserved gene in animals, and the similarity in amino acid sequence among KLF7s of vertebrates is greater than 70% [5].

Over the past 20 years, the biological roles of KLF7 in neurogenesis, adipose tissue formation, type 2 diabetes and blood diseases have been demonstrated by several groups. Recently, important oncogenic functions have been defined for KLF7 in several cancers. To promote the medical application of its biological functions, we integrate the available information on the role of KLF7 in biology, with a focus on its genetic association, molecular properties, and biological function in this review.

Genetic Association with Human *KLF7*

Genetic traits associated with variations in the human *KLF7* gene

The DNA sequence encoding KLF7 in humans is located in the q33.3 region of chromosome 2 (2q33.3), which is associated with early-onset arthritis [6] and early-onset obesity (age of obesity rebound) [7]. Genetic studies have shown that *KLF7* may be a candidate gene for obesity and type 2 diabetes mellitus (T2DM) in humans. A single nucleotide polymorphism (SNP, rs2302870) in the 2nd intron of *KLF7* is associated with the development of T2DM in the Japanese population [8]. However, this SNP (rs2302870) is not associated with T2DM and obesity in the Danish population. Meta-analysis with a random effects model showed that the odds ratios with 95% CIs of T2DM for allele A vs C, AA genotype vs others, CC genotype vs others, and AC genotype vs others of this locus in the mixed Japanese and Danish population are 1.2739 [0.9454; 1.7165], 1.2735 [0.9291; 1.7455], 0.5984 [0.3022; 1.1849], and 0.8161 [0.6090; 1.0938], respectively, indicating that this locus is not an ideal genetic marker for T2DM in populations with large samples or complex genetic backgrounds.

Another SNP (rs7568369) in the putative promoter region of the human *KLF7* gene is associated with obesity in the Danish population. In detail, the minor A-allele of this locus protects against obesity, and this variant is associated with decreased body mass index and waist circumference [9]. In addition, a case-control study of patients with ischemic heart disease showed that this SNP is also associated with the development of ischemic heart disease with arterial hypertension, T2DM, and hypercholesterolemia but is not associated with the development of simple ischemic heart disease or simple ischemic heart disease with hypertension [10] (Table 1). Together, these results suggested that the SNP rs7568369 may be a useful marker of metabolic diseases.

In addition, KLF7 may be a candidate gene for the cognitive and psychological state of human beings. A GWAS analysis of 111749 individuals from the UK biological library showed that a SNP (rs2360675) on chromosome 2 close to the KLF7 gene is associated with human self-rated health [11]. A SNP microarray and pooling (SNP-map) study showed that the SNP (rs991684) that may be in linkage disequilibrium with KLF7 and located in the genome region between KLF7 and CREB1 is associated with mild mental retardation [12]. In addition, KLF7 was proposed as a candidate gene for autism in patients with 2q33.3-q34 deletion, and four unrelated individuals with de novo KLF7 missense variants were reported to share similar clinical features of developmental delay/intellectual disability, hypotonia, feeding/swallowing issues, psychiatric features, and neuromuscular symptoms [13] (Table 1).

Additionally, *KLF7* may be associated with inflammation and tissue repair in humans. A GWAS followed by fine mapping of highly significant genes showed that the SNP (rs2284932) in the 1st intron of *KLF7* is associated with the development of lachrymal/salivary gland lesions in type 1 autoimmune pancreatitis [14]. Genome-wide resequencing of 5 individuals (4 keloid patients and 1 healthy person) from a keloid family showed that the copy number variations of *KLF7* are associated with keloid formation [15] (Table 1).

Epigenetic and integrated genomics study advances of KLF7

A case-control study showed that abnormal DNA methylation in the genomic sequence of *KLF7* is not associated with the development of gastric adenocarcinoma with intestinal-type precursors [16], but it is associated with the course of gastric adenocarcinoma with diffuse-type precursors [16,17]. Compared with cancer-free controls, the DNA methylation level of *KLF7* was increased in the gastric mucosa of patients with diffuse gastric cancer [16]. For patients with diffuse gastric carcinoma, the DNA methylation level of *KLF7* in the stomach mucosa of patients with poorly differentiated gastric cancer is greater than that of patients with signet ring cell carcinoma [17]. The DNA methylation level of *KLF7* might be a specific marker of gastric cancer with diffuse-type precursors.

In addition, our previous study showed that the DNA methylation of the chicken *KLF7* promoter is associated with its transcripts in abdominal adipose tissue, and it might influence fasting glycemia and abdominal fat content [18].

An integrated genomic study based on genomic and proteomic data identified KLF7 as a key regulator in the regulatory network of serum markers of cardiovascular disease [19]. Compared to that in the control group, *KLF7* expression is upregulated in the blood of patients with coronary artery disease (CAD). Bioinformatic analysis showed that there are many *KLF7* binding sites in the promoters of CAD marker genes, including *Factor VII*, plasminogen activator inhibitor-1 (*PAI-1*), platelet-derived growth factor (*PDGF*), *Plasminogen*, von Willebrand factor (*vWF*), interleukin-10 (*IL-10*), *IL-12A*, matrix metalloproteinase-9 (*MMP-9*), leptin (*LEP*), myeloperoxidase (*MPO*), heat shock protein 27 (*HSP27*) and *HSP60*, and KLF7 may play a role in the development of cardiovascular disease by regulating the expression of these genes [19].

Molecular Properties of KLF7

Protein structure of KLF7

Human *KLF7* transcribes more than one transcript and produces at least 4 kinds of proteins of different sizes and 1 kind of long-chain noncoding RNA. The largest protein of human KLF7 was reported as a transcription factor containing 302 amino acids (aa) [4]. The transcriptional regulation domain and DNA binding domain of KLF7 are located at the N-terminus and C-terminus, respectively (Figure 1).

There are two functional subdomains in the transcriptional regulation domain of human KLF7. They are the acidic amino acid domain (aa 1–47) and the serine-rich hydrophobic domain (aa 76–211). There is an evolutionarily conserved leucine zipper (aa 59–119) in the transcriptional regulatory domain of human KLF7 (Figure 1), and it is involved in the protein interaction of KLF7 with its cofactor MOKA [20]. Its transcriptional regulatory domain is followed by a nuclear localization sequence (NLS) (aa 212–218). These protein structures of KLF7 share greater than 85% similarity among mammalian and avian species [5].

Similar to *KLF5* and *KLF6* [21,22], the expression of *KLF7* is regulated by its N-terminal sequence, and loss of aa 1–76 at the N-terminus obviously increases its protein expression [23]. The VP16-KLF7 chimeric protein constructed by substituting the N-terminal aa 1–76 of KLF7 with the transactivation domain of VP16 eliminated the negative effect of the N-terminal sequence on *KLF7* expression and greatly enhanced its expression and activity in neural cells, especially its ability to promote the activity of the *P21* promoter [23].

The electrophoretic mobility shift assay *in vitro* showed that KLF7 could bind to the CACCC motif and Sp1 binding site, and KLF7 was more capable of binding to the CACCC motif than to the Sp1 binding site [4]. To date, the target genes of *KLF7* identified by both

Table 1. Associations of KLF7 with genetic traits of humans

Location	Relationship with *KLF7*	Genetic traits	Number/ population	Instructions	Ref.
Chr2: 2q33.3 (Marker: D2S155)	Genome region containing *KLF7*	Early-onset osteoarthritis	7 families/Dutch[a]	Two-point LOD=6.05 (θ=0.00)	[6]
Chr2: 2q33.2-q36.3 (Marker: D2S112-D2S396)	Genome region containing KLF7	Young-onset obesity	*N*=115/French[a]	PCT99: MLB LOD=2.73, MLS LOD=3.05 PCT97: MLB LOD =2.08, MLS LOD=2.33	[7]
Chr2: 2q33.3-q34	Missense mutation/ haploid deficiency	Developmental delay/ intellectual disability	*N*=4/Dutch	Case report	[13]
SNP: rs2302870	SNPs in the 2nd intron	Type 2 diabetes mellitus (T2DM)	*N*=2548/Japanese	Odds ratio (95% CI): A vs C: 1.51 (1.26–1.81) AA vs others: 1.53 (1.25–1.86) CC vs others: 0.38 (0.18-0.83) AC vs others: 0.69 (0.56-0.84)	[8]
			N=8777/Danish	Odds ratio (95% CI) A vs C: 1.01 (0.91–1.11) AA vs others: 0.98 (0.89–1.09) CC vs others: 0.91 (0.6–1.37) AC vs others: 1.02 (0.92–1.14)	[9]
SNP: rs7568369	SNPs in 5′-UTR	Obesity: BMI≥25	*N*=18,463/Danish	Odds ratio (95% CI) C vs A: 1.09 (1.03–1.15) CC vs others: 1.12 (1.05–1.20) CA vs others: 0.94 (0.88–1.00) AA vs others: 0.90 (0.82–1.00)	
		Obesity: waist≥80cm (w) or ≥94cm (m)	*N*=19,254/Danish	Odds ratio (95% CI) C vs A: 1.14 (1.08–1.20) CC vs others: 1.28 (1.20–1.36) CA vs others: 0.78 (0.73–0.83) AA vs others: 1.00 (0.91–1.11)	
		Cardiovascular continuum diseases	*N*=931/Russian	Odds ratio (95% CI) C vs A: 0.45 (0.28–0.73) CC vs others: 0.34 (0.16–0.68)	
SNP: rs2360675	SNPs in 5′-UTR	Poorer self-rated health	*N*=111,749/British[b]	B(A)=−0.027 MAF=0.44	[8]
SNP: rs991684	SNPs in the region between *KLF7* and *CREB1*	Mild mental impairment	*N*=2551/British[c]	r=0.060 Estimated effect size: 0.36% AA: −0.05, AG: −0.003, GG: 0.105	[12]
SNP: rs2284932	SNPs in the 1st intron	Lachrymal/salivary gland lesions	*N*=103/Japanese	Odds ratio (95% CI) C vs T: 2.98 (1.58–5.65) Others vs TT: 4.37 (1.90–10.02)	[14]
Coding region	Copy number variations	Keloid formation	*N*=5/Chinese	Case report	[15]

[a]Caucasians; [b]UK Biobank sample; [c]London. w, wemen; m, men; PCT99, BMI ≥ 99th percentile; PCT97, BMI ≥ 97th percentile; SNP, single nucleotide polymorphism.

expression analysis and chromatin immunoprecipitation analysis include *P21*, *P27*, *TRKA*, *TRKB*, *OMP*, *L1* and *IL-6* [20,24–27]. Target genes verified only by expression analysis include CCAAT/ enhancer-binding protein α (*C/EBPα*), peroxisome proliferator-activated receptor γ (*PPARγ*), *LEP*, and *adiponectin* [28].

Co-factor of KLF7

Modulator of KLF7 activity (MOKA), with a molecular weight of approximately 140 kDa, is the first cofactor of KLF7 discovered in the mouse nervous system [20]. There is an F-box domain in MOKA [20]; thus, according to the systematic approach, MOKA was designated F-box protein 38 (FBXO38) by the HUGO Gene Nomenclature Committee. In addition, FBXO38 was also named FBX38, HMN2D and SP329 in some early publications.

In the embryos and adults of mice, the expression patterns of *FBXO38* are similar to those of *KLF7*, and it is also highly expressed in the nervous system and adult testis [20]. FBXO38 is important for the proper growth and fitness of animals, and the loss of FBXO38 in mice results in growth retardation, affecting several organs, including the liver, brain, testes, and kidneys [29]. This is different from the phenotype of *KLF7*$^{-/-}$ mice [27], indicating that other important functions of FBXO38 exist.

In addition, FBXO38 can act as a substrate-binding receptor for the multisubunit ubiquitin ligase SCF^{FBXO38} (SKP1-CUL1-FBXO38), and the T-cell-specific transmembrane receptor programmed cell death 1 (PD1) has been identified as a substrate of SCF^{FBXO38} [30].

Mouse FBXO38 can recognize the leucine zipper domain of KLF7 by its F-box motif and form a KLF7-FBXO38 protein complex that

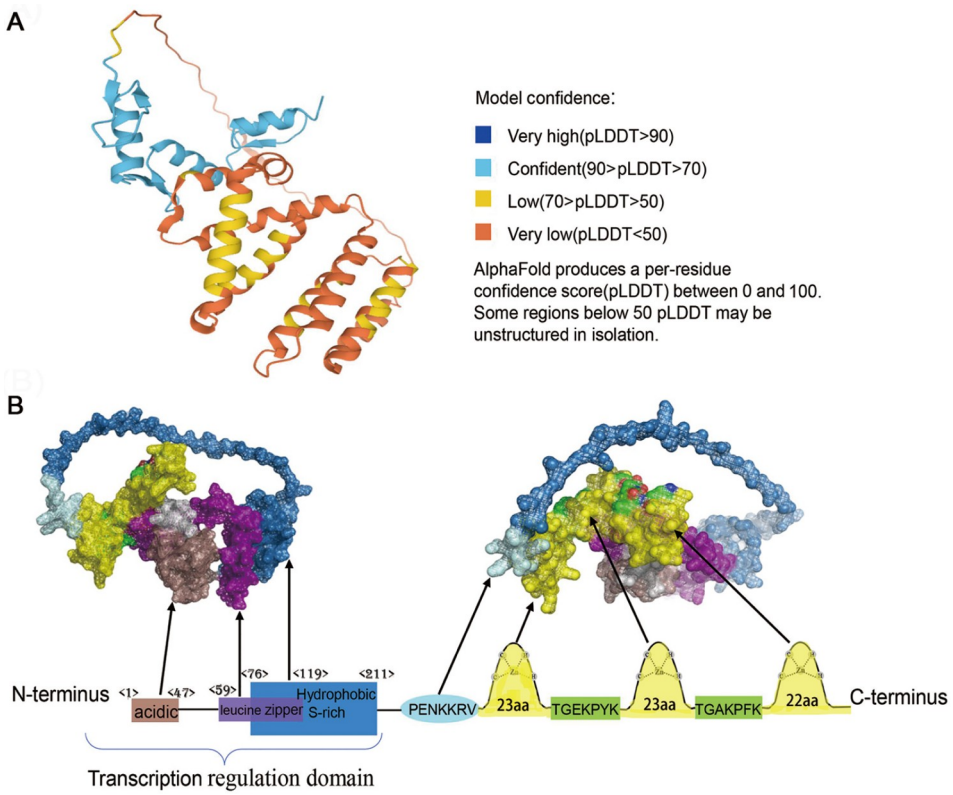

Figure 1. Protein structure of Krüppel-like factor 7 (KLF7) in humans (A) The tertiary structure of human KLF7 predicted by the AlphaFold Protein Structure Database. (B) Sequence annotation of the tertiary structure of human KLF7. The original picture was downloaded from the AlphaFold Protein Structure Database (https://www.alphafold.ebi.ac.uk) and subsequently processed with VMD software.

enhances the activation effect of KLF7 on its target genes, including *P21* [20]. In contrast to the interaction of KLF7 and F-box and WD repeat domain-containing 7 (FBXW7), KLF7 has been identified as a substrate of the SCF^{FBXW7} ubiquitin ligase complex [31]. The interaction of KLF7 with FBXO38 is independent of the SCF complex, and it neither causes the ubiquitination of KLF7 nor forms an SCF protein complex [20].

Mechanistically, the aa 473–766 region of mouse FBXO38 between the nuclear export signal sequence (NES) and NLS is a transcriptional activation domain, and it may mediate the activation of KLF7 by FBXO38 [32]. In addition, FBXO38 regulates the subcellular location of KLF7 in the nucleus and cytoplasm through its multiple NESs and NLSs [32].

Our previous studies showed that there are at least 2 kinds of FBXO38 transcripts in animals, and their expression patterns in chicken adipose tissues are different [33]. The coordinated effect of different FBXO38 transcripts on the function of KLF7 needs to be further studied.

Additionally, a recent study showed that PU.1 may be another cofactor of KLF7. Both *PU.1* and *KLF7* are highly expressed in the nucleus of 3T3-L1 cells, and a fluorescence resonance energy transfer study showed that the PU1 and KLF7 proteins interact with each other directly in the nucleus [34].

Chemical Substances Targeting KLF7

There is substantial evidence that chemical substances, including clinically approved drugs, affect *KLF7* expression. Morphine could reduce leukocyte chemotactic migration to sites of inflammation and upregulate *KLF7* expression at the transcriptional and translational levels in human lymphocytes with an effect of naloxone reversible [35]. Thus, the regulation of *KLF7* expression might be of significance in morphine-mediated physiological responses (Table 2).

Green tea polyphenols have antioxidant, anti-inflammatory, anti-obesity, anti-diabetes and other pharmacological activities. The polyphenol catechin, (–)-catechin, in green tea promoted the expression and secretion of adiponectin and the ability to take up glucose in 3T3-L1 adipocytes, while it inhibited *KLF7* expression [36]. Catharanthus roseus leaf aqueous crude extract (CRACE) containing 1α,25-dihydroxy vitamin D3, which decreased adipogenesis and increased lipid catabolism, increased *KLF7* expression in 3T3-L1 cells after 2 h of induction into adipogenesis [37]. Borrelidin, isolated from Streptomyces sp. TK08330, identified by spectroscopy as an 18-membered macrolide, enhanced the mRNA expression of *KLF7* and inhibited adipogenesis in 3T3-L1 cells [38]. The regulation of *KLF7* expression may be a mechanism by which active substances of biological extracts affect obesity and endocrine regulation.

Pitavastatins are a class of highly effective lipid-lowering drugs and have good plaque stabilization in patients with myocardial infarction. A study on the gene expression affected by statins in the hearts of mice showed that pitavastatin has an inhibitory effect on *KLF7* expression [39]. In addition, lipopolysaccharide (LPS), an inflammatory irritant, upregulated *KLF7* expression in epicardial adipose tissue of patients with coronary heart disease [40]. Regulation of *KLF7* expression may be a potential target of drugs for cardiovascular disease.

Table 2. Substances that affect KLF7 expression

Substance	Function	Effect on *KLF7* expression	Study model	Ref.
Morphine	Analgesia, sedation, respiratory depression, antitussive	Upregulated (at transcriptional and translational levels)	CEM × 174 cell line	[35]
(–)-Catechin	Antioxidant, anti-inflammatory, anti-obesity, and antidiabetic activities	Downregulated	3T3-L1 cell line	[36]
Catharanthus roseus leaf aqueous crude extract	Maybe benefited to the treat of cancer, diabetes and liver disease	Upregulated	3T3-L1 cell line	[37]
Borrelidin	Anti-bacteria, anti-fungi and anti-malaria, inhibit angiogenesis, anti-tumor	Upregulated	3T3-L1 cell line	[38]
Pitavastatin	Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, and potent cholesterol-lowering drug	Downregulated	Normal male C57BL/6J mice	[39]
Lipopolysaccharide	An inflammatory irritant	Upregulated	Epicardial adipose tissue in human	[40]
Caprylic acid (C8:0)	A serum component	Upregulated	PC3 cells	[41]
Trametinib	MEK inhibitor	Downregulated (at transcriptional and translational levels)	PDAC cells	[42]

High concentrations of serum octanoic acid could promote the proliferation, invasion and migration of prostate cancer cells by upregulating *KLF7* expression [41] (Table 2). Additionally, *KLF7* could protect hippocampal neurons after traumatic injury by activating the JAK2/STAT3 pathway, and AG490 eliminated the protective effect of *KLF7* on cell injury [43]. These results indicated that the regulation of *KLF7* expression may be a target for some chemicals to affect cancers and nervous system damage.

KLF7 and Development

KLF7 and the nervous system

Expression pattern of KLF7 during nervous system development

KLF7 is highly expressed in three periods during the development of the central and peripheral nervous systems in mice [44]. First, *KLF7* expression is gradually increased in the spinal cord at the early stage of embryonic development [44]. Second, *KLF7* is highly expressed in the cerebral cortex in the early postnatal period, and then its expression gradually decreases [44]. Third, the expression of *KLF7* is consistently high in the cerebellum and dorsal root ganglion of adult mice [44]. These three periods are in line with the morphological formation of embryonic spinal cord neurons, the formation of synapses in the postnatal cerebral cortex, and the survival and functional maintenance of sensory neurons and cerebellar granule cells in adult animals, respectively, suggesting that KLF7 plays an important role in the development of the nervous system in mice [44]. Consistent with this, knockdown of *KLF7* in mice confirmed the important role of KLF7 in nervous system development [27,45,46].

KLF7 regulates sensory nervous development

KLF7 is crucial to the development of sensory and sympathetic neurons. Apoptosis of *TRKA*+ sensory neurons occurr in *KLF7*$^{-/-}$ mice [27]. Most *KLF7*$^{-/-}$ mice die within 2 days after birth, and less than 3% of *KLF7*$^{-/-}$ mice survive [27]. When *KLF7*$^{-/-}$ mice were mature, there were no obvious behavioral abnormalities [27]. However, *KLF7*$^{-/-}$ mice showed a reduction in pain sensitivity, including chemical injury, cold and hot stimulation, and tail pinching [27].

An *in situ* hybridization study showed that *KLF7* and *TRKA* are coexpressed in the sympathetic and sensory neurons of embryonic and adult mice [47]. KLF7 could initiate and maintain the expression of *TRKA* in embryos and adults by binding to a specific *Ikaros2* (GAAAAATAGTGGGAGAGAAGAGT) binding site in the enhancer of *TRKA* [47]. In the embryos and adults of mice, KLF7 and BRN3A work together to promote *TRKA* expression. Knocking out either *KLF7* or *BRN3A* does not reduce *TRKA* expression in the trigeminal ganglia (TG); however, knocking out both simultaneously does [48]. The interaction between KLF7 and BRN3A is necessary for endogenous *TRKA* expression and the survival of pain sensory neurons [48], and KLF7 may regulate the development of sensory and sympathetic neurons at least in part by targeting *TRKA* expression (Figure 2A).

One of the organs most affected by the loss of KLF7 activity in mice is the olfactory system. Compared to their littermates, the expression of tyrosine hydroxylase (*TH*) and dopamine transporter (*DAT*) was downregulated in the olfactory bulb and ventral midbrain of *KLF7*$^{-/-}$ mice at birth, suggesting that KLF7 is a necessary factor for the development of dopaminergic neurons in the olfactory bulb [57].

In addition, during the development of olfactory neurons, the transcription of the prototypical olfactory sensory neuron (OSN) marker *OMP* and the neural cell adhesion protein *L1* is under the control of KLF7, and their expression is downregulated in the olfactory epithelium of *KLF7*$^{-/-}$ mice [26]. Thus, KLF7 may regulate the development of olfactory neurons at least by controlling the expression of *OMP* and *L1* [26].

KLF7 regulates neuronal process projections

KLF7 plays a crucial role in neuronal process projections. The loss of KLF7 activity resulted in damage to axons of the olfactory system, visual nervous system, cerebral cortex, and hippocampal neurons and a reduction in the dendritic branches of hippocampal neurons [46]. Consistent with this, overexpression of VP16-KLF7 in the damaged spinal cord blocked age-related axonal growth loss in the cortex and enhanced axonal development of the corticospinal tract (CST) [23], and overexpression of KLF7 in cultured retinal ganglion

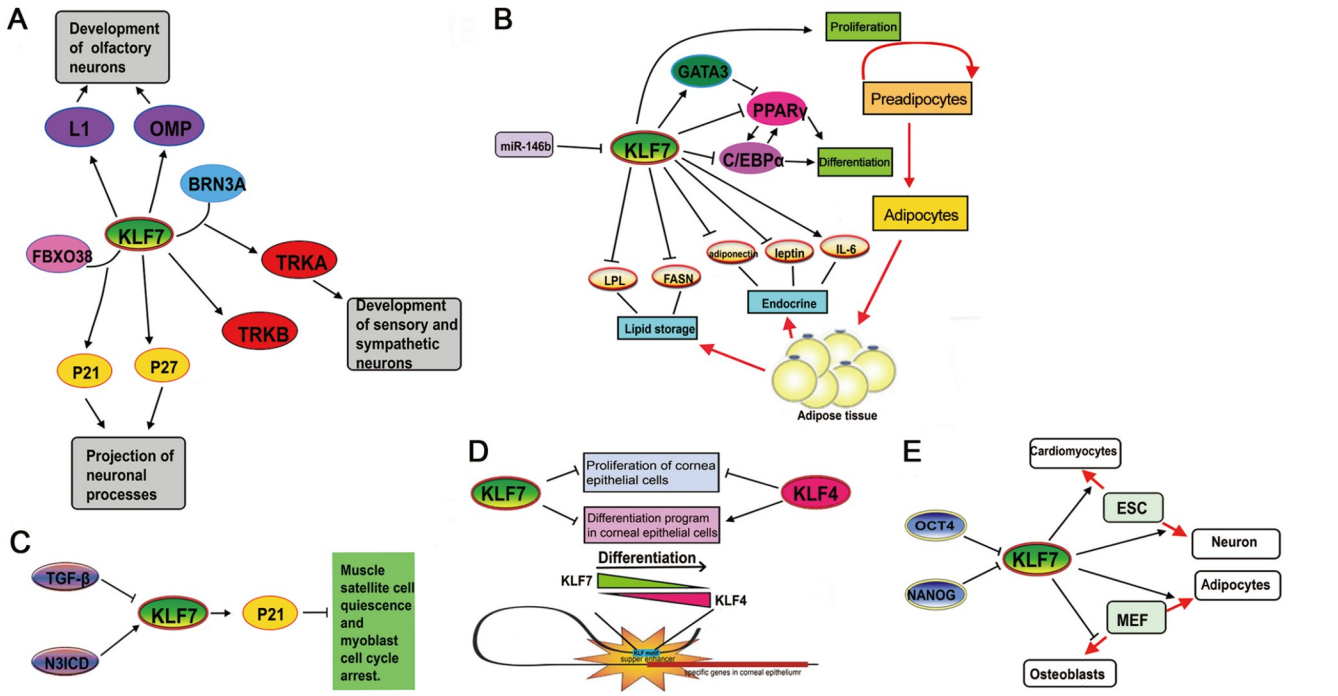

Figure 2. The molecular roles of Krüppel-like factor 7 (KLF7) during the development of tissues (A) KLF7 regulates the survival of sensory and sympathetic neurons and axon projection and regeneration during the development of the nervous system (Reference to the literature [26,27,46–48]). (B) KLF7 suppresses the differentiation of preadipocytes, promotes the proliferation of preadipocytes and regulates the secretion of adipocytokines in adipose tissue (Reference to the literature [28,49–52]). (C) KLF7 regulates muscle satellite cell quiescence and myoblast cell cycle arrest in muscle tissue (Reference to the literature [53]). (D) KLF7 regulates the development of the corneal epithelium (Reference to the literature [54–56]). (E) KLF7 regulates the differentiation of pluripotent cells *in vitro* (Reference to the literature [50]). The pictures were made using Adobe Illustrator software.

cells (RGCs) and cortical neurons promoted the outwards growth of neuronal processes [58].

The Cip/Kip protein is not only a key regulator of the cell cycle but also of neurite remodelling [59]. The expressions of *P21* and *P27* in olfactory sensory neurons (OSNs) of *KLF7*$^{-/-}$mice are downregulated [46]. KLF7 may promote the growth of neuronal axons by boosting the expression of *P21* and *P27* [46] (Figure 2A). Consistent with this, sustained overexpression of FBXW7 in Neuro2A cells resulted in the ubiquitylation of KLF7 and downregulation of *P21* mRNA [31].

Other functions of KLF7 in the nervous system

KLF7 can regulate *TRKB* expression by binding to the conserved *TRKB* Ca2 + response element 3 (*TCARE3*) in its promoter, and KLF7 may mediate the signal of brain-derived neurotrophic factor (BDNF) through *TRKB*, which is essential for neuron survival and differentiation, neurite outgrowth, axon guidance, and activity-dependent synaptic plasticity [25].

KLF7 and the treatment of nerve injury

Upregulation of *KLF7* expression may be an effective way to treat nerve injury. Animal studies showed that the migration of either Schwann cells with *KLF7* overexpression or spinal matrix stem cells with *KLF7* overexpression promoted sciatic nerve regeneration in mice [60,61]. In addition, injection of *AAV2-KLF7* is helpful for the treatment of spinal cord neuronal injury in mice [62]. Additionally, miR-146b might inhibit sciatic nerve regeneration by targeting *KLF7* [63].

KLF7 and adipose tissue

KLF7 is involved in the regulation of adipose tissue development. The expression level of *KLF7* in abdominal adipose tissue of lean broilers was greater than that of fat broilers [49]. KLF7 may be a negative regulator of adipose tissue development.

Studies *in vitro* showed that knockdown of *KLF7* inhibited the transformation of mouse embryonic fibroblasts (MEFs) into adipocytes [50]. *KLF7* is highly expressed in preadipocytes and facilitates the proliferation of chicken preadipocytes [49]. In addition, *KLF7* expression fluctuates during the differentiation of 3T3-L1 preadipocytes, and it initially decreases and then increases [28]. Overexpression of KLF7 inhibited the differentiation of preadipocytes, including 3T3-L1 cells, human preadipocytes and chicken preadipocytes [28,49], suggesting that KLF7 inhibits terminal differentiation of preadipocytes. Together, these results indicated that KLF7 blocks adipogenesis by maintaining preadipocyte status. Mechanistically, *GATA3*, *C/EBPα*, and *PPARγ* might be the target genes of KLF7 in adipogenesis [28,50,51]. Consistent with this, miR-146b, whose expression is altered in human obesity, inhibited the proliferation of human visceral preadipocytes and promoted their differentiation by inhibiting *KLF7* expression [52] (Figure 2B).

KLF7 is also highly expressed in mature adipocytes [28,49] and regulates the expressions of several functional genes in fat synthesis and metabolism, including fatty acid synthase (*FASN*) [49], lipoprotein lipase (*LPL*) [49], and fatty acid binding protein 4 (*FABP4*) [28,49], as well as the expression and secretion of adipocytokines (adiponectin and leptin) and IL-6 [28] (Figure 2B). Thus, KLF7 also regulates the energy storage and endocrine function of mature adipocytes.

KLF7 and muscle development

Consistent with Krüppel protein, which regulates muscle formation during embryogenesis in Drosophila [64], KLF7 plays a role in the development of muscle tissue. KLF7 promoted the differentiation of embryonic stem cells (ESCs) into cardiomyocytes *in vitro*, and the unique pulsatile capacity of cardiomyocytes was reduced in *KLF7*-knockdown ESCs [50]. In addition, *KLF7* was highly expressed in skeletal muscle and the quiescent phase of muscle stem satellite cells (SCs) [53], and knockdown of *KLF7* expression promoted SC activation and the entrance of the myogenic cell cycle [53]. Additionally, mechanistic studies showed that *KLF7* expression is regulated by TGF-β and Notch signaling in myoblasts, and KLF7 plays a role in myogenic cell cycle withdrawal induced by TGF-β signaling blockade and in SC quiescence induced by canonical Notch signaling [53] (Figure 2C). Furthermore, the function of KLF7 in SCs is dependent on the acetylation of Lys227 and/or Lys231 in their DNA binding domain and the expression of *P21* [53]. However, the mRNA expression of *KLF7* is downregulated in the transition of myoblasts to myotubes, and KLF7 plays a limited role in myogenic differentiation.

KLF7 and corneal development

Immunofluorescence staining analysis showed that *KLF7* is expressed in the corneal epithelium at both embryonic (E18.5) and early postnatal (P5) time points but not at P50, when the corneal epithelium is fully differentiated during corneal development in mice [54]. Knockdown of *KLF7* resulted in aberrant expression of cell cycle regulators, including *CCNB1*, *CCNE2* and *CCNB2*, and increased proliferation in undifferentiated HCE cells [54]. Thus, similar to KLF4 [55], KLF7 tempers the proliferation of corneal epithelial cells. In addition, *KLF7* knockdown upregulated the expressions of the key corneal differentiation genes *Pax6* and *Aldh3a1* in proliferating HCE cells [54]. In contrast to KLF4[56], KLF7 may be a progenitor factor that represses the differentiation program in corneal epithelial cells [54].

Transcriptome analysis showed that KLF7 and KLF4 regulate specific genes and similar functional categories of genes in opposite directions in proliferating HCE cells but not in differentiated HCE cells [54]. There are KLF motifs enriched in the super enhancers (SEs) unique to human corneal epithelial (HCE), and KLFs may carry out their functions at least by binding to and activating cell type-specific enhancers during corneal epithelial development [54]. It is possible that KLF7 antagonizes KLF4 in the control of corneal epithelial cell differentiation by binding to the KLF motif in SEs, and a differentiation-dependent switch in activation-repression regulatory mechanisms for these two factors exists during corneal development [54].

KLF7 and preservation of pluripotent stem cells

OCT4 and NANOG, which regulate stem cell self-renewal, were found to regulate *KLF7* expression [50]. The differentiation potential of neuroectoderm and mesoderm cells is changed after *KLF7* knockdown. Knockdown of *KLF7* expression inhibits the differentiation of ESCs into neural cells and cardiomyocytes. In addition, knockdown of *KLF7* expression inhibited the differentiation of MEFs into adipocytes and promoted the differentiation of MEFs into osteoblasts [50]. Moreover, overexpression of *KLF7* could turn terminal effector T cells back into a poorly differentiated state [65]. Based on these studies, KLF7 may be an important regulator in the maintenance of pluripotent stem cells (Figure 2D).

KLF7 and Diseases

KLF7 and T2DM

Consistent with genetic reports in the Japanese population [8], *in vitro* studies suggested that high expression of *KLF7* may be a risk factor for T2DM. *KLF7* overexpression inhibits the biosynthesis and secretion of insulin in pancreatic cells (Figure 3A), as evidenced by the overexpression of *KLF7* inhibiting the transcription of insulin, glucose transporter 2 (*GLUT2*), inwards rectifier potassium channel (*Kir6.2*), and sulfonylurea receptor 1 (*SUR1*) in HIT-T15 cells [28] (Table 3). In addition, *KLF7* overexpression inhibited *GLUT2* expression in human hepatocytes (HepG2) and hexokinase expression in rat skeletal muscle cells, demonstrating that *KLF7* overexpression might reduce insulin sensitivity in peripheral tissues [28]. Additionally, *KLF7* is also implicated in the pathogenesis of T2DM by inhibiting adipocyte formation as well as the expression and secretion of adipocytokines (adiponectin and leptin) in adipose tissue [28] (Figure 3A).

KLF7 and hematologic diseases

Increased *KLF7* expression is an independent predictor of poor prognosis of pediatric acute lymphoblastic leukemia [66] (Table 3). The activity of hematopoietic stem and progenitor cells (HSPCs) in the livers of $KLF7^{-/-}$ mice is similar to that of $KLF7^{+/+}$ mice, and a serial transplantation experiment showed that there is no difference in the activity of long-term multilineage engraftment and self-renewal between $KLF7^{-/-}$ cells and $KLF7^{+/+}$ cells *in vivo* [65]. However, overexpression of *KLF7* inhibited the growth of multiple hematopoietic stem and progenitor cell lineages in mice after transplantation, including hematopoietic stem cells (HSCs), common myeloid progenitors (CMPs), granulocyte-monocyte progenitors (GMPs), megakaryocytic-erythroid progenitors (MEPs) and common lymphoid progenitors (CLPs), and it did not affect the growth of T lymphocytes [65] (Figure 3B). In contrast, it enhanced the survival of early thymocytes [65]. Thus, KLF7 might not be essential for the function of normal hematopoietic stem and progenitor cells; however, increased *KLF7* expression inhibited bone marrow cell proliferation and promoted early thymocyte survival [65]. Moreover, RNA expression analysis showed that the inhibitory effect of KLF7 on myeloid progenitor cell growth is not mediated by the expression of *P21*, and the loss of *P21* does not rescue the replantation defect [65].

KLF7 and cancers

Lung cancer

KLF7 may be an oncogene of lung adenocarcinoma (LAC), and the high expression of KLF7 in LAC is an independent factor for poor clinical prognosis [67]. Compared with adjacent noncancerous tissues, *KLF7* is upregulated in LAC tissues, and high protein expression of *KLF7* in LAC is associated with greater tumor size, positive lymph node metastasis, and poor tumor-node-metastasis (TNM) staging, resulting in a lower overall survival [67] (Table 3). Furthermore, *KLF7* knockdown inhibited the proliferation and invasion of A549 and H1299 lung carcinoma cells *in vitro* [67] (Figure 3D). In addition, miR-185 inhibited the progression of non-small cell lung cancer (NSCLC) by targeting *KLF7* expression [68]. Additionally, long noncoding RNA LINC0068 induced by miR-193a and STAT3 inhibited the proliferation and invasion of NSCLC by

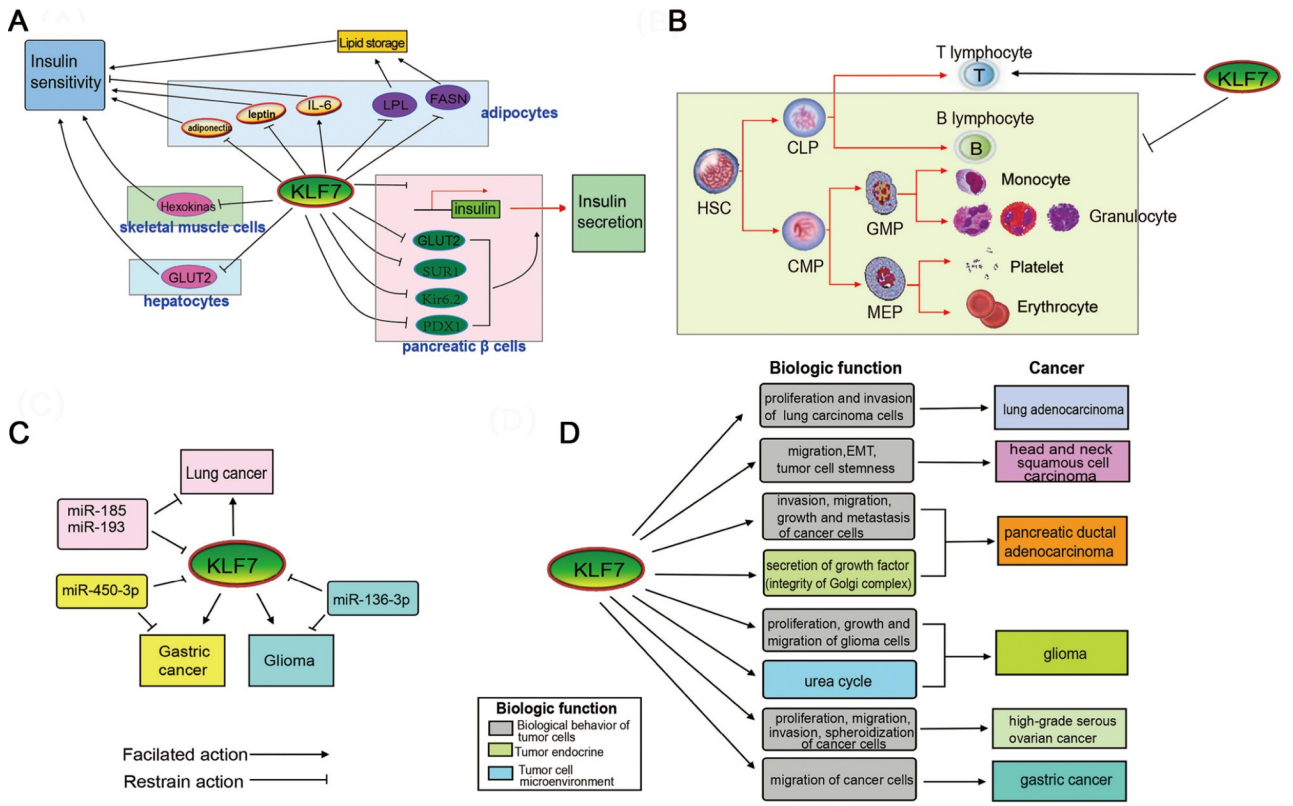

Figure 3. The molecular functions of KLF7 in diseases (A) KLF7 might regulate the occurrence and development of type 2 diabetes mellitus. (Reference to the literature [28,49–51]). (B) KLF7 inhibits the formation of multiple lineages of cells in hematogenesis but promotes T-cell survival and plays a role in the development of pediatric acute lymphoblastic leukemia (Reference to the literature [65]). (C) Inhibition of *KLF7* expression is a way by which some miRNAs inhibit carcinogenesis (Reference to the literature [68,69,80,81]). (D) The role of KLF7 in the occurrence of some cancers (Reference to the literature [67,71,73,75,76]). The pictures were made using Adobe Illustrator software.

inhibiting *KLF7* expression [69] (Figure 3C). However, when miR-103 inhibited *KLF7* expression [70], it promoted the proliferation, migration, and invasion of A549 and H1299 cells.

Gastric carcinoma

Abnormal changes in the DNA methylation level of *KLF7* were detected in gastric adenocarcinoma with diffuse-type precursors [16,17] (Table 3). A validation cohort study of 252 Chinese patients showed that *KLF7* expression is upregulated in gastric cancer tissues compared with adjacent normal tissue, and high expression of *KLF7* is associated with poor prognosis of TNM staging and lymphatic vascular invasion [71]. In addition, *KLF7* expression is inversely associated with 5-year overall survival and disease-free survival in gastric cancer patients [71]. Knockdown of *KLF7* did not affect the proliferation of AGS and MGC803 cells but inhibited their migration [71], suggesting that KLF7 could promote the migration of gastric cancer cells, facilitate their separation from primary sites, and exacerbate the progression of gastric cancer (Figure 3D). Additionally, miR-450b-3p inhibited gastric cancer growth by inhibiting KLF7 expression, and overexpression of *KLF7* reversed the inhibitory effect of miR-450b-3p mimics on the malignant development of gastric cancer [80] (Figure 3C).

Squamous cell carcinoma of the head and neck

High expression of *KLF7* is an independent factor of poor prognosis for head and neck squamous cell carcinoma (HNSCC) [42]. *KLF7* is upregulated in squamous cell carcinoma compared with normal tissues [72,73], and elevated *KLF7* expression is associated with poor prognosis in squamous cell carcinoma [42,72,73] (Table 3). Gene set enrichment analysis (GSEA) showed that neurotrophin and *GnRH* signaling pathways are activated in *KLF7*-upregulated squamous cell carcinoma samples [72]. KLF7 overexpression altered the migration ability of oral squamous cancer and induced epithelial-mesenchymal transition (EMT) and lymphatic metastasis by promoting *SNAIL* expression [73] (Figure 3D). *In vitro*, *KLF7* enhanced the expression level of *GnRH* in SCC9 and CAL27 cells [72]. Furthermore, *KLF7* is a common target gene of the carcinogens YAP1 and SOX2, and inhibition of *KLF7* expression reduced the incidence of CD44 variant 9 (CD44v9)-positive cancer stem cells (CSCs) and their spheroidization ability in HSC4 cells [82]. Additionally, bioinformatics analysis showed that *KLF7* is a target gene of several miRNAs associated with the pathogenesis of HNSCC and SNAIL [42].

Pancreatic ductal adenocarcinoma

Regulation of *KLF7* expression may be a pharmacological target for the treatment of pancreatic ductal adenocarcinoma (PDAC). Compared with normal pancreatic tissue, the expression of *KLF7* was upregulated in PDAC tissues [74]. Knockdown of *KLF7* expression inhibited the invasion and migration of transplanted PDAC cells in mice, and downregulation of *KLF7* expression inhibited the expression of interferon-stimulated genes, decreased Golgi complex integrity, and inhibited the growth and metastasis of PDAC [74] (Figure 3D). The MEK inhibitor trametinib and the tumor suppressor P53 inhibited PDAC progression by inhibiting *KLF7*

Table 3. KLF7 and human diseases

Disease	Function of KLF7	Ref.
Type 2 diabetes mellitus	Overexpression of KLF7 inhibited the biosynthesis and secretion of insulin in pancreatic β cells, as well as decreased insulin sensitivity in peripheral tissues.	[28]
Blood disease	Increased expression of *KLF7* was an independent predictor for poor prognosis in pediatric acute lymphoblastic leukemia. Overexpression of *KLF7* inhibited the proliferation of bone marrow cells and promoted early thymocyte survival.	[65,66]
Lung cancer	*KLF7* expression was upregulated in many kinds of lung cancers, such as lung adenocarcinoma and non-small cell lung cancer.	[67–70]
Gastric carcinoma	The DNA methylation level of *KLF7* in diffuse-type gastric adenocarcinoma was changed. KLF7 could promote the migration of gastric cancer cells and accelerates the progression of gastric cancer.	[16,17,71]
Squamous cell carcinoma	*KLF7* was upregulated in squamous carcinoma, and the elevated KLF7 expression was related to poor squamous carcinoma prognosis.	[42,72,73]
Pancreatic ductal adenocarcinoma	Knockdown of *KLF7* expression inhibited the invasion and migration of transplanted PDAC cells. Trametinib and P53 could inhibit the progression of PDAC by suppressing *KLF7* expression.	[74]
Glioma	Overexpression of KLF7 induced an increase of polyamine production and the occurrence of glioma.	[75]
Ovarian cancer	High-expression of *KLF7* was an unfavorable prognostic marker for the overall survival rate of advanced high-grade serous ovarian cancer patients.	[76]
Osteosarcoma	*KLF7* was upregulated in the tissues and cells of osteosarcoma (OS), and it mediated the tumor promotion role of KCNQ1OT1 in the development of OS.	[77]
Rectal cancer	High expression of *KLF7* might be a marker for insensitivity to preoperative radiotherapy and chemotherapy in patients with locally advanced rectal cancer.	[78]
Prostate cancer	The *KLF7* expression of prostate cancer tissue was lower than that of normal tissue, however, high expression of *KLF7* was associated with the poor prognosis of prostate cancer.	[79]

expression [74] (Table 3). In addition, a transcription factor enrichment prediction performed among the survival-associated splicing gene (AS) events using FunRich software showed that KLF7 is a transcription factor associated with survival-associated alternative AS events in pancreatic cancer [83].

Glioma

KLF7 is upregulated in glioma tissues, and its expression is inversely correlated with the survival of patients [75]. Knockdown of *KLF7* inhibited the tumorigenicity of glioma cells in mice and the proliferation, growth, and migration of glioma cells *in vitro* [75]. Mechanistically, KLF7 can promote the urea cycle by activating the transcription of argininosuccinate lyase (ASL), which in turn leads to increased polyamine production and glioma development [75] (Figure 3D and Table 3). Additionally, KLF7 might mediate the antitumour effect of miR-136-3p in glioma cells, and overexpression of miR-136-3p inhibits the growth, migration, and apoptosis of glioma cells by inhibiting *KLF7* expression [81] (Figure 3C).

Other cancers

High expression of *KLF7* is an adverse prognostic marker for overall survival in advanced high-grade serous ovarian cancer (HGSOC) [76]. Knockdown of *KLF7* inhibited the proliferation, migration, invasion, and spheroidization of HGSOC cells and downregulated the expressions of EMT-related genes and stem cell marker genes in OV-90 and PEO1 cells [76] (Figure 3D and Table 3).

In addition, the upregulation of *KLF7* expression in osteosarcoma tissues and cells may mediate the tumor-promoting effect of KCNQ1OT1 in osteosarcoma [77]. In osteosarcoma cells, KCNQ1OT1 promoted *KLF7* expression by taking up its expression inhibitor miR-3666, and overexpression of *KLF7* counteracted the suppression of *KCNQ1OT1* knockdown on the proliferation, migration, and invasion of osteosarcoma cells [77] (Table 3).

Additionally, high expression of *KLF7* may be a marker of insensitivity to preoperative radiotherapy and chemotherapy in patients with locally advanced rectal cancer [78]. The *KLF7* expression of prostate cancer tissue is lower than that of normal tissue; however, high expression of *KLF7* in cancer tissue is associated with poor prognosis in prostate cancer [79] (Table 3).

Oncogenic Mechanisms of KLF7

The oncogenic role of KLF7 in a variety of cancers has been gradually discovered. Considering its ubiquitous expression in adult tissues and high expression in many cancer tissues, it is possible that *KLF7* is an oncogene and that its expression will be upregulated by some unknown factors during cancer development.

During the development of cancers, the oncogenic mechanisms of KLF7 reported in a previous study involve at least three aspects: the biological behavior of tumor cells, tumor endocrine factors, and the tumor cell microenvironment. In detail, KLF7 can regulate cell behavior and plays roles in the processes of proliferation, growth, invasion, migration, EMT, and stemness of tumor cells. In addition, KLF7 can also regulate the integrity of the Golgi complex in cancer cells and affect tumor endocrine function. Additionally, KLF7 can target the urea cycle to affect the microenvironment of cancer cells (Figure 3D).

Conclusions

KLF7 is an important transcription factor with multiple biological functions. Substantial ongoing progress has been made in the understanding of KLF7 over the past two decades (Figure 4); however, the molecular function of KLF7 in biology is still not well

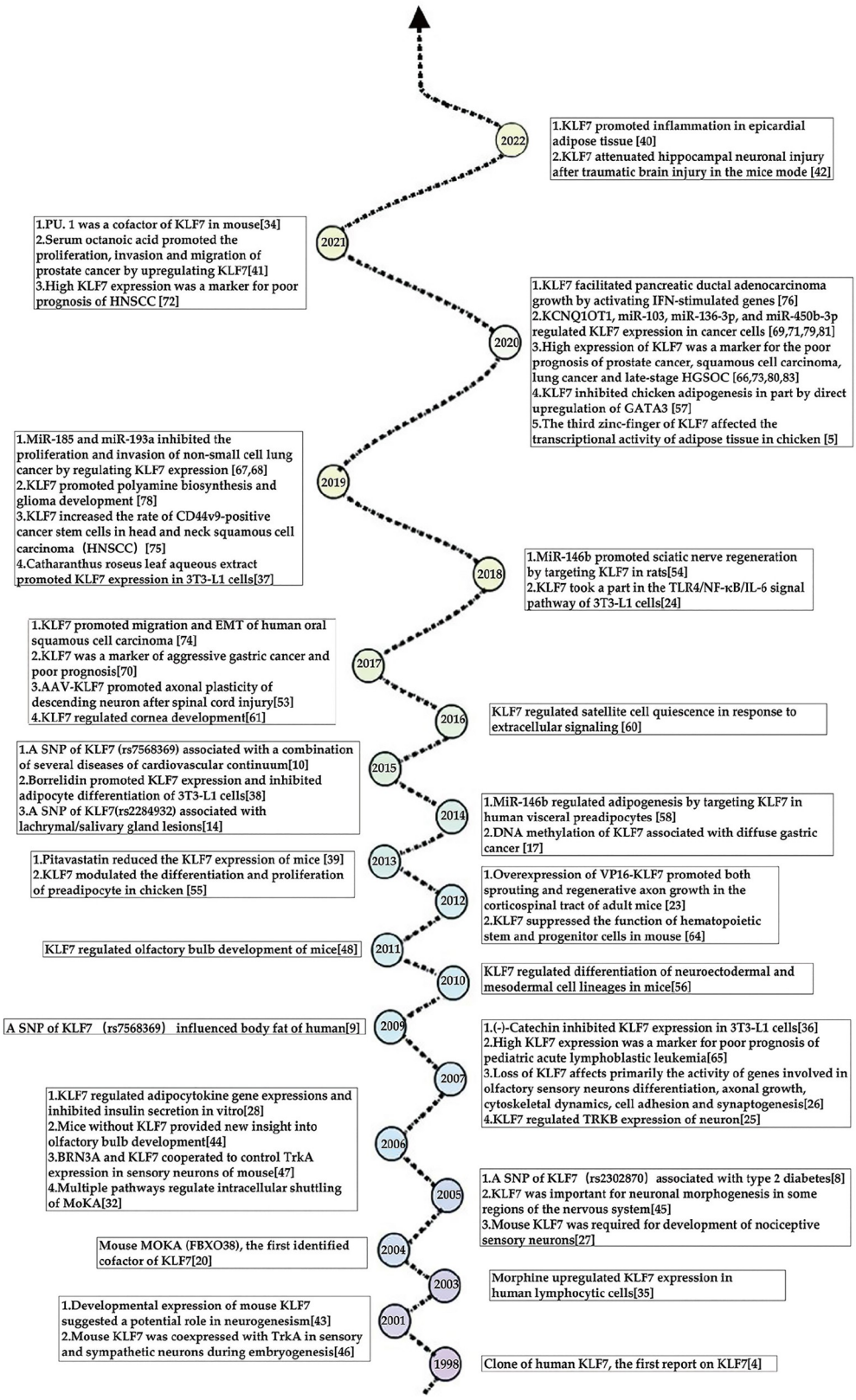

Figure 4. The discovery of *KLF7* and its report history KLF7 was first discovered in 1998. Earlier studies showed that it is a key regulator in the development of nervous system and type 2 diabetes. Later studies showed that KLF7 regulates cell stemness and the differentiation of cells from mesoderm and neuroectoderm. In recent years, great advances in KLF7 function have been made in the field of cardiovascular diseases and tumorigenesis.

elucidated.

On the one hand, in the field of developmental biology, the regulatory roles of KLF7 in the development of the nervous system, adipose tissue, muscle tissue and corneal epithelium and stem cell maintenance need to be further investigated *in vivo*, especially in some nonrodent animal models. On the other hand, in the field of medical science, the target genes and molecular mechanism of KLF7 in obesity, diabetes and hematologic diseases need to be further elucidated. In addition, the functions of KLFs are in some cases overlapping and in others widely divergent; however, few studies have been performed to explore the biological or molecular function of KLF7 in the context of other KLFs. Undoubtedly, more studies are needed to enhance our understanding of the roles of KLF7 in biology and diseases and to reveal how it fits in with the rest of the KLF7 family in biological function.

In addition, important tumor oncogenic functions have been defined for KLF7 in cancer, and the roles of KLF7 in many cancers have been demonstrated in the past 5 years. *KLF7* is highly expressed in lung cancer, gastric cancer, head and neck squamous cell carcinoma, pancreatic ductal adenocarcinoma, glioma and ovarian cancer and acts as an oncogene in these cancers. Downregulation of KLF7 expression may be a new clinical idea for the treatment of these cancers.

Additionally, overexpression of KLF7 has shown promising therapeutic effects on neurological damage and degenerative diseases in rodents. It is possible that upregulation of KLF7 expression is a target for the treatment of these diseases in humans.

Some progress has been made in the field of chemical substances targeting *KLF7*. The (–)-catechin, pitavastatin, and trametinib could downregulate *KLF7* expression in some cells, and morphine, CRACE, borrelidin, lipopolysaccharide and caprylic acid might upregulate *KLF7* expression *in vitro*. However, whether these substances have similar functions *in vivo* is not clear. Thus, their clinical application value in human disease still needs to be evaluated.

In addition, genetic factors that regulate *KLF7* expression have also attracted the attention of researchers, and GATA2/3 have been reported as regulators of KLF7 transcription by targeting its proximal promoter in chicken preadipocytes [84]. In addition, miRNAs targeting KLF7 expression have also been widely reported in some cancer studies. However, the regulatory mechanism of *KLF7* expression deserves further study to provide a basis for drug development.

Additionally, the protein structure of KLF7 is still unclear, and it is necessary to clarify the protein structure of KLF7 to screen drugs targeting KLF7 function. Focusing on the expression regulation mechanism and protein structure of KLF7 may be of great value for the treatment of neurological diseases, obesity, T2DM, cancers and hematologic diseases.

Funding

This work was supported by the grants from the National Natural Science Foundation of China (Nos. 31960647 and 31501947) and the Youth Innovative Talents Project of Shihezi University (Nos. CXBJ201905 and ZZZC202183).

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