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Chapter

Transcriptional and Epigenetic Regulation of Krüppel-Like Transcription Factors

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Abstract

Krüppel-like factors (KLFs) are a family of zinc finger transcription factors (ZF-TF) that are now known to be involved in complex biological processes including cancer, proliferation, and cardiovascular disease as well as developmental processes. KLFs first gained notoriety when it became known that they are crucial for promoting and maintenance of stem cell pluripotency. Over the past 20 years since the discovery of Krüppel-like factor 1 (KLF1), this transcription factor family has grown to include 18 members and 7 closely related members of the specificity protein 1 (Sp1) family. In the present study, we review the mechanisms related to regulation of KLFs by direct promoter activation or repression. We will also review and discuss some mechanisms of posttranslational modifications that could affect KLF function. We seek to understand how these transcriptional regulators are themselves regulated and how that regulation could become aberrant during various disease processes.

Keywords: Krüppel-like zinc finger proteins, transcription, posttranslational modification, epigenetics, RNA, promoters

1. Introduction

The specificity protein 1 (Sp1)/Krüppel-like factor (KLF) proteins are a family of highly conserved transcription factors that are characterized by the presence of three highly homologous Cys2/His2-type zinc fingers near the C-terminus that bind GC/CACCC box. Amino acid sequences in the transcription activation/repression domains are less conserved among family members; however, there are subfamilies based on sequence similarities within this group. These subfamilies tend to share co-activators or co-repressors to aid in how they regulate genes. So far, seven members in the specificity protein (Sp) subgroup and 18 members in the KLF subgroup have been identified in mammalian cells [1]. This family of transcription factors is able to function as both transcriptional activators and repressors based on the gene and cellular contexts. KLFs gained notoriety as Krüppel-like factor 4 (KLF4), Krüppel-like factor 2 (KLF2), and Krüppel-like factor 5 (KLF5) were suggested to be important for embryonic stem cells and stem cell reprogramming [2–7] alongside Oct4, Sox2, and Nanog. However, we have only begun to touch the surface of the transcriptional control these factors exert during embryonic development, maintenance of normal function, and the breakdown of normal processes seen in many diseases.

The goal of this chapter is to begin to describe our current knowledge of how the KLFs are regulated during development or disease. We seek to begin to understand the ways cells either promote or repress the presence of the KLFs through a variety of transcriptional and translational mechanisms.

2. Regulation by and of KLFs

2.1 Krüppel-like factor 1

Krüppel-like factor 1 (KLF1) or erythroid Krüppel-like factor is an essential transcription factor for erythroid development and was found to be key in the regulation of many facets of blood development. KLF1 is expressed in the developing blood as well as being weakly expressed in mast cells [1]. KLF1 is key to blood development as Klf1−/− mice die around E14 due to severe anemia [8]. Several studies also showed KLF1 is able to directly bind to the β-globin promoter to activate the gene's transcription as part of fetal hematopoiesis in the liver [9, 10]. The null embryos provided a wealth of knowledge about KLF1 early on, suggesting that β-thalassemia could be linked with KLF1 deletions [11]. More recent studies have also shown that KLF1 is able to either directly or indirectly repress the transcription of the γ-globin gene to promote the expression of β-globin during blood development [12].

In humans, >140 KLF1 variants, causing different erythroid phenotypes, have been described. The KLF1 Nan variant, a single amino acid substitution (p.E339D) in the DNA-binding domain, causes hemolytic anemia and is dominant over wild-type KLF1 [13]. This variant in the developing liver demonstrates defects in erythroid maturation that resemble those seen with the KLF1−/−, again demonstrating the importance of KLF1 in blood development. Furthermore, recent studies suggest that there is an enhancer element in the KLF1 gene that is susceptible to methylation and that elevated levels of methylation in that region correlate with patients with juvenile myelomonocytic leukemia (JMML) [14]. KLF1 was also found to play a role in the inhibition of megakaryocytes while also stimulating erythroid lineages at the same time [15].

2.2 Krüppel-like factor 2

Krüppel-like factor 2 or lung Krüppel-like factor (LKLF) was isolated in humans in 1999 and found to be 85% similar in nucleotide identity and 90% similar in its amino acids to mouse and located on chromosome 19p13.1 [16]. Of special interest, a region of 75 nucleotides within its proximal promoter was found to be identical between human and mouse [16]. This identical region in the mouse and human promoters for KLF2 has been found to be critical for its regulation in lung, blood, endothelial cell, and T lymphocyte development [15–22]. KLF2 was shown to be essential for normal development within mice, and knockout embryos were lethal around day 12.5 and lung function was also severely impaired in KLF2−/− chimeras [22]. KLF2 expression appears to also be important for the maintenance of normal lung function, as methylation of KLF2 was associated with metastasis and worsening prognosis in non-small-cell lung cancer [23].

KLF2 was also shown to be essential for early erythropoiesis and regulation of the β-globin gene, and klf2−/− mice also exhibited hemorrhage in developing blood cells [17]. In mature T cells, KLF2 is required for T-cell trafficking, and elimination of KLF2 in T cells affects the expression of sphingosine-1-phosphate receptor and CD2L and beta7 integrins, receptors all important in T-cell trafficking [18, 24].

ERK5 was also shown to be important in T-cell activation, and ERK5−/− cells were unable to activate genes for T-cell function [25, 26].

KLF2 is also an important regulator of heart and aorta development and normal maintenance of endothelial cells [27–29]. KLF2 has been shown to be activated by shear stress through the conserved 75-base pair region in the human and mouse promoters [30]. This region was shown to requite PI3K for activation and PCAF (p300/CAMP-response element-binding protein-associated factor) and heterogeneous nuclear riboprotein D to induce acetylation of H3 and H4 histones [31]. Additional riboproteins and acetyltransferases such as HnRNP-U, hnRNP-D, and p300 were also found to bind via this conserved region in the KLF2 promoter [32]. KLF2 was also found to be activated by nucleolin in endothelial cells following shear stress, and activation via nucleolin was also PI3K dependent [33].

In terms of a negative regulation of KLF2 in endothelial cells, KLF2 was shown to be negatively regulated by p53, which bound to the KLF2 promoter to induce deacetylation of the KLF2 histone H3 [34]. Tumor necrosis factor alpha (TNF-α) was shown to activate NF-Kβ p65 to complex with histone deacetylase 4 to prevent MEF2 binding to the KLF2 promoter, demonstrating a possible additional mechanism of the downregulation of KLF2 in endothelial cells in response to injury. Finally, low-density lipoprotein (LDL) cholesterol was found to stimulate the methylation of both DNA and histones on the KLF2 promoter and to contribute to the downregulation of KLF2 in response to LDL cholesterol. These mechanisms suggest there are a number of complex pathways that control the expression of KLF2 in a number of different tissue types.

2.3 Krüppel-like factor 3

Krüppel-like factor 3 (KLF3) or basic Krüppel-like factor (BKLF) is widely expressed and abundant in erythroid cells. KLF3 is believed to regulate adipogenesis, erythropoiesis, and B-cell development [35, 36]. KLF3 is able to interact with the co-repressor CtBP to repress gene transcription much like Krüppel-like factor 8 (KLF8) and Krüppel-like factor 12 (KLF12), and the N-terminal repression domain is important for this interaction in KLF3 [37–39]. KLF3 has been found to be sumoylated and that this sumoylation also affects its interaction with CtBP [37]. KLF3 has been shown to have a role in adipogenesis as forced expression of KLF3 was shown to block adipocyte differentiation [40]. Recent methylation data from endothelial cells demonstrates that KLF3 is highly methylated in flow-dependent conditions but can be reversed with 5-aza-2′-deoxycytidine treatments [41]

2.4 Krüppel-like factor 4

Krüppel-like factor 4 or gut-enriched Krüppel-like factor (GKLF) or endothelial zinc finger (EZF) protein is most similar to KLF2 and functions in the regulation of the epithelial of the gut and skin, endothelial cells, smooth muscle cells in vascular disease, and induced pluripotent stem cells (iPSC) [1, 42]. KLF4−/− mice died shortly after birth due to epithelial barrier defects in skin and gut barriers [43]. KLF4 is regulated by AP-2alpha during early and mid-embryogenesis to help regulate proliferation [44].

KLF4 became well-known after the discovery that it was one of the regulating factors along with Oct4, Sox2, and Nanog of induced pluripotent stem cells [4–7]. Oct4 was later found to regulate the expression of KLF2, while LIF/Stat3 was thought to regulate the activation of KLF4 in embryonic stem cells [45, 46]. Additional studies have suggested that posttranslational modifications increase or

decrease the stability of KLF4 mRNA and these modifications control the exit from pluripotency [47]. Furthermore, these modifications mediate the ability of KLF4 to complex with other pluripotency transcription factors and bind DNA. Finally, Oct4 has been shown to contain a linker region that is important for loosening chromatin, complexing with Brg1, and allowing for KLF4 to bind during cellular reprogramming [2]. Clearly, the interactions and mechanisms of pluripotency factors in stem cells are complex and require further investigation.

KLF4 is required for normal functioning of the gut epithelial as deletion of KLF4 resulted in altered proliferation [48]. KLF4 and KLF5 are often found in the same types of tissues, bind to similar or identical DNA elements, and often exert opposing affects in different tissue types. KLF4 has been found to bind with p53 on the p21 genes in epithelial cells and in smooth muscle cells to inhibit proliferation [42, 49, 50].

In the case of smooth muscle cell proliferation, sumoylation of KLF4 causes it to fall off the p21 promoter and decreases p21 transcription following PDGF-BB treatments [51]. Sumoylation is also believed to affect binding of KLF4 to smooth muscle marker genes in TGFβ treatment [52, 53]. In smooth muscle cells in vascular disease, KLf4 has been shown to be activated by Sp1 and Oct4 binding to the KLF4 promoter [54, 55]. Separately, in macrophages KLF4 sumoylation promotes an IL-4-induced macrophage polarization to an M2 state, suggesting KLF4 plays a role in inflammation and macrophage polarization states [56]. However, in endothelial cells KLF4 is important along with KLF2 for the maintenance of endothelial cell integrity and normal endothelial barrier function [29]. KLF4 function in vascular disease could fill chapters of books investigating its many roles and functions; however, our goal is to highlight some of the mechanisms of its regulation in these processes.

Finally, KLF4 is also regulated by DNA methylation in several different types of cancers. KLF4 was found to be hypermethylated in renal cell carcinomas [57] and endometrial cancers [58]. However, a surprising discovery was KLF4 can bind to methylated regions of chromatin to mediate activation of transcription without the need for demethylation of the DNA in some types of cancer cells [59, 60]. These studies demonstrate a new role for some transcription factors as methylation readers in the transcription process.

2.5 Krüppel-like factor 5

Krüppel-like factor 5 or intestinal-enriched Krüppel-like factor (IKLF) or basic transcription element-binding protein 2 (BTEB2) is located on chromosome 13q22.1 and is important in the expression of the gut epithelia, vascular smooth muscle cells, and white adipose tissues [1, 61]. KLF5 is important in epithelial cells as it is located in the base of the crypts where cells are proliferating toward the villi. In general, KLF4 and KLF5 have been shown to compete to the same sites on DNA [62] and have also been suggested to be involved in their own regulation [42]. KLF5 has been shown to be important in gastric tumor progression and initiation and often correlate with KRAS mutations [63, 64].

KLF5 has also demonstrated to be important in the development and maintenance of the heart, aorta, and lung systems [20, 65–69]. Following angiotensin II induction, KLF5 was shown to bind to PDGF-A and activate it. KLF5 was also shown to be activated by RARα binding site in the KLF5 promoter [65, 70]. KLF5 has been shown to be regulated by acetylation. When KLF5 is associated with p300, it is acetylated and able to activate gene expression. Conversely, when SET is bound to KLF5, it prevents acetylation of KLF5 and its transcriptional activity [71]. These studies suggest that KLF5 can be regulated directly by modifications to control its transcriptional activity.

Expression of KLF5 in breast cancers was found to be correlated with a negative prognosis and decreased survival [72], while in clear cell renal cell carcinoma, hypermethylation and decreased expression of KLF5 were associated with a poorer prognosis [73]. Hypermethylation of KLF5 in acute myeloid leukemia was also associated with a poorer prognosis [74]. These studies suggest that KLF5 function in cancer is cell and perhaps even cell lineage specific. Within various cancers, KLF5 has also been demonstrated to be regulated by micro-RNAs. In gastric cancer, miR-145-5p directly targets KLF5 and promotes the differentiation of gastric cancer via KLF5 downregulation [75]. Separately, in hepatocellular carcinoma miR-214-5p acted as a tumor suppressor that could directly target and promote the downregulation of KLF5 [76]. These data demonstrate complex regulatory pathways involved in KLF5 regulation in cancer progression.

2.6 Krüppel-like factor 6

Krüppel-like factor 6 (KLF6) or zinc finger transcription factor 9 (ZF9) has been shown to be important for endothelial biology, adipogenesis, and tumor suppression in a wide variety of cancers. During embryogenesis, it is expressed in a time-sensitive manner in the kidney, cornea, gut, and yolk sac [77–80]. KLF6−/− mice are embryonic lethal due to yolk sac abnormalities [77–80]. KLF6 has been suggested to have a role in endothelial vascular remodeling following injury as it binds and activated urokinase plasminogen activator 1, endoglin, and matrix metalloproteinase 9 [81]. Interestingly, KLF6 has an alternative form of regulation because the gene produces at least four different isoforms that are able to affect DNA binding and transcription [82]. The full-length isoform of KLF6 is believed to function as a tumor suppressor and can be regulated by loss of heterozygosity, mutation, or decreased expression in different cancer types. The full-length KLf6 was found to have one deleted allele in prostate cancer, and the leftover allele was mutated 71% of the time, preventing KLF6 from functioning to activate p21 [83]. Of the isoforms of KLF6, the Krüppel-like factor 6 splice variant 1 (KLF6-SV1) was found to be oncogenic and upregulated in prostate, lung, and breast cancers and inhibits the activity of the full-length KLF6 [82]. This is the first KLF to be regulated in part by alternative splicing and suggests that directed targeting of the splice variants of KLF6 could represent a potential target for elimination therapy.

KLF6 can be regulated by methylation both to downregulate its expression and to prevent its binding to certain sites in cancer. Studies have suggested a possible role for methylation of KLF6 in hepatocellular carcinoma and in colorectal cancer [84, 85]. Separately, KLF6 can be prevented from binding on the SIRT5 promoter by the presence of DNA methylation during adipocyte differentiation [86]. KLF6 also could not bind the tissue factor pathway inhibitor-2 promoter following hypermethylation of its promoter during adipocyte formation [87].

2.7 Krüppel-like factor 7

Krüppel-like factor 7 (KLF7) or ubiquitous Krüppel-like factor (UKLF) has high expression in the brain and spinal cord and is important in the developing brain and nervous system [88]. KLF7 was identified originally in 1998, located on chromosome 2, and was believed to share a strong similarity with KLF6 [89]. Studies by Laub et al. found that KLF7 was important for upregulation of p21, repression of cyclin D1, and growth arrest in neuronal cells, thereby helping to lead to their differentiation and maturation [88]. In separate but related studies, the same laboratory found that elimination of KLF7 leads to neonatal lethality and the elimination affected areas of the olfactory, visual system, cerebral cortex, and hippocampus [90].

They also further investigated the roles of p21 and p27 and found KLF7 affected their expression in these areas during development [90]. Additional studies suggest that KLF7 regulates a number of genes in olfactory neuron development and axonal growth [91, 92]. In corneal epithelial differentiation, KLF7 was found by ChIP-sequencing to inhibit the activity of KLF4 to promote a corneal "progenitor"-like state [93].

KLF7 has also been suggested to play a role in type 2 diabetes. Studies have suggested that there are single nucleotide polymorphisms (SNPs) in the KLF7 gene that are associated with increased type 2 diabetes in Asian populations [94]. The same group further investigated the role of KLF7 and found that overexpression of KLF7 impaired the insulin production system and secretion in pancreatic beta cells while also inhibiting insulin sensitivity in the peripheral tissues [95]. KLF7 was also found to activate the TLR4/NF-kB/IL-6 pathway in adipocytes [96]. Finally, KLF7 has recently been also been found to be elevated in gastric cancers in patient samples in some populations and has been suggested to be a possible biomarker for the disease [97].

2.8 Krüppel-like factor 8

Krüppel-like factor 8 is expressed at low level in most tissue types [1]. KLF8 is a member of the same subfamily of Krüppel-like factors that includes KLF3 and KLF12 as all three KLFs recruit CtBP to repress transcription [37–39, 98]. These data also demonstrated that KLF8 needs its own DNA-binding domain to bind DNA but needs its repression domain for interaction with CtBP. KLF8 has been shown to be upregulated and activated during several types of cancers including those from ovarian, breast, and renal carcinomas [99–101]. KLF8 was also shown to activate the FHL2 gene in pancreatic cancer cells and to promote metastasis and epithelial-to-mesenchymal (EMT) transitions in pancreatic tumor cells [100, 101]. Furthermore, KLF8 was shown in gastric cancer to induce HIF-1 expression and promote epithelial-to-mesenchymal transitions in gastric cancer [102]. Finally, KLF8 methylation levels were also tested in prostate cancer cell lines but did not prove to be causally related to the progression of prostate tumors [103].

2.9 Krüppel-like factor 9

Krüppel-like factor 9 (KLF9) or basic transcription element-binding protein (BTEB) is broadly expressed, but its expression is especially high in the developing brain and thymus and in the smooth muscle of the gut and bladder [1, 104]. Interestingly, it has been demonstrated that although the mRNA for KLF9 is transcribed in many areas, the brain is the main organ where it is translated into protein [105]. The zinc fingers of the KLF9 gene are commonly now thought to be very closely related to Sp1 as they have a high sequence similarity. However, beyond their DNA-binding domains, these proteins share little sequence similarity [105]. In the brain expression, there is a thyroid hormone response element in the promoter of the KLF9 gene that accounts for its transcription and expression in the postnatal brain [105, 106]. KLF9 was also found to bind to a number of proximal promoter regions on genes important for brain function to repress transcription in hippocampal neurons [106, 107].

KLF9 expression has been noted in cancers of the mammary glands and uterus because of its ability to interact with the progesterone response elements to stimulate progesterone response elements [108, 109]. KLF9 is also required for the development of fertility in females as KLF9−/− mice were subfertile and were unable to differentiate their reproductive tissue without KLF9 [109]. KLF9−/− mice also were

found to have aberrant regulation of their intestinal crypt cell proliferation and villus migration [110]. These data suggest that KLF9 also regulates the smooth muscle and the turnover of intestinal cells.

Finally, in follicular lymphoma, KLF9 was found to be hypermethylated and silenced in tumors along with a number of polycomb genes [111]. Separately, in breast cancer hypermethylation of KLF9 was correlated with a favorable cancer prognosis [112].

2.10 Krüppel-like factor 10

Krüppel-like factor 10 (KLF10) or transforming growth factor-inducible early gene 1 (TIEG1) is known as a TGFβ-inducible gene as it is rapidly induced by TGFβ treatments and then quickly returns back to basal levels [113, 114]. KLF10 is induced by multiple members of the TGFβ superfamily and then goes on to suppress Smad7 and co-activate together with Smad2. It is believed that KLF10 plays a major role in the mediation of TGFβ inhibition of cell proliferation and inflammation and induction of apoptosis [113, 115]. The rapid induction and then degradation of KLF10 are believed to be accounted for by SIAH proteasomal degradation [113]. In these studies, KLF10 was found to interact directly with SIAH which then mediates its degradation [113]. These studies suggest a protein degradation method of regulation.

KLF10 has been cited to be important in bone development and osteoporosis, adipocyte development, and heart, lung, brain, and T-cell activation [1, 116]. In adipocyte differentiation, C/EBPβ was found to bind and activate the KLF10 promoter, while KLF10 bound to the C-EBPα promoter to inhibit its activation [117]. In bone development, SNP analysis revealed that variants in the KLF10 gene were associated with bone loss in older men [118]. Conversely, studies in KLF10 null mice suggest a gender-specific role of KLF10 in the maintenance of bone density [19]. KLF10 null osteoblasts were also found to be defective in mineralization and in osteoblast support of osteoclast differentiation [119]. Finally, KLF10 null mice had impaired tendon function as adults with corresponding difficulty in tendon function [120].

In heart development, KLF10−/− mice developed cardiac hypertrophy and an increase in ventricle size and an increase in wall thickness, suggesting the importance of KLF10 to the maintenance of normal heart function [121]. KLF10 is also important in T-cell and Treg development along with TGFβ as deletion of KLF10 in T cells augmented atherosclerosis and led to impaired T-cell function [122].

KLF10 has been shown to be methylated in pancreatic cancers by DNMT1 with a correlation between methylation status and tumor grade [123]. The more the methylation and repression of the KLF10 promoter, the worse the tumor grade. These studies suggest that an important regulatory mechanism for KLF10 is also via methylation of its promoter.

2.11 Krüppel-like factor 11

Krüppel-like factor 11 (KLF11) or transforming growth factor-inducible early gene 2 (TIEG2) or FKLF is known to be expressed in the pancreas and in erythroid cells in the fetal liver. KLF11 is located in humans at chromosome 2p25 [1, 124–126]. KLF11 shares 91% homology with KLF10 in the zinc finger domain and 44% homology with the N-terminus of KLF10 [127]. These studies also demonstrated that overexpression of KLF11 inhibits cell proliferation [127] and is induced by TGFβ signaling pathways.

KLF11 contains three repression domains that are believed to be important for its repressor activities [128]. TGFβ signaling pathway induction means that KLF11

often cooperates with Smads to induce changes in transcription following TGFβ treatment. KLF11 later was found to be activated by several members of the TGFβ superfamily and not just by TGFβ treatment alone [114]. Studies have shown in neuronal cells that KLF11 regulates the transcription of the dopamine D2 receptor by complexing with p300, a histone acetylase, to promoter transcription [129]. KLF11 was also found to regulate collagen gene expression through the heterochromatin protein 1 gene-silencing pathway, as mutants defective for coupling to this epigenetic modifier lose the ability to repress COL1A2 and to prevent fibrosis in KLF11−/− mice [130]. As part of the TGFβ induction of KLF11, TGFβ induction allows KLF11 to interact with Smad3 and to repress certain promoters. In the case of pancreatic cancer, KLF11 was found to bind with Smad3 to the c-myc promoter following TFG-β treatment [131].

KLF11 is important not only for its TGFβ response but also for its associations with diabetes and obesity [132, 133]. A variant of KLF11 was found that could lead to type 2 diabetes and obesity [134]. Further studies revealed additional variants that may affect KLF11 regulation of the insulin promoter and type 2 diabetes [133]. KLF11 was also found to interact with p300 in maturity-onset diabetes of the young to induce transcriptional changes in the pancreas [135]. In converse, KLF11 can also interact with mSin3a in pancreatic cancer by repression of the Smad7 promoter [136]. Ectopic expression of KLF11 increased the sensitivity of cells to oxidative drugs [137]. Methylation of KLF11 has been suggested to be one mechanism of its downregulation in several types of cancers [138, 139].

2.12 Krüppel-like factor 12

Krüppel-like factor 12 or BETB1 was first identified in the regulation of the AP-2α gene and is located on chromosome 13q21-13q22 [140]. In the case of the AP-2α gene, KLF12 functions as a transcriptional activator and appears to relate back to KLF12's function as a marker of tumor development [141–143]. KLF12 is a marker for gastric cancer progression, and overexpression of KLF12 promotes tumor cell invasion and progression [142]. However, in lung cancer cell lines, it was shown that KLF12 was important for the regulation of anoikis and the progression through the S phase of cell cycle [141]. These data suggest that KLF12 may have multiple different roles in cancer beyond what was previously identified. KLF12 is also one of the KLF factors to interact with the mSin3a repressor complex via an alpha-helical motif in a repression domain of the transcription factor [144].

KLF12 not only plays roles in tumor progression but is also believed to play a role in the developing kidney after birth. KLF12 was shown to be expressed in the collecting ducts of the kidney after birth and could directly regulate the UT-A1 but not the ENaC promoters, two genes important for the development of the collecting ducts [145]. A recent study suggests that KLF12 might in part be regulated in cancer by the methylation of miR-205 by long noncoding RNA ELF3-antisense RNA 1. These data suggest that miR-205 and RNA ELF3-antisense RNA 1 exist in a complex regulatory loop involving KLF12 [146].

2.13 Krüppel-like factor 13

Krüppel-like factor 13 (KLF13) or BTEB3, FKLF2, or RFLAT-1 was first discovered along with Krüppel-like factor 14 (KLF14) using an expressed sequence tag database to search for additional conserved KLF DNA-binding domains [129]. KLF13−/− mice are one of the few KLF mice that are viable and fertile; however, they display abnormal blood cell development [147, 148] suggesting that KLF13 is

critical for both B- and T-cell developments [148–150]. One part of this developmental process is KLF13's interaction with PPAR4 [151] to regulate CCL5. Not only is KLF13 important for blood cell development, it has also been shown to be important for the developing heart [104, 152]. To this end, KLF14 can also be linked to Holt-Oram syndrome, an inherited disorder characterized by abnormalities of the upper limbs and heart, via its interaction with the TBX5 promoter [153].

KLF13 has also recently been suggested to be a tumor suppressor in glioma cells [154]. These studies found that KLF13 was downregulated by hypomethylation across the gene to promote its silencing; however, decreases in DNMT1 expression or decreases in hypomethylation patterns of KLF13 decreased proliferation and migration of glioma cells [154]. Another example of KLF13 methylation is the methylation of the obesity-related variant of KLF13: cg07814318. The methylation of this particular SNP appears to be related to increased childhood obesity [155]. These studies suggest that methylation of promoters could be one possible mechanism of regulation of KLFs in development or disease.

Another possible mechanism of regulation of KLF13 is through the co-repressor complex mSin3a [144]. In this instance, KLF13 was found to interact with the mSin3a repressor complex via an alpha-helical motif in a repression domain [144]. Additional studies from this group suggest that multiple KLF factors (BTEB1, BTEB3, BTEB4) could also contain this alpha-helical domain in their repression regions.

2.14 Krüppel-like factor 14

Krüppel-like factor 14 was first discovered using expressed sequence tag databases to search for the presence of additional conserved KLF DNA-binding domains [129]. KLF14 has 72% similarity with the human Sp2; however, the majority of its similarity exists within its DNA-binding domain [129]. Most reports suggest that its expression is ubiquitous [1]. Interestingly, KLF14 is intron-less and exists on chromosome 7q32. KLF14 is a mono-allelic expression pattern and shown to be hypomethylated in many tissues, further suggesting a pattern of ubiquitous expression [156]. Further evidence also suggests that KLF14 could be derived from a retro-transposed copy of Krüppel-like factor 16 (KLF16) [156] and could be an example of accelerated evolution. KLF14 deletion has recently been linked with centrosome amplification, aneuploidy, and spontaneous tumorigenesis because KLF14 functions as a repressor of polo-like kinase 4 (PLK4). Without the repressive activities of KLF14 on PLK-14, PLK-14 can cause chromosomal abnormalities and promote tumorigenesis in cancer cells. The KLF14 gene has been linked to genomic variants that are highly correlative with basal cell carcinoma [157].

Genome-wide association studies not only revealed that KLF14 was linked with basal cell carcinoma, it also has revealed that KLF14 is linked with cholesterol metabolism, metabolic disease, and coronary artery disease. These studies suggest that KLF14 might function as an imprinted master regulator of metabolic function and that mutation of certain SNPs within the KLF14 gene can lead to a large-scale deregulation of metabolic gene function [158]. KLF14 was also found to regulate levels of HDL-C and hepatic ApoA-I production [159]. Guo et al. were able to find evidence that perhexiline was able to activate KLF14 and to reduce lesions in ApoE−/− atherosclerotic mice [159]. Separate but related studies suggest that this activity is related to the phosphorylation of KLF14 by both p38 MAPK and ERK kinase [160]. However, KLF14 was found to be decreased in endothelial cells in atherosclerosis, and overexpression of KLF14 actually inhibited NF-KB signaling by suppressing p65 [161]. KLF14 has also been shown to interact with p300 to promote sphingosine kinase activation and to enhance sphingosine production [162].

These data suggest a complicated pattern of expression for a ubiquitous transcription factor that could produce paradoxical effects in inflammatory disease such as cardiovascular disease or cancer. Interestingly, there still appears to be less known about how KLF14 itself is regulated.

2.15 Krüppel-like factor 15

KLF15 or kidney-enriched Krüppel-like factor (KKLF) demonstrates low levels of cardiac-specific expression during development but then exhibits adult expression in the kidney, liver, pancreas, heart, skeletal muscle, lung, and ovary. KLF15 was originally thought to be important for the regulation of different cell types in the kidney and repressed genes such as CLC-K1 and CLC-K2 [163]. However, its regulatory effects can be seen in the heart, skeletal muscle, gluconeogenesis, and circadian rhythms. In terms of the heart, KLF15 was demonstrated to be an inhibitor of cardiac fibrosis by repression of connective tissue growth factor (CTGF) [164]. In this mechanism, KLF15 inhibits the recruitment of the co-activator P-CAF but does not prevent SMAD3 from binding to the promoter [164]. Additional studies by the same group demonstrated that KLF15 was a negative regulator of cardiac hypertrophy via inhibition of GATA4 and MEF2 functions [165]. Recent studies further suggest that KLF15 was identified as a putative upstream regulator of metabolic gene expression in the heart via RNA-Seq and methylation sequencing and that KLF15 was itself regulated by EZH2 in a SET domain-dependent manner [166]. KLF15 was demonstrated to be silenced via methylation in ischemic cardiomyopathy which in turn leads to the silencing of many cardiac-specific genes.

KLF15 has been shown to also be important for metabolism [167]. In terms of the skeletal muscle, overnight fasting and endurance exercise induce KLF15 expression, while knockout of KLF15 induces abnormal energy flux, excessive muscle fatigue, and impaired endurance capacity [168]. KLF15 was later shown to complex in the liver with liver X receptor (LXR) to inhibit SREBF1 during fasting by recruiting the co-repressor RIP140 [169]. Finally, KLF15 is also important for nitrogen homeostasis and the maintenance of circadian rhythm as KLF15 knockout mice had no amino acid rhythm and no rhythm of the production of urea from ammonia [170]. These studies suggest the importance of KLF15 and suggest that investigations into how it is regulated by chromatin readers and writers will become important to these metabolic diseases.

2.16 Krüppel-like factor 16

Krüppel-like factor 16 or dopamine receptor regulating factor (DRRF) was first discovered in its regulation of the dopamine receptors in the developing brain and eye [171]. It is now known that KLF16 is expressed not only in the developing brain but also in the thymus, intestine, kidney, liver, heart, and bladder. KLF16 has recently been shown to not only regulate the dopamine receptor but also to regulate the ephrin receptor A5 (EphA5), but this regulation was methylation specific as methylation of the EphA5 promoter prevented KLF16 from binding [171]. These data suggest that one possible epigenetic mechanism regulating KLF16 is methylation of regions near its binding site.

KLF16 was found by Daftary et al. to bind to all three types of KLF binding site, the GC, CA, and BTE boxes using electromobility shift assays but prefers binding to the BTE box in cells and to mediate its effects via mSin3a, a transcriptional co-repressor complex but suggests that this function is both promoter and cell context dependent [172]. To further study this interaction, site-directed mutagenesis was performed of all of the serine, threonine, and tyrosine residues

believed to be possible targets for kinase phosphorylation signaling and found that mutation of tyrosine-10 altered the ability of KLF16 to interact with mSin3a [172]. Finally, KLF16 was also found to be regulated by nuclear localization and to be excluded from heterochromatin within the nucleus [172]. These studies suggest complex posttranslational regulatory mechanisms for KLF16 function in a cell- and promoter-dependent manner.

2.17 Krüppel-like factor 17

Krüppel-like factor 17 (KLF17) was first discovered in mouse as zinc finger protein 393 (ZFP393) or ZNF393 where it was shown to be expressed in the testis and ovaries, and the gene spans 8 kb in the distal portion of chromosome 4 in the mouse [173]. In humans KLF17 maps to chromosome 1p34.1. When it was discovered back in 2002, it was believed to be the first C2H2 germ cell-specific zinc finger protein. Identification of KLF17 in the human revealed that KLF17 was expressed not only in the testis but also in the brain and bone, albeit at relatively low amounts [174]. KLF17 also contains low sequence similarity between the human and mouse orthologues; however, a detailed transcriptional binding analysis by van Vliet et al. was able to demonstrate that KLF17 was a Krüppel-like transcription factor rather than being more closely linked to the specificity protein factor family (Sp family) [173].

KLF17 is hypothesized to be a tumor suppressor in multiple types of cancers, and a decrease in its expression has become correlated with a poor cancer prognosis [175]. KLF17 was demonstrated to be a tumor suppressor gene in metastatic breast cancer lines whose downregulation promotes the epithelial-to-mesenchymal transition in cancer cells [176]. These studies also suggested that KLF17 is a direct negative regulator of inhibitor of DNA binding 1 (ID1). Sadly, they do not offer a direct mechanism for the downregulation of KLF17 during breast cancer metastasis, but they do provide compelling data to suggest that KLF17 might have multiple functions in the male and female sex organs and that suppression of this factor could lead to increased tumorigenic potential [176].

Further evidence in non-small-cell lung cancer also suggests that KLF17 could function as a tumor suppressor [177]. These studies suggested that p53 recruits p300 to the KLF17 promoter to acetylate and turn on transcription [177]. In addition, p53 also physically interacts with KLF17 and promotes binding of KLF17 to certain gene promoters and promotes transcription of p53, p21, and pRB [177]. These data suggest an intricate cross-talk between KLF17 and p53 in tumorigenesis. Another way KLF17 is believed to inhibit cancer progression is through inhibition of proliferation via repression of UPAI-1 [178], which Cai et al. proposed inhibited the invasive properties of small-cell lung cancer cells. KLF17 was also suggested to be a tumor suppressor through a TGFB-/SMAD-dependent mechanism where KLF17 physically interacts with SMAD3 to target genes to prevent metastases [179]. MiR-9, a micro-RNA important for tumor invasion and metastasis, has been shown to inhibit the activation of KLF17 by directly binding to the 3′-untranslated region (3′-UTR) [175]. These pathways suggest that KLF17 can be regulated both by direct promoter activation and by posttranscriptional modifications such as RNA degradation by micro-RNAs.

In converse, in endometrial cancer KLF17 was found to be an inducer of epithelial-to-mesenchymal transition and resulted in activation of TWIST1 [180]. This finding demonstrated that KLF17 bound directly to the TWIST promoter to activate its transcription [180]. KLF17 was also shown to bind directly to estrogen receptor alpha (ERα) to prevent it from being able to bind directly to chromatin [181]. ERα then also contributed to the suppression of KLF17 using the

co-repressor histone deacetylase 1 (HDAC1) to promote KLF17 deacetylation and chromatin condensation [181].

2.18 Krüppel-like factor 18

Krüppel-like factor 18 (KLF18) was identified in 2013 from sequence similarity searches and gene synteny analyses and was shown at that time to be highly related to KLF17 [182]. Like KLF17, it is believed to be expressed in the developing testis and restricted to that area. Little data currently exists examining its function; however, a detailed analysis of its structure and phylogenic tree in placental mammals has been investigated in detail by Pei et al. [182]. This group also suggested that KLF18 might be a pseudogene of KLF17 since its expression pattern is restricted and it is similar in sequence to KLF17. Despite this hypothesis, three genes in mouse and rat were identified that closely resemble KLF18: Zfp352, Zfp352-like, and Zfp353 [182]. The promoter and/or details into the transcriptional activation of this KLF are currently unknown. A more detailed analysis of the functions and regulations of KLF18 would provide more insight into this transcription factor's function.

3. Concluding remarks

Over the past 20 years since the discovery of the first KLF transcription factor, there continues to be a growing body of evidence to suggest that KLFs are important to tumor progression, cardiovascular disease, metabolism, and even circadian rhythm [1]. While much of the work has focused on the functions of these factors and their roles in various disease processes, there still remains additional needed work to explain how the various KLFs become activated and/or repressed during diseased states. There is a growing body of evidence, which we have attempted to discuss in some detail in this chapter, in the more extensively studied KLFs such as KLF4, KLF5, and KLF2 that suggest that the KLFs are regulated extensively by posttranslational modifications such as phosphorylation, acetylation, ubiquitination, and sumoylation. These modifications appear to be critical for co-factor recruitment and determination of whether KLFs interact with either activators or repressors of transcription. It has been interesting to see the wealth of information that has developed over the past 20 years investigating the roles of these various factors in various diseases; however, relatively speaking, we still know little about how these factors are activated and/or repressed transcriptionally during diseased states.

Since the onset of the era of big data, more of the KLF field has come to focus on the roles of pathway analysis following genetic ablation of a KLF in a cell-specific manner. These studies have yielded enormous amounts of data that offer valuable insight into the overlap between various KLF factors in diseases [183]. It will be of interest in the future to see how the integration of single-cell genomics will come into play with various different roles of the same KLF in various cell types in diseased states [184]. For example, the integration of single-cell RNA-Seq [184] with Assay for Transposase-Accessible Chromatin using sequencing (ATAC-Seq) [185, 186] in cells where a single KLF bear separate functions could offer deeper insight of the role of the niche environment on KLF function and/or on the roles of KLFs in downstream activations of different types of pathways during disease. Cardiovascular diseases have recently begun to investigate single-cell sequencing with other factors, such as Tcf21, and were able to use these innovative studies to investigate the role of this factor in smooth muscle cell to fibroblast transitions during atherosclerosis [184]. It will be exciting to see how KLF biology will use this technology to further investigate how these transcription factors regulate disease.

Not only will the integration of single-cell studies with KLF function give us greater insight into KLF function in development and disease, but the study of the role of RNA posttranscriptional modifications will most likely play an emerging role in the KLF field in the near future [184]. Since the sequencing of the human genome and the growing realization of the stronger role of RNA in transcriptional and translational control, there has been a re-emergence of interest in the field of RNA posttranscriptional modifications [187]. There are over 100 different types of RNA modifications of which the N^6-methyladenosine (m^{6}A) modification is the most common [187]. Interestingly, m^{6}A has recently been shown to be concentrated in the 3′-UTR of many messenger RNAs and that micro-RNAs are capable of mediating this modification via a sequence pairing mechanism to help promote stem cell pluripotency [187–192]. This new role for RNA modification and stem cell maintenance has immense implications for KLFs involved in induced pluripotent stem maintenance like KLF4. Therefore, it will be of interest to determine whether RNA modifications affect other disease processes by similar sequence pairing mechanisms.

In conclusion, the KLF field has offered many insights to different disease processes since the discovery of the first KLF over the past 20 years. New insights into the regulation of these factors will hopefully grant novel methods to directly and properly target these factors to inhibit diseased states that currently have no medical treatment therapy. Perhaps the newly emerging CRISP technology will be able to directly target KLFs in a cell-specific manner as many KLFs have opposing functions in many different cell types. In any case, this transcription factor family has offered much excitement since its discovery and hopefully will offer new insights as the field studies these factors in more depth in the future.

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Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

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Nomenclatures

DNMT1	DNA methyltransferase 1
EphA5	Ephrin receptor A5
EMT	Epithelial-to-mesenchymal transition
ER	Estrogen receptor
HDAC	Histone deacetylase
ID1	Inhibitor of DNA binding 1

IL-4	Interleukin-4
IL-6	Interleukin-6
NF-KB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
KLF	Krüppel-like factor
M6A	N^6-methyladenosine
mSin3A	Co-repressor complex used for repression
p300	Histone acetylase
P53	TP53 or tumor protein
P50	Subunit of NF-KB
P65	Subunit of NF-KB signaling
P21	p21CIP1, cyclin-dependent protein inhibitor
PDGF-BB	Platelet-derived growth factor BB
pRB	Phosphorylated RB
SMC	Smooth muscle cells
Smad	Proteins transduce signals from transforming growth factor beta
SM-actin	Smooth muscle alpha actin
Sp	Specificity proteins
TFG-β	Transforming growth factor beta
TNF-α	Tumor necrosis factor alpha
TWIST	TWIST1-protein
ZF-TF	Zinc finger transcription factor
ZFP	Zinc finger protein

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