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Mammalian Krüppel-Like Factors in Health and Diseases

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Abstract

The Krüppel-like factor (KLF) family of transcription factors regulates diverse biological processes that include proliferation, differentiation, growth, development, survival, and responses to external stress. Seventeen mammalian KLFs have been identified, and numerous studies have been published that describe their basic biology and contribution to human diseases. KLF proteins have received much attention because of their involvement in the development and homeostasis of numerous organ systems. KLFs are critical regulators of physiological systems that include the cardiovascular, digestive, respiratory, hematological, and immune systems and are involved in disorders such as obesity, cardiovascular disease, cancer, and inflammatory conditions. Furthermore, KLFs play an important role in reprogramming somatic cells into induced pluripotent stem (iPS) cells and maintaining the pluripotent state of embryonic stem cells. As research on KLF proteins progresses, additional KLF functions and associations with disease are likely to be discovered. Here, we review the current knowledge of KLF proteins and describe common attributes of their biochemical and physiological functions and their pathophysiological roles.

Keywords

Krüppel-Like Factor; Proliferation; Differentiation; Inflammation; Cardiovascular Diseases; Tumorigenesis; Fat Metabolism; Induced Pluripotent Stem Cell

Chapter I: Background

A. Introduction

Krüppel-like factors (KLFs) are zinc finger-containing transcription factors that regulate proliferation, differentiation, development, and programmed cell death. Alterations in their functions have been associated with the pathobiology of numerous human diseases, including cardiovascular disease, metabolic disorders, and cancer. KLF family members have homology to the *Drosophila melanogaster* Krüppel protein, a member of the ‘gap’ class of segmentation gene products that regulates body segmentation in the thorax and anterior abdomen of the *Drosophila* embryo (361). KLFs also share homology with the transcription factor Sp1, one of the first mammalian transcription factors to be identified and characterized (205). Sp1 binds GC-rich regions in DNA via three C₂H₂-type zinc fingers. Because KLF proteins also contain this zinc-finger structure, they are classified as part of the Sp1/KLF family. Although Sp1 was initially viewed as a general transcription factor that regulates basal expression of housekeeping genes, it was later discovered that Sp1/KLF family members regulate a complex set of genes

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that have distinct roles in development and homeostasis of many tissue types. KLF proteins share common mechanisms of regulation, recruiting transcriptional regulatory proteins that include transcriptional co-activators and co-repressors, and other chromatin remodeling proteins. Together, KLFs function in the physiology and pathophysiology of many organ systems, including cardiovascular, respiratory, digestive, hematological, and immune systems. Many KLFs are also involved in tumor biology, in reprogramming somatic cells into inducible pluripotent stem (iPS) cells, and maintaining the pluripotent state of embryonic stem (ES) cells (198,300,415,416). As the study of KLF proteins progresses, new biological and pathobiological roles for these factors are constantly being discovered. This review addresses the current understanding of biochemical, biological, and pathophysiological functions of KLF family members.

B. Conservation and Phylogenetic Analysis of KLFs

KLF proteins are conserved among mammals from human to rat, with many KLFs also having homologs in *Gallus gallus* (chicken), *Danio rerio* (zebrafish) and *Xenopus laevis* (frog). In addition, the *Caenorhabditis elegans* genome contains 3 predicted KLF homologs, *klf-1*, *klf-2* and *klf-3* (42). Tissue expression of the KLFs varies—some family members are expressed ubiquitously (e.g. KLFs 6, 10, and 11) whereas others are expressed in specific tissues—KLF1 is expressed predominantly in erythroid cells, KLF2 is highly expressed in lung, and KLFs 4 and 5 are very abundant in the gastrointestinal tract (331). KLF proteins exhibit homology in their carboxyl-terminal zinc finger domains that allow KLFs to bind GC-rich sites in promoter and enhancer regions of the genes they regulate. These structural similarities create overlap in their transcriptional targets. For example, in ES cells, KLFs 2, 4, and 5 can all bind and activate *Esrrb*, *Fbxo15*, *Nanog*, and *Tcl1* (198). However, KLF proteins have distinct amino-terminal sequences that provide unique regions for interaction with specific binding partners. Phylogenetic analysis of protein sequences of the 17 human KLFs defines evolutionary distances of individual family members (Figure 1). Structural homologies of KLFs correlate with functional similarities; this connection is likely due to homologous protein interaction motifs in amino-terminal domains. Based on functional characteristics, KLF proteins can be divided into three distinct groups. KLFs in Group 1 (KLFs 3, 8, and 12) serve as transcriptional repressors through their interaction with the C-terminal binding protein (CtBP). Family members in Group 2 (KLFs 1, 2, 4, 5, 6, and 7) function predominantly as transcriptional activators. KLFs in Group 3 (KLFs 9, 10, 11, 13, 14, and 16) have repressor activity through their interaction with the common transcriptional co-repressor, Sin3A. KLFs 15 and 17 are more distantly related based on phylogenetic analysis and contain no defined protein interaction motifs.

C. Protein Structure of the KLFs

1. The Zinc Finger Domain—Zinc finger domains are common motifs in transcription factors. The most frequently encountered zinc finger motif is the C₂H₂ type, in which a zinc atom is tetrahedrally coordinated by two conserved cysteine and histidine residues that allow the domain to fold into a ββα structure (40). All members of the KLF family have three zinc finger motifs at the carboxyl-terminal ends of the proteins that are highly conserved. Their location within KLF protein structures are shown in Figure 2. The first and second zinc fingers contain 25 amino acids and the third contains 23 amino acids. Each zinc finger recognizes three base pairs in the DNA sequence and interacts with nine base pairs in total (294). Several studies have examined the preferred DNA binding motifs for a number of KLFs, based on binding studies of promoter regions and oligonucleotide screens (279,376). DNA binding sites are similar among the KLF proteins; they include GC-rich sequences with a preference for the 5'-CACCC-3' core motif, which is present in the β-globin gene promoter recognized by KLF1 (279). A number of other KLF proteins also bind this motif (431,432,464).

In addition to its role in DNA binding, the zinc finger region may be important for nuclear import. Nuclear localization signals have been identified in the zinc finger domains of KLFs 1, 4, 8, and 11 (275,325,377,400) and in a basic region of KLF4 immediately amino-terminal to the zinc fingers (377).

2. Functional Binding Domains—The amino-terminal regions of KLFs vary significantly and allow them to bind different co-activators, co-repressors, and modifiers, resulting in functional diversity and specificity. Through the identification of KLF binding partners, several protein interaction domains have been characterized for subgroups of the KLFs that help define their function. Figure 2 shows the protein-binding domains within the protein structures of the KLFs.

C-Terminal Binding Protein (CtBP)-Binding Site: Although KLF3 was initially thought to function as a transcriptional activator, it was later shown to be a strong repressor, with its activity localized to a 74 amino-acid sequence in the amino-terminal region (427). In a yeast two-hybrid screen, KLF3 interacted with the transcriptional co-repressor CtBP. KLF3, as well as KLFs 8 and 12, bind CtBP via the consensus sequence PXDLS (362,427,432). This interaction mediates the repressor activities of KLFs 3 and 8, and the ability of KLF12 to repress expression of the *AP-2 α* gene.

Sin3A-Binding Site: KLFs 10 and 11 also act as transcriptional repressors (90). This activity maps to three distinct repression sites in amino-terminal regions of the proteins designated R1, R2 and R3. The R1 domain was later shown to contain a Sin3-interacting domain (SID), a hydrophobic-rich motif that forms a α -helical structure to support interaction with Sin3 proteins, which are histone deacetylase-dependent co-repressors (488). KLFs 9, 10, 11, 13, and 16 share a conserved α -helical motif AA/VXXL that mediates their binding to Sin3A and their activities as transcriptional repressors (488). Whereas the protein sequence of KLF14 contains a putative SID, physical interaction between KLF14 and Sin3A has not been established. Surprisingly, KLF1, which does not contain a SID, binds and recruits Sin3A to function as a transcriptional repressor (65). However, this interaction was mediated through the carboxyl-terminal zinc finger domain of KLF1 rather than an amino-terminal hydrophobic consensus site.

Chapter II: Biochemical Mechanisms of KLFs

A. Common Interacting Proteins

1. Histone Acetyltransferases (HATs)—Sequence-specific DNA-binding factors like KLFs regulate transcription by recruiting chromatin modifiers, cofactors, and transcription machinery to promoters of specific genes. A number of KLFs from Group 1 of the phylogenetic analysis bind to co-regulators that have acetyltransferase activity, such as cAMP response element binding-binding protein (CBP), p300, and p300/CBP-associated factor (P/CAF) (127,246,283,395,491). KLF1 binds CBP/p300 and P/CAF *in vivo* and is subsequently acetylated at K288 and K302 (494) (Figure 2). Whereas acetylation of KLF1 at K288 is associated with its transactivation (370), acetylation at K302 is required for its interaction with the transcriptional repressor, Sin3A (64). KLFs 5 and 6 also bind CBP/p300 and are acetylated at defined sites (163,246). KLFs 2 and 4 interact with CBP/p300 (127,147,369) and have putative acetylation sites that are conserved with the K288 site of KLF1, but these sites have not been empirically determined.

2. CtBP—KLFs 3, 8, and 12 interact with the transcriptional regulator CtBP through a consensus binding sequence in their amino-terminal regions (362,427,432). CtBP1 was originally characterized for its ability to bind the adenovirus E1A protein (39); and vertebrate

CtBP1 and CtBP2 are established transcriptional repressors. One mechanism by which CtBPs promote gene silencing is through recruitment of histone deacetylases (HDACs) and histone methyl transferases to transcriptional complexes. These proteins deacetylate and methylate histones, respectively, to cause chromatin compaction and transcriptional silencing (78). CtBPs also have HDAC-independent mechanisms of action; CtBP1 and CtBP2 bind and inhibit HAT co-activators such as p300/CBP (78) and recruit other repressors that promote chromosome silencing, such as Ikaros (223) and members of the polycomb group (371). Therefore, the primary mechanism by which CtBP proteins repress transcription is through the recruitment of proteins that affect chromatin remodeling.

KLF3 is a negative regulator of adipogenesis and thereby a regulator of fat metabolism (409). Adipocyte differentiation is normally accompanied by decreased expression of KLF3, and overexpression of KLF3 blocks differentiation of 3T3-L1 cells in a CtBP-dependent manner. Given that CtBP binds NADH, CtBP might be a metabolic sensor for KLF3-related repressor function.

3. Sin3A—KLFs 9, 10, 11, 13, 14, and 16 contain a hydrophobic consensus sequence in their amino terminus that recruits the transcriptional repressor Sin3A (488). Mammalian Sin3 proteins (Sin3A and Sin3B) are large, multi-domain proteins made up of four highly conserved imperfect repeats, each of which fold into two amphipathic helices (221). These proteins bind HDAC1 and HDAC2 and other proteins, including Mad, Ume6, MeCP2, N-CoR, silencing mediator of retinoid and thyroid receptor (SMRT), and Ikaros (96). Given their size and various protein interaction sites, Sin3 proteins are likely to provide a scaffold for assembly of multi-unit complexes that modify chromatin conformation (221). HDACs, as part of these complexes, are essential for mediating repressor activity, as mutation of the HDAC binding sites in Sin3A or use of HDAC inhibitors abrogates repressor activity (206,392).

B. Post-translational Modifications

Co-regulatory proteins modify KLF family members via acetylation, phosphorylation, ubiquitination, and sumoylation to refine their transcriptional activity.

1. Acetylation—A role for acetylation in regulating KLFs first came to light with the modulation of KLF1 activity by histone acetyltransferases (HATs) (491). Acetylation of KLF1 at K288 is required for binding of KLF1 to the *β-globin* locus, for recruitment of CBP to the locus, and for changes in chromatin structure that activate transcription (370). The zinc finger domain of KLF1 interacts with the amino terminus of histone H3 to coordinate this process. KLFs 4, 5, 6, and 13 are also acetylated, resulting in enhanced transcriptional activity (127, 246,283,395). In contrast, interaction of KLF5 with HDAC1 blocks binding of KLF5 to p300, reducing KLF5 binding and activation of transcriptional targets (269).

The acetylation of KLFs is regulated by signaling pathways that affect the association of HATs and HDACs with KLF proteins. For example, treatment of vascular smooth muscle cells (SMCs) with all-*trans* retinoic acid (ATRA) induces phosphorylation of HDAC2, which disrupts its interaction with KLF4 and allows KLF4 to become acetylated and bind the *SM22α* promoter (276). Furthermore, treatment of HaCaT epidermal cells with transforming growth factor- β (TGF- β) induces an interaction between KLF5 and p300 that results in KLF5 acetylation (166). This modification not only affects the cofactors recruited by KLF5 to the promoter of the gene encoding the cell cycle inhibitor p15 (*CDKN2B*), but also alters KLF5's regulation of *CDKN2B*, resulting in transcriptional activation rather than repression (166).

2. Phosphorylation—The transcriptional activity of several KLFs is regulated by phosphorylation. KLF1 is phosphorylated at serine and threonine residues within its

transactivation region by casein kinase II, which increases transcription of KLF1 target genes (323). Phosphorylation and dephosphorylation of KLF5 have been reported to affect its binding to various effector proteins, including c-Jun (176), CBP (499), retinoic acid receptor- α (496), and the ubiquitin ligase, F-box and WD40 domain protein (Fbw7/hCDC4) (254). In T cells, phosphorylation of KLF13 by the serine/threonine kinase PRP4 increases KLF13 nuclear localization and transcriptional activation of chemokine C-C motif ligand 5 (*CCL5*) (187). In contrast, phosphorylation of KLF11 by extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) disrupts the interaction of KLF11 with Sin3A to prevent repression of *Smad7* (122).

3. Ubiquitination—Ubiquitination is a multi-step protein modification process mediated by an E1 ubiquitin-activating enzyme, an E2 ubiquitin-conjugating enzyme, and an E3 ubiquitin ligase (460). E3 ubiquitin ligases bind to the E2 ubiquitin conjugase and a substrate-specific domain in the target protein. Polyubiquitination provides a signal for the degradation of substrate proteins by the 26S proteasomal complex whereas monoubiquitination usually alters the activity of a protein (227). KLFs 1, 2, 4, 5, 6, and 10 are regulated by ubiquitination. KLF1 is ubiquitinated *in vivo*, and inhibition of the 26S proteasomal complex results in accumulation of KLF1 protein (341). Thus, ubiquitin-targeted degradation of KLF1 functions to maintain cellular levels of the protein. Levels of KLFs 4 and 6 are also regulated by degradation via ubiquitination, depending on physiological requirements. Following serum stimulation of quiescent HCT116 cells, KLF4 undergoes ubiquitin modification and rapid degradation through the proteasome pathway (74). Degradation of KLF4 eliminates its cell cycle inhibitory effects, allowing the cells to re-enter the cell cycle. KLF6 is ubiquitinated and undergoes proteasomal degradation in cultured cells following exposure to DNA damaging agents (17). In this study, KLF6 is degraded only with high levels of DNA damage. Lower levels of damage actually increase KLF6 levels, resulting in cell cycle arrest. Degradation of KLF6 might therefore regulate cell fate decisions between cell cycle arrest and death, depending on the extent of DNA damage. A splice variant of KLF6, KLF6-SV1, is ubiquitinated and subject to rapid degradation (112). In cancer cells that overexpress KLF6-SV1, which is often associated with poor survival, KLF6-SV1 binds to the pro-apoptotic protein NOXA, resulting in ubiquitination and degradation of both proteins, promoting cancer cell survival.

KLFs 2 and 5 bind the ubiquitin ligase WWP1, and ubiquitination of these KLFs promotes their rapid degradation by the proteasomal complex (60,495). In some prostate and breast cancer cell lines, overexpression of WWP1 has been reported to increase degradation and loss of KLF5 (59). Similarly, KLF5 interacts with and is ubiquitinated by the E3 ubiquitin ligase and tumor suppressor, Fbw7/hCDC4, in a CDC4 phosphodegron (CPD)-dependent manner (254). However, deficiency of Fbw7/hCDC4 from some cancer cells delays turnover of KLF5, leading to the accumulation of KLF5.

KLF10 provides an example of regulation by mono-ubiquitination. KLF10 is a target of the E3 ligase Itch, which mediates both mono- and poly-ubiquitination in response to TGF- β signaling in naïve T cells (438). Mono-ubiquitination of KLF10 by Itch promotes transcriptional activation of the KLF10 target *Foxp3*.

4. Sumoylation—Many transcription factors and co-regulators are modified by the small ubiquitin-like modifier (SUMO) peptide, resulting in enhancement or suppression of their transcriptional activity. KLF3, which normally functions as a transcriptional repressor, interacts with the E2 SUMO-conjugating enzyme Ubc9 and is covalently modified by SUMO-1 *in vitro* and *in vivo* (332). KLF3 is sumoylated at lysines K10 and K197, and mutations at these sites compromise the transcriptional repressor activities of KLF3. KLF8 promotes cell cycle progression through positive regulation of the *CCDN1* (cyclin D1) promoter. KLF8 can be sumoylated through interaction with several SUMO E3 ligase family members including

protein inhibitor of activated STAT1 (PIAS1), PIASy and PIASx α (455). Overexpression of SUMO-1 suppresses the cell-cycle promoting effects of KLF8, whereas mutation of the primary sumoylation site in KLF8 increases its effects on cell cycle progression. KLFs 4 and 5 also interact with the SUMO E3 ligase, PIAS1. PIAS1 promotes KLF4 sumoylation and subsequent degradation so it no longer represses α -smooth muscle actin (α -SMA) in SMCs (213). Alternatively, sumoylation of KLF5 increases its nuclear localization and promotes its activation of the cell cycle genes *cyclin D1* and *Cdc2* (119,120).

The physiological roles of KLFs 1 and 5 are modulated by sumoylation. In erythroid progenitor cells, KLF1 acts as a transcriptional repressor of megakaryocyte differentiation by blocking expression of the transcription factor FLI-1, which is required for megakaryopoiesis (144). This activity depends on sumoylation of KLF1 at K74—mutation of this site attenuates its activity as a repressor (380). KLF5 has an important role in lipid metabolism through peroxisome proliferator-activated receptor- δ (PPAR- δ) signaling (317). Under basal conditions, KLF5 is sumoylated and associates with transcriptional repressor complexes that regulate genes associated with lipid oxidation, including *Cpt1b*, *Ucp2* and *Ucp3*. When PPAR δ interacts with an agonist, KLF5 is de-sumoylated and binds to transcriptional activation complexes that drive expression of genes that control lipid metabolism (317). Thus, KLF5 can “switch” from transcriptional repression to activation, depending on its sumoylation status.

Chapter III: Cell-Based Functions of KLFs in Normal Biological Processes

A. Proliferation

Many KLF family members function as regulators of cell growth. KLFs 4 and 5, which are highly expressed in intestinal tissues, have been studied extensively in regulating proliferation. KLF5 is localized to actively proliferating cells at the base of intestinal crypts and promotes proliferation of different types of cultured cells, including fibroblasts and epithelial cells (54, 410,473). KLF5 is upregulated in proliferating vascular SMCs and is activated by serum stimulation of quiescent NIH3T3 cells. KLF5 participates in several growth factor signaling pathways, including the RAS/MAPK, protein kinase C, and phosphatidylinositol-3-kinase (PI3K) pathways (115). KLF5 promotes proliferation by accelerating cells through G₁/S and G₂/M phases of the cell cycle. A number of transcriptional targets of KLF5 promote cell cycle progression, including cyclin D1 (301), cyclin B1 and Cdc2 (297). KLF5 also represses expression of the cell cycle inhibitory proteins p27 and p15 (56). However, the ability of KLF5 to promote proliferation can be downregulated or reversed in cultured cells through activation of signaling pathways that suppress cellular proliferation, including retinoic acid receptor signaling and TGF- β signaling (54,163,164).

In contrast to KLF5, KLF4 inhibits cell cycle progression. In the intestinal mucosa, KLF4 is expressed in differentiated cells at the luminal surface that have undergone growth arrest (272,375). Studies in NIH3T3 cells indicate that KLF4 is expressed at very low levels in actively proliferating cells but is induced as cells enter quiescence following serum-starvation or contact inhibition (375). Furthermore, transcriptional profiling studies reveal a global inhibitory function of KLF4 in regulating genes that promote transcription and the biosynthesis of proteins and cholesterol (458). The primary mechanism by which KLF4 contributes to cell cycle arrest has been determined from studies of KLF4 in DNA damage-induced growth arrest. Exposure of cultured cells to DNA damaging agents or γ -irradiation increases the levels of KLF4 in a p53-dependent manner (479,493). KLF4 binds directly to the promoter of the gene that encodes the cell cycle inhibitor p21^{Cip1/Waf1} and recruits p53 to activate expression of *p21^{Cip1/Waf1}* (493). KLF4 also inhibits expression of the cell cycle-promoting genes *CCND1* (cyclin D1) (373) and *CCNB1* (cyclin B1) (481). Furthermore, in response to DNA damage, KLF4 suppresses transcription of the gene that encodes cyclin E and prevents chromosomal

amplification (480). Thus, KLF4 activates cell cycle checkpoints to prevent inappropriate cell cycle progression and maintain DNA integrity.

KLFs 6 and 8, which are ubiquitously expressed, also regulate cell cycle progression. KLF6 induces G₁ cell cycle arrest by upregulating expression of *p21^{Cip1/Waf1}* and repressing *CCND1*, thus disrupting formation of cyclin D1/cyclin-dependent kinase 4 (CDK4) complexes (27,373). However, KLF8, as a mediator of focal adhesion kinase signaling, activates the *CCND1* promoter, and ectopic expression of KLF8 promotes cell cycle progression (500).

KLFs 10 and 11, initially identified as TGF- β -inducible genes, play significant roles in TGF- β mediated cell growth control and differentiation. Ectopic expression of KLF10 can mimic many of the effects of TGF- β signaling including suppression of proliferation (92,177). KLF10 mediates TGF- β signaling by blocking expression of Smad7, a negative regulator of TGF- β (202), and activating expression of the positive effector, Smad 2 (203). These events promote expression of *p21^{Cip1/Waf1}* and thereby inhibit cell cycle progression (202). KLF11 mediates TGF- β /Smad signaling through downregulation of Smad7 by recruiting the transcriptional repressor Sin3A to the *Smad7* promoter (122). KLF11 also suppresses cell growth through TGF- β dependent regulation of *c-Myc* (122). Upon TGF- β stimulation of epithelial cells, KLF11 interacts with Smad3 to bind a TGF- β -inhibitory element (TIE) within the *c-Myc* promoter and blocks its expression (43).

As another example of regulating cell growth, KLFs participate in the maintenance of quiescence in lymphocytes. Naïve lymphocytes are held in a non-cycling, G₀ growth phase until they are activated by specific antigens. Quiescence requires negative regulation of cell cycle progression and expression of genes that maintain small cell size and low metabolic activity. Overexpression of KLF2 in Jurkat leukemia T cells inhibits growth and DNA synthesis. KLF2 promotes a quiescent phenotype by blocking expression of the growth-promoting *c-Myc* (44) and upregulating the cell cycle inhibitor *p21^{Cip1/Waf1}* (462). Similar activities have been ascribed to KLF4 in B lymphocytes. KLF4 levels are decreased upon B cell activation, and ectopic expression of KLF4 induces G₁ cell cycle arrest (484). As with KLF2, the arrest is associated with increased expression of *p21^{Cip1/Waf1}* and decreased expression of *c-Myc*, as well as reduced expression of *CCND1*.

KLFs therefore regulate proliferation in a variety of cell types through transcriptional control of cell cycle regulatory components. Transcriptional targets include cyclins D1, D2, B1, E, and cyclin-dependent kinase inhibitors *p21^{Cip1/Waf1}*, p15 and p27, as well as the proliferative factor *c-Myc*.

B. Differentiation

KLFs play critical roles in differentiation during development and in maintenance of tissue homeostasis. As a primary example, KLF1 regulates differentiation during erythropoiesis. The development of red blood cells requires carefully regulated changes in cell morphology, globin expression, and heme synthesis. KLF1 mediates the switch from expression of fetal γ -globin to adult β -globin and regulates transcription of genes that encode cytoskeletal proteins, heme synthesis enzymes, and blood group antigens (118,183,339). Binding of KLF1 to the CACCC consensus site at nucleotide position -90 in the β -globin promoter initiates the recruitment of large transcriptional complexes, including the mammalian SWI/SNF chromatin-remodeling proteins, BRG1, BAF155, and CBP/p300 (204). KLF1 therefore regulates the maturation of erythroid cells by allowing the chromatin structure to open and become transcriptionally active.

KLF1 also regulates the lineage progression of megakaryocyte-erythroid progenitor (MEP) cells. While promoting erythroid maturation, KLF1 simultaneously suppresses megakaryocyte differentiation by antagonizing the transcription factor FLI-1. FLI-1 is an ETS-related factor

that is normally expressed in the MEP and its activity is required for megakaryopoiesis. Expression of *FLI-1* is negatively regulated in the MEP by a SUMO-modified form of KLF1 (380). Upon sumoylation, KLF1 interacts with the Mi-2 β component of the NuRD repression complex and recruits HDAC, indicating that Mi-2 β /HDAC activity is involved in the SUMO-dependent repression of *FLI-1*.

In the intestinal epithelium, KLF4 expression is restricted to terminally differentiated epithelial cells of the mucosa, where it promotes differentiation (272). Transcriptional targets of KLF4 include *Lama1*, which encodes the basement membrane component Laminin-1, and the gene that encodes the enterocyte differentiation marker intestinal alkaline phosphatase (181,336). A specific role for KLF4 in goblet cell differentiation is demonstrated in studies of *Klf4*^{-/-} mice. In these mice, the number of colonic goblet cells is significantly reduced and goblet cells have aberrant morphology, with low levels of the cell-specific marker MUC2 (211).

A number of KLFs participate in differentiation during adipogenesis. KLFs 2, 3, 4, 5, 6, 7, 11, and 15 have all been reported to function as positive or negative regulators of adipocyte differentiation, and their roles are described in detail in Chapter IV, Section F, “The Role of KLFs in Metabolic Regulation.” Other tissues in which KLFs regulate differentiation include KLFs 2, 4, and 5 in vascular SMCs (1,234,378), KLF2 in thymocytes (51), KLF13 in cardiomyocytes (307), KLF7 in olfactory sensory neurons (207), KLF4 in corneal epithelial cells (413), KLF4 in monocytes (6), KLF5 in lung respiratory epithelial cells (440), and KLF9 in hippocampal adult born neurons (363).

C. Apoptosis

Many of the studies examining the role of KLFs in apoptosis have arisen from observations of up or downregulation of KLFs in cancer. The most highly characterized KLFs in regard to apoptosis are KLFs 4, 5, and 6. KLF4 is generally regarded as a tumor suppressor due to its ability to induce cell cycle arrest. However, when the ability of KLF4 to induce growth arrest is inactivated (351), it can actually contribute to tumor progression because it also inhibits apoptosis. KLF4 regulates apoptosis following DNA damage, when cells must either activate cell cycle checkpoints and repair machinery or commit to apoptosis. In γ -irradiated RKO colon cancer cells, ectopic expression of KLF4 significantly reduces the percentage of apoptotic cells, causing them to instead undergo growth arrest (149). In this study, upregulation of KLF4 blocks expression of the pro-apoptotic protein BAX by inhibiting p53-dependent transactivation of the *BAX* promoter. In another study of MDA-MB-134 breast cancer cells, KLF4 modulates apoptosis by binding directly to the promoter of *p53* and suppressing its transcription (352). KLF4 may be a determining factor in the outcome of p53 responses to DNA damage, depending on the extent of damage (507). Following low, cytostatic doses of adriamycin, KLF4 is induced and promotes cell cycle arrest. However, when cells are exposed to high levels of adriamycin, KLF4 expression is inhibited and p53-dependent apoptosis proceeds. Ectopic expression of KLF4 prevents cell death in response to high levels of adriamycin. KLF4 is therefore an important determinant of cell cycle arrest or death induction by p53.

KLF6 is similar to KLF4 in that it regulates growth arrest and can function as a tumor suppressor. *KLF6* is often mutated or deleted in human prostate tumors (305), and ectopic expression of KLF6 in prostate cancer cells or non-small cell lung cancer induces apoptosis (189,193). However, silencing of *KLF6* in HepG2 and COS-7 cells sensitizes these cells to apoptosis and increases the sub-G₁ population (98,388). Situations in which KLF6 appears to suppress apoptosis may be attributable to specific splice variants of the *KLF6* gene that can act in a manner distinct from full-length KLF6. For example, the KLF6-SV1 isoform is overexpressed in ovarian cancer and binds the BH3-only protein NOXA to block apoptosis (112). Downregulation of this splice variant induces spontaneous apoptosis in ovarian, lung,

and prostate cancer cell lines (111,112,302,358), suggesting that KLF6-SV1 might be a therapeutic target for cancer.

Although the exact role of KLF6 in apoptosis is controversial, KLF5 is clearly a suppressor of apoptosis. In EU-8 leukemia cells that have low levels of KLF5, introduction of ectopic KLF5 induces the expression of survivin, an inhibitor-of-apoptosis (IAP) protein (509). Conversely, blocking KLF5 expression with small interfering RNA (siRNA) downregulates survivin and sensitizes leukemia cells to chemotherapeutic-induced apoptosis. As a mechanism of action, KLF5 binds directly to p53 and blocks p53-regulated repression of survivin (509). In HCT116 colon cancer cells, KLF5 is activated following exposure to 5-fluorouracil and ultraviolet irradiation (502). Depletion of KLF5 from these cells increases their sensitivity to apoptosis in response to DNA-damaging agents. In this study, KLF5's pro-survival activity does not depend on the activity of p53, but is instead associated with regulation of Pim1—a kinase that negatively regulates the pro-apoptotic protein BAD. Finally, Suzuki *et al.* have shown that KLF5 inhibits apoptosis of SMCs in vascular lesions by interacting with poly(ADP-ribose) polymerase-1, a nuclear enzyme that controls DNA repair and apoptosis (411).

Chapter IV: Organ-Based Functions in Physiology and Pathophysiology

KLF family members regulate key events in development, maintenance of homeostasis, and adaptive responses to physiological or pathobiological stimuli in mammalian tissues. The following sections describe the functions of KLF proteins in various organs and ways in which their dysregulation contributes to the pathogenesis of diseases. Table I summarizes the expression, function, and pathobiological roles of mammalian KLFs.

A. The Cardiovascular System

1. Development of the Cardiovascular System—KLF13 is required for cardiac development—it is expressed in a variety of tissues in the mouse embryo, including the developing heart (265). At E10.5, Klf13 is present predominantly in the atrial myocardium and endocardial layer (242). By E12.5, the atria and ventricles both contain Klf13 (242). KLF13 functionally and physically interacts with GATA-4, which regulates cardiac-specific genes during embryonic and postnatal heart development (55,284). Knockdown of KLF13 in *Xenopus* leads to atrial septal defects and hypotrabeulation similar to those observed in humans or mice with hypomorphic GATA-4 alleles (242). One of the transcriptional targets of KLF13 is *cyclin D1*, through which KLF13 regulates cardiac cell proliferation (307). *Klf13*^{-/-} mice have enlarged hearts and increased susceptibility to cardiac vacuolar lesions (157); patients with microdeletion of chromosome 15q13, which includes *KLF13*, have cardiac defects (429).

During embryonic development, KLF2 is expressed in vascular endothelial cells (10). *Klf2*^{-/-} mice die *in utero* from intra-embryonic and intra-amniotic hemorrhage, despite normal vasculogenesis, angiogenesis, and cardiogenesis (234,447). However, the recruitment of pericytes and vascular SMCs to the tunica media of *Klf2*^{-/-} embryos is defective, resulting in compromised vessel integrity that is manifested by aneurysmal dilatation of arteries and veins and subsequent rupture (234). A subsequent study demonstrated the failure of mural SMCs to migrate around normally developed endothelial cells in the aorta of *Klf2*^{-/-} embryos (461). Interestingly, in mouse embryos, endothelial expression of *Klf2* correlates with the rise of fluid shear forces; conditional deletion of *Klf2* from the endothelium results in embryonic lethality from high-output heart failure (243). In contrast to *Klf2*^{-/-} mice, mice with endothelial-specific loss of *Klf2* do not suffer from primary vascular abnormality or hemorrhage; instead, increased cardiac output is a result of loss of peripheral vascular resistance and reduced vessel tone (243). KLF2 is therefore an important *in vivo* regulator of hemodynamics whose regulation in response to fluid shear stress is necessary for normal cardiovascular development.

2. Pathobiology of the Heart—Whereas KLF13 is highly expressed in fetal heart, expression of KLF15 in the heart increases significantly following birth and is highest in the adult heart (134). KLF15 levels are reduced in hypertrophic hearts of rodents following pressure overload and in biopsy samples from patients with left ventricular hypertrophy due to chronic valvular aortic stenosis (134). Similarly, expression of KLF15 in neonatal rat ventricular muscle cells is reduced by prohypertrophic stimuli such as phenylephrine and endothelin-1 (134). Overexpression of KLF15 in cardiomyocytes reduces cell size and expression of atrial natriuretic factor and B-type natriuretic peptide—both are expressed in the fetal heart and associated with cardiac hypertrophy (134). *Klf15*^{-/-} mice are viable but have exaggerated, hypertrophic remodeling of the heart in response to pressure overload, manifested by increased heart weight, left ventricular cavity enlargement, impaired left ventricular systolic function, and increased expression of hypertrophic genes (134). KLF15 might inhibit cardiac hypertrophy by attenuating the functions of GATA-4 and myocyte enhancer factor 2 (MEF2)—transcription factors that are critical effectors of cardiac hypertrophy (97,338).

Following pressure overload, *Klf15*^{-/-} mice also develop fibrosis and deposition of excessive amounts of collagen in the heart (441). This phenotype is associated with increased expression of connective tissue growth factor (CTGF), which has been implicated in the pathogenesis of fibrotic diseases of the heart (62,312). CTGF expression is regulated by diverse stimuli, including TGF-β1, which promotes fibrosis (62). Incubation of neonatal rat ventricular fibroblasts with TGF-β1 reduces expression of KLF15 and increases that of CTGF (441). Conversely, overexpression of KLF15 suppresses basal and TGF-β1-induced expression of CTGF (441). These studies demonstrate that KLF15 is a negative regulator of cardiac fibrosis.

In contrast to the anti-fibrotic action of KLF15 in the heart, KLF5 promotes fibrosis. Following infusion of angiotensin II, a potent mediator of cardiac hypertrophy (270), *Klf5*^{+/-} mice have less cardiac hypertrophy and interstitial fibrosis than wild-type mice given angiotensin II (378). In addition, the level of TGF-β in the hearts of *Klf5*^{+/-} mice given angiotensin II is significantly lower than that of wild-type mice, suggesting that TGF-β lies downstream from KLF5 (378). In cultured cardiac fibroblasts, angiotensin II increases expression of KLF5 and platelet-derived growth factor (PDGF)-A, which controls tissue remodeling (340). Moreover, KLF5 is directly responsible for the induction of PDGF-A expression in response to angiotensin II stimulation (378). The essential role of cardiac fibroblasts in mediating the adaptive response to pressure overload was recently confirmed in mice with cardiac fibroblast-specific deletion of *Klf5* (417). An attempt to identify compounds that regulate KLF5 activity yielded several retinoid acid receptor (RAR) ligands. Am80, a synthetic retinoid agonist, reduces *PDGF-A* promoter activity in cells that co-express KLF5 and RAR-α (378). Wild-type mice given Am80 have reduced angiotensin II-induced cardiac hypertrophy, which approximates that observed in *Klf5*^{+/-} mice given angiotensin II (378). Reagents that alter KLF5 activity might therefore be developed to control cardiac remodeling.

KLF10 is important during development of the heart. Male *Klf10*^{-/-} mice develop cardiac hypertrophy by 16 months (343); other phenotypes include asymmetric septal hypertrophy and increased ventricular size, wall thickness, and heart weight (343). The hearts of *Klf10*^{-/-} mice have evidence of myocyte disarray and myofibroblast fibrosis (343), but the mechanisms by which KLF10 prevents cardiac hypertrophy are not known.

3. Endothelial Biology and Pathobiology—KLFs 2, 4, and 6 are expressed in endothelial cells (36,226,477), where they have important roles in cell function and pathobiology (13). Expression of KLF4 in endothelial cells is induced by shear stress (274) and pro-inflammatory stimuli (172). Overexpression of KLF4 in endothelial cells activates expression of anti-inflammatory and anti-thrombotic genes, such as those that encode endothelial nitric-oxide synthase (eNOS) and thrombomodulin, whereas reduction of KLF4 levels increases tumor

necrosis factor- α (TNF- α)-induced expression of vascular cell adhesion molecule-1 (VCAM-1) and tissue factor (172). In one study, overexpression of KLF4 in endothelial cells significantly reduces TNF- α -induced E-selectin and VCAM-1 expression (277). Moreover, KLF4 significantly reduces adhesion of inflammatory cells to endothelial cells and prolongs clotting time under inflammatory conditions. These findings support an anti-inflammatory function for KLF4 in endothelial cells (172).

Endothelial expression of KLF6 is induced after vascular injury and is responsible for the transcriptional activation of several genes involved in vascular remodeling, including urokinase plasminogen activator, endoglin, collagen α 1(I), TGF- β 1, and TGF- β receptor type I (36,226). This transactivation requires the participation and interaction between KLF6 and Sp1 (36). KLF6 was shown to regulate endothelial cell motility by negatively regulating, in conjunction with Sp2, transcription of the gene encoding matrix metalloproteinase-9 (MMP-9) (105). Disruption of the KLF6/Sp2 repressor complex by small heterodimeric partner, which is activated by farnesoid X receptor, results in upregulation of MMP-9 and increased cell motility. KLF6 is therefore an important mediator of vascular remodeling and response to injury.

Most information on the function of KLFs in endothelial cell biology and pathobiology have come from studies of KLF2 (13). KLF2 expression is highly upregulated in cultured endothelial cells subjected to prolonged laminar flow shear stress (108,190,369). These results were supported by the *in vivo* observation that KLF2 is restricted to the endothelium of healthy human aorta, in regions predicted to be exposed to laminar shear stress (108). In contrast, KLF2 expression is decreased or absent from regions of vessels exposed to non-laminar shear stress, such as bifurcations of the aorta to the iliac and carotid arteries (109)—these bifurcation areas are also susceptible to atherosclerosis. KLF2 is one of several differentially expressed genes in endothelial cells subjected to ‘atheroprotective’ waveforms, relative to ‘atheroprone’ waveforms, which are modeled after the flow patterns in arteries from healthy human subjects (100). Consequences of flow-induced KLF2 expression in endothelial cells include activated expression of eNOS (107,109,329,369) and repressed expression of angiotensin-converting enzyme, endothelin-1, and adrenomedullin—all of which are involved in the control of vascular tone in response to flow (107,109). KLF2 therefore has flow-dependent, atheroprotective functions in endothelial cells.

The atheroprotective activity of KLF2 was demonstrated by its induction in response to 3-hydroxy-3-methylglutaryl coenzyme A inhibitors (statins) (195,330,368,426), which protect against atherosclerosis (24,249). Importantly, upregulation of KLF2 is required for many of the transcriptional effects of statins in endothelial cells, so KLF2 might mediate their atheroprotective effects (330). In a background of apolipoprotein E (*ApoE*^{-/-}) deficiency, *Klf2*^{+/-} mice have increased diet-induced atherosclerosis, compared with *ApoE*^{-/-} mice (14). Interestingly, peritoneal macrophages isolated from *Klf2*^{+/-} mice have increased lipid uptake, compared with wild-type macrophages; this increase might be mediated by the ability of KLF2 to activate expression of aP2, a lipid chaperon involved in macrophage lipid accumulation and atherogenesis (35,263).

Contrary to the upregulation of KLF2 by shear stress and statins, expression of KLF2 in endothelial cells is suppressed by pro-inflammatory cytokines such as TNF- α and interleukin (IL)-1 β , which are important in the pathogenesis of atherosclerosis (233,369). TNF- α inhibits KLF2 via NF- κ B and HDAC4, which cooperatively inhibit MEF2—an essential transcriptional activator of *KLF2* (190). Conversely, overexpression of KLF2 in endothelial cells inhibits IL-1 β -dependent induction of the pro-inflammatory molecules VCAM-1 and E-selectin (369). Consistent with these findings, T-cell rolling and attachment are significantly reduced in endothelial monolayers transduced with KLF2 (369). Similarly, IL-1 β -induced leukocyte-

endothelial cell interactions are inhibited by ectopic expression of KLF2 (329). Importantly, KLF2 inhibits endothelial activation by many pro-inflammatory stimuli, including IL-1 β , TNF- α , lipopolysaccharide (LPS), and thrombin (13,329,369). The mechanisms by which KLF2 achieve its anti-inflammatory function are multiple and include inhibition of NF- κ B (369), activator protein-1 (AP-1) (34), and activating transcription factor 2 (137). Thus, KLF2 is an important regulator of pro-inflammatory cytokine-mediated activation of endothelial cells.

In addition to its anti-inflammatory activity, KLF2 regulates endothelial thrombotic function by controlling expression of factors that maintain an anti-thrombotic endothelial surface. Overexpression of KLF2 in endothelial cells induces thrombomodulin and eNOS (253), which inhibit blood coagulation and platelet aggregation, respectively (125). In contrast, KLF2 inhibits expression of the pro-coagulant factors plasminogen activator inhibitor-1 (PAI-1) and cytokine-mediated induction of tissue factor (253). KLF2 also inhibits thrombin-mediated activation of endothelial cells by inhibiting expression of the thrombin receptor protease activated receptor-1 (329). Consequently, KLF2 overexpression increases blood clotting time and flow rates under basal and inflammatory conditions (253). These studies demonstrate that KLF2 is an important transcriptional regulator of endothelial thrombotic function.

KLF2 regulates vascular remodeling through inhibition of angiogenesis, proliferation, and cell migration (13). *In vivo*, KLF2 overexpression inhibits vascular endothelial growth factor (VEGF)-mediated angiogenesis and tissue edema (28). *In vitro*, ectopic KLF2 expression slows VEGF-mediated activation of endothelial cells, resulting in reduced intracellular calcium influx, proliferation, and expression of pro-inflammatory genes (28). KLF2 exerts these anti-angiogenic effects via its ability to inhibit expression of VEGF receptor 2 (VEGFR2) (28). Furthermore, KLF2 attenuates endothelial migration by regulating expression of genes that control cell migration, including VEGFR2 and semaphorin-3 (107). Endothelial expression of KLF2 has paracrine effects, reducing migration of co-cultured SMCs (261); this is similar to the failure of SMCs to properly migrate to the developing aorta in *Klf2*^{-/-} mouse embryos (461). These findings reveal the important link between endothelial KLF2 expression and SMC function.

4. Vascular Smooth Muscle Biology and Pathobiology—Several KLFs have important roles in the biology and pathobiology of vascular SMCs, which contribute to blood vessel walls; KLFs 4 and 5 are the best characterized (170). In rabbit SMCs, KLF5 regulates transcription of embryonic smooth muscle myosin heavy chain by binding to a specific sequence in the gene's promoter (451). Expression of KLF5 in SMC is developmentally regulated—it is abundant in fetal but not in adult aortic SMCs of humans and rabbits (184, 451). However, under pathological conditions, such as coronary atherosclerosis, vein graft hyperplasia, and response to vascular injury, KLF5 expression is reactivated (15,184,313, 314). Following aortic balloon injury, KLF5 becomes expressed in the neointimal layer of the blood vessels (184). KLF5 is also highly expressed in most human coronary lesion samples (both primary and restenotic) collected during atherectomy (184)—the presence of KLF5-positive lesions has been correlated with the incidence of restenosis (184). KLF5 is more frequently expressed in SMCs cultured from human coronary atherectomy samples that have the ability for outgrowth; the ability for outgrowth correlates with a shorter time to restenosis in patients (357). In SMCs, KLF5 expression is induced by various proliferative or inflammatory stimuli, including angiotensin II, TNF- α , survivin, and MAPKs. Overexpression of KLF5 induces factors that regulate the vascular injury response such as inducible nitric oxide synthase (iNOS), PAI-1, PDGF-A, and VEGFRs (15,214,293,378). Together, these findings indicate that KLF5 induces SMC proliferation in response to injury.

The role of KLF5 in blood vessel pathobiology was demonstrated by the vascular phenotype of *Klf5*^{+/-} mice, which also have a cardiac phenotype (see section A2. Pathobiology of the

Heart) (378). The medial and adventitial layers of the aortas from *Klf5*^{+/-} mice are thinner than those of wild-type mice. The femoral arteries of *Klf5*^{+/-} mice have impaired response to cuff-induced injury, with reduced activation and proliferation of SMCs and fibroblasts, inflammatory responses, and angiogenesis (378). These defects result in smaller areas of neointimas, and reduced granulation tissues and angiogenesis around the cuffs of femoral arteries (378). Importantly, Am80, a synthetic retinoid agonist that attenuates KLF5's transcriptional activity, reduces neointima and granulation tissues in cuff-injured femoral arteries of wild-type mice, compared with *Klf5*^{+/-} mice (378). KLF5 is therefore involved in several facets of vascular remodeling, including mesenchymal-cell activation, development of interstitial fibrosis, and angiogenesis.

The mechanisms by which KLF5 promotes vascular SMC proliferation have been examined. Angiotensin II stimulates proliferation of vascular SMCs and increases the levels of KLF5 mRNA and protein (15,146). Incubation of vascular SMC with angiotensin II stimulates phosphorylation of KLF5, which increases its interaction with c-Jun and subsequent repression of the cell cycle inhibitor p21^{Cip1/Waf1} (176). The phosphorylation of KLF5 in response to angiotensin II is mediated in part by the MAPK/extracellular signal-regulated kinase (ERK) kinase-1 (MEK1); incubation of vascular SMCs with the MEK1 inhibitor PD98059 inhibits KLF5 phosphorylation and its interaction with c-Jun (176). Overexpression of KLF5 stimulates SMC proliferation, increases cyclin D1 expression, and inhibits apoptosis (412). Moreover, KLF5 interacts with RAR- α to regulate the smooth muscle phenotype; this interaction is interrupted by the synthetic retinoid Am80 (145). Am80 inhibits the interaction between KLF5 and RAR- α by inducing dephosphorylation of KLF5 that is mediated by PI3K-AKT signaling in vascular SMCs (496). These studies delineated the signaling pathways by which KLF5 is regulated by various stimuli.

In addition to its physiological function in endothelial cells (see section A3. Endothelial Biology and Pathobiology), KLF4 regulates vascular smooth muscle function. KLF4 binds to the promoter of the smooth muscle gene *SM22 α* , in a region identified as the TGF- β control element (TCE), and suppresses the TGF- β -dependent increase in transcription of *SM22 α* and *α -SMA* (1). KLF4 also represses serum response factor/myocardin-induced activation of *α -SMA* and mediates the repressive effect of PDGF-BB on this gene (256). Expression of KLF4 in SMCs is activated in response to members of the TGF- β superfamily, including TGF- β 1 and several bone morphogenetic proteins (BMPs), which regulate the vascular SMC phenotype (219). These results indicate that KLF4 is involved in determining the SMC phenotype by repressing expression of specific genes in response to external stimuli.

Similar to KLF5, expression of KLF4 is very low in normal blood vessels but is increased in the medial layer following vascular injury (1,482,483). Following injury, SMC differentiation markers are repressed—this repression is transiently delayed in mice with conditional deletion of *Klf4* (483). Moreover, neointimal formation increases in *Klf4* mutant mice in response to vascular injury, primarily from an increase in cell proliferation (483). KLF4 therefore regulates expression of differentiation markers and proliferation in SMCs following injury. Furthermore, KLF4 expression in SMCs is induced by oxidized phospholipids, including 1-palmytoyl-2-(5-oxovaleroyl)-sn-glycero-3-phosphocholine (POVPC), that accumulate in atherosclerotic lesions (337). POVPC strongly inhibits expression of SMC differentiation marker such as *α -SMA* and SM-myosin heavy chain, but activates those of inflammatory mediators, including MCP-1 and TGF- β (337). The inhibitory effect of POVPC on SMC gene expression is coordinated by KLF4, the transcription factor Elk-1, and several HDACs (482). Moreover, in SMCs, POVPC induces expression of several extracellular matrix proteins (including type VIII collagen α 1 chain) and cell migration—both of these are reduced in the absence of KLF4 (77). Thus, there is much evidence for the role of KLF4 in the pathogenesis of atherosclerotic vascular diseases.

Overexpression of KLF4 in vascular SMCs inhibits proliferation via a process that depends on p53 (450) and is antagonized by the inhibitor of DNA binding 3 (Id3), which promotes proliferation (449). KLF4 is also required for ATRA to inhibit vascular SMC proliferation (442); ATRA upregulates KLF4 at transcriptional and post-transcriptional levels (276,442). KLF4 inhibits SMC proliferation by inhibiting expression of several genes that encode growth factor receptors, including PDGF receptor β (503). However, KLF4 appears to have pleiotropic effects on expression of smooth muscle genes—although KLF4 induces expression of *SM22 α* and *α -SMA* in response to ATRA (442), it inhibits that of the same genes in response to TGF- β and PDGF-BB (1,256). This context-dependent nature of KLF4 activity has also been described in other systems.

Therefore, KLF4 and KLF5 have opposite effects in regulating proliferation of vascular SMCs. Similar findings have been observed in other cell or tissue types (151). Induction of a combination of KLF4 and KLF5 in vascular SMCs after injury might provide the balanced gene expression required to achieve homeostasis. MicroRNA (miR)-145, a non-coding RNA that regulates expression of KLFs 4 and 5, is highly expressed in normal vascular walls and freshly isolated vascular SMCs (76,93). Expression of miR-145 is significantly downregulated in vessel walls with neointimal lesion formation and in vascular SMCs that have de-differentiated in response to PDGF. MiR-145 controls SMC fate and expression of SMC markers by regulating transcription factors that include KLFs 4 and 5 (76,93). MicroRNAs can therefore direct SMC fate and regulate vascular SMCs proliferation under pathological conditions, in part by influencing expression of KLFs 4 and 5.

B. The Respiratory System

Although there is much information about the functions of KLFs in the cardiovascular system, few studies have investigated KLFs in the respiratory system; these have focus on the roles of KLFs in lung development and morphogenesis. KLF2 is expressed at a high level in the lung (10). *Klf2*^{-/-} mice die *in utero* between embryonic days (E) 11.5 and 13.5, making it difficult to study the function of KLF2 in lung development (447). However, *in vitro* cultures of lung bud tissues removed from E11.5 *Klf2*^{-/-} embryos form normal tracheobronchial trees (448). To examine lung development at a later stage, chimeric mice were generated by injection of *Klf2*^{-/-} ES cells into blastocysts of wild-type mice (448). In mice that survived to adulthood, *Klf2*^{-/-} ES cells contribute to all internal organs except lung. In contrast, animals with high levels of chimerism die at birth and have abnormal lung development and function (448). The lungs of these animals do not expand, appear to stop growing in the late canalicular stage, and have undilated acinar tubules and buds in peripheral regions (448). These results indicate that KLF2 is an important regulator of late-stage lung development.

Klf5 expression is developmentally regulated in mice (315). At E16.5, *Klf5* is expressed at high levels in the bronchiolar epithelium and epithelial lining of the trachea (315). *Klf5*^{-/-} mice die at E8.5 (378), so the exact role of KLF5 in lung development cannot be determined. Mice with conditional, lung-specific deletion of *Klf5* (*Klf5* ^{Δ/Δ}) survive until birth but die shortly afterward from respiratory failure (440). They have abnormalities in lung maturation and morphogenesis in the respiratory epithelium, bronchiolar smooth muscle, and pulmonary vasculature; respiratory epithelial cells of the conducting and peripheral airways are immature. Levels of surfactant phospholipids are reduced and lamellar bodies, the storage form of surfactant, are rarely found. Expression profiling studies demonstrated that KLF5 regulates genes involved in surfactant lipid and protein homeostasis, vasculogenesis (including VEGF-A), and SMC differentiation (440). These observations indicate that KLF5 is required for perinatal maturation of lung morphology and function.

KLF4 suppresses TGF- β -dependent induction of *α -SMA* in vascular SMCs via interaction with the TCE (1) (see section A4, Vascular Smooth Muscle Biology and Pathobiology). A similar

effect was observed in fibroblasts isolated from rat lungs (185), although the ability of KLF4 to inhibit α -SMA transcription does not solely depend on the TCE (185). Instead, KLF4 physically interacts with Smad3, which mediates the stimulatory effect of TGF- β on α -SMA transcription through an upstream element called Smad-binding element (SBE) (185). Interaction between KLF4 and Smad3 therefore prevents binding of Smad3 to the SBE and TGF- β -dependent, *de novo* differentiation of lung myofibroblasts (185).

KLF4 might also be involved in the inflammatory response of airway smooth muscle (ASM) cells, via a post-transcriptional mechanism (231). Several microRNAs are repressed in human ASM cells following stimulation with inflammatory cytokines such as IL-1 β , TNF- α , or interferon- γ (IFN- γ) (231). One of these, miR-25, targets KLF4, which is upregulated in ASM cells following cytokine stimulation (231). KLF4 might therefore have a role in the pathophysiology of lung diseases such as pulmonary fibrosis and inflammatory airway disease.

C. The Hematopoietic System

KLFs regulate erythropoiesis, lymphopoiesis, and formation and functions of monocytes and macrophages. Erythropoiesis is a complex physiologic process in which pluripotent hematopoietic stem cells undergo several stages of commitment to precursor and progenitor cells with gradually restricted potential; this process is controlled by lineage-specific transcription factors (for review, see (48)). Erythropoiesis requires the highly regulated expression of β -globin and related proteins that constitute an essential subunit of hemoglobin. The β -globin gene locus contains a cluster of several related genes on chromosome 11, arranged in the order in which they are expressed during development: 5'- ϵ - γ G- γ A- δ - β -3' (245). Thus, hemoglobin ϵ is the first globin gene expressed (in the yolk sac), followed by fetal hemoglobins A γ and G γ (in the liver), and eventually β -globin at birth (in the bone marrow). Each globin gene is controlled by specific *cis*-acting DNA elements in its own promoter. In addition, the differentiation- and development-specific expression of the β -globin gene locus depends on a distal regulatory sequence called the locus control region (LCR), which is located approximately 6 kb upstream from the ϵ -globin gene (245). The LCR interacts with multiple, sequence-specific DNA binding transcription factors and is required for high levels of expression of the β -globin genes at all developmental stages (180).

To understand the regulation of expression of the globin genes, Miller and Bieker performed subtraction hybridization studies using a Friend mouse erythroleukemia cell line. They identified a cDNA clone they named erythroid KLF or EKLF (279). Since EKLF was the first mammalian KLF identified, it was given the name KLF1. KLF1 binds the CACCC element in the β -globin gene promoter and LCR enhancer and activates a heterologous promoter that contained the CACCC sequence, as well as the endogenous β -globin promoter (31,279). Mutations in the CACCC element of the β -globin gene have been associated with β -thalassemia (232,320,321)—KLF1 cannot transactivate a reporter gene that contains the mutated elements (132). Expression of *Klf1* is restricted to two hematopoietic organs of the adult—mouse the bone marrow and spleen—and to cell lines of the erythroid lineage (279). KLF1 therefore has erythroid-specific distribution and function.

The developmental expression pattern of KLF1 indicates its importance in erythropoiesis. *Klf1* expression begins on E7.5 in mice, within primitive erythroid cells at the beginning of blood island formation in the yolk sac (399). By E9.0, *Klf1* is expressed in the hepatic primordia and liver, which becomes the sole source of *Klf1* mRNA in an E14.5 fetus (399). In the adult spleen, which is an erythropoietic organ in mice, *Klf1* is exclusively expressed in the red pulp (399). This is consistent with data from cell line studies showing that *KLF1* is expressed in erythroid but not lymphoid cell lines (279). The physiological function of KLF1 in erythropoiesis was demonstrated in experiments with *Klf1*^{-/-} mice; these mice have normal embryonic hematopoiesis but develop fatal anemia during early fetal life (E14.5), when

hematopoiesis starts to occur in the liver (311,335). *Klfl*^{-/-} mice form enucleated erythrocytes that are deficient in β -globin, similar to patients with β -thalassemia (311,335). In contrast, expression of embryonic globin genes during the early stages of embryogenesis is not affected. These findings indicate that KLF1 is not required for yolk sac erythropoiesis or erythroid commitment but is essential for the final stage of definitive erythropoiesis in the fetal liver. The stage-specific and β -globin-specific requirement for KLF1 indicates that it is involved in the switch from fetal-to-adult hemoglobin (γ to β) in humans. This concept is supported by the finding that KLF1 binds with higher affinity to the CACCC element from the adult globin gene promoter than to a similar element in the mouse embryonic (and human fetal) globin gene promoter (116). The reduction in β -globin transcription in the fetal livers of *Klfl*^{-/-} mice that have a single copy of the entire human β -globin locus is accompanied by increased transcription of the human γ -globin gene (333,459). KLF1 is therefore involved in the fetal-to-adult hemoglobin switch, mediating an adult stage-specific interaction between the β -globin gene promoter and the LCR that excludes the γ -globin gene (333,459). Studies in which KLF1 was expressed in immortalized cell lines from *Klfl*^{-/-} fetal liver progenitor cells indicated that KLF1 is involved in coordinating differentiation, hemoglobinization, and erythroid-cell proliferation (88); erythroid cells from *Klfl*^{-/-} have defects in cell cycle regulation and terminal differentiation (339).

ES cells isolated from *Klfl*^{-/-} mice differentiate into definitive erythroid colonies that contain reduced levels of hemoglobin. When the *Klfl*^{-/-} ES cells were injected into blastocysts, they did not contribute to the mature erythrocyte compartment of the resulting chimeric mice, indicating that *Klfl*^{-/-} erythrocytes are short-lived (251). Fetal expression of a human γ -globin transgene restored globin gene expression to *Klfl*^{-/-} embryos, but mice do not survive due to hemolysis (334). Other KLF1 gene targets, beyond the globin genes, therefore appear to be required for erythrocyte development—several studies have shown that KLF1 regulates expression of proteins involved in membrane and cytoskeletal stability (118,183,310). Loss of their regulation might contribute to the severity of the *Klfl*^{-/-} phenotype of disrupted erythropoiesis.

In addition to regulating erythrocyte maturation, KLF1 controls the development of megakaryocytes. Megakaryocytes and erythrocytes are derived from a common progenitor called the MEP (326). Studies indicate that KLF1 is directly involved in determining the bi-potential fate of MEP—KLF1 inhibits the formation of megakaryocytes while stimulating erythroid differentiation (144). Expression of KLF1 is uniquely downregulated in megakaryocytes after formation of the MEP (144). KLF1 might inhibit megakaryocyte differentiation by repressing expression of *FLI-1* (37,144), which is required for their development (173,212). Conversely, FLI-1 represses KLF1-dependent transcription (403), so cross-antagonism between KLF1 and FLI-1 controls erythrocytic versus megakaryocytic differentiation (403). Lastly, sumoylation of KLF1 is required for it to suppress megakaryocyte differentiation (380).

The developmental- and erythroid-specific patterns expression patterns of KLF1 prompted investigations of the mechanisms that regulate *KLF1*. An enhancer element in the distal promoter of *KLF1*, approximately 700 bp upstream of the transcription start-site, and a proximal promoter element are required for its erythrocyte-specific expression (67). The erythroid-specific transcription factor GATA-1 binds the enhancer and promoter elements and transactivates the *KLF1* promoter (9,94). Studies in transgenic mice showed that 950 bp of the *KLF1* 5'-flanking region is sufficient to induce erythroid-specific expression of a reporter gene and requires the GATA-1-binding sites (8,466). Using an *in vitro* system in which ES cells differentiate into embryoid bodies (EB), it was shown that the BMP-4/SMAD pathway controls differentiation-dependent expression of KLF1 (2). This study also showed that KLF1 expression is activated before terminal erythroid differentiation in two stages: it is expressed

at low levels in progenitor cells (before erythroid commitment), which depends on GATA-2 and SMAD5, and then at high levels by committed erythroid cells, which depends on GATA-1 (258). The stage- and lineage-specific dependent control of KLF1 expression indicates that it is a regulator of lineage fate decisions during hematopoiesis (258).

Although KLF1 has important functions in erythropoiesis, other KLFs are also involved. A functional screen for KLFs that regulate the human γ -globin promoter through the CACCC element revealed the presence of 8 KLFs aside from KLF1 in human erythroid cell lines (490). Levels of KLFs 2, 4, 5, and 12 increase significantly during erythroid differentiation. Co-transfection studies indicated that KLFs 2, 4, and 13 activate, whereas KLF8 represses, the γ -globin promoter through its CACCC element (490). The roles of KLF2, and to some extent, KLF6, in erythropoiesis have been examined. $Klf2^{-/-}$ mice die *in utero* between E12.5 and E14.5 from intra-embryonic hemorrhage (234,447). Compared with wild-type mice, E10.5 $Klf2^{-/-}$ embryos are anemic and have significant reductions in expression of mouse embryonic *Ey*- and $\beta h1$ -globin but not ζ -globin genes (21). Expression of the adult β^{maj} - and β^{min} -globin genes is unaffected in the fetal livers of E12.5 $Klf2^{-/-}$ embryos. In mice that carry the entire human globin locus, KLF2 also regulates the expression of the human embryonic ϵ -globin gene but not the adult β -globin gene, suggesting that this developmental stage-specific role is evolutionarily conserved. KLF2 also regulates maturation and/or stability of erythroid cells in the yolk sac; $Klf2^{-/-}$ embryos have a significant increase in numbers of primitive erythroid cells that undergo apoptotic cell death (21).

KLF6 also regulates hematopoiesis (267). $Klf6^{-/-}$ ES cells have significant hematopoietic defects following differentiation into EBs (267), prolongation of epiblast-like cells, delays in mesoderm induction, and delayed expression of *Klf1* and *Gata1* (267). Ectopic expression of KLF6 increases the hematopoietic potential of wild-type EBs (267), so KLF6 appears to be an important regulator of ES cell differentiation and hematopoiesis.

KLF1 and KLF2 have compensatory roles in controlling embryonic β -globin gene expression and primitive erythropoiesis (20). $Klf1^{-/-}/Klf2^{-/-}$ double mutant mice are anemic at E10.5, with greatly reduced levels of *Ey*- and $\beta h1$ -globin mRNAs. Examination of the E9.5 $Klf1^{-/-}/Klf2^{-/-}$ yolk sacs indicated that erythroid and endothelial cells are more abnormal than in either $Klf1^{-/-}$ or $Klf2^{-/-}$ mice (20). KLF1 and KLF2 might therefore have redundant functions in regulating expression of the embryonic β -like globin gene, primitive erythropoiesis, and endothelial development (20).

D. The Immune System and the Inflammatory Responses

1. T Lymphocytes—Kuo *et al.* were the first to identify a KLF that regulates T cell functions (235)—they found that KLF2 is expressed in lymphoid organs, including the thymus, and exclusively in the medulla, which contains mature, single-positive (SP; CD4⁺ or CD8⁺) T cells (235). In addition, KLF2 is expressed in SP splenocytes but not in the less mature double-positive (CD4⁺CD8⁺) T cells. SP T cells circulate through the blood and peripheral lymphoid organs in a quiescent state and are activated when the T-cell receptor binds antigen. When T cells are activated, KLF2 mRNA and protein are rapidly degraded (124,235)—potentially via WWP1 E3-ubiquitin ligase-mediated degradation (100). $Klf2^{-/-}$ T cells have a spontaneously activated phenotype and die in the spleen and lymph nodes from Fas ligand-induced apoptosis (235). KLF2 is therefore required for the quiescent state of mature T cells and for maintenance of viability in the peripheral lymph organs and blood.

Additional evidence supports a role for KLF2 in T cell quiescence. Ectopic expression of KLF2 in Jurkat T cells induces quiescence, characterized by decreased proliferation, reduced cell size and protein synthesis, and decreased expression of surface markers of activation (44). Conversely, $Klf2^{-/-}$ T cells have increased proliferation, cell size, and cell-surface markers of

activation (44). The mechanism by which KLF2 inhibits T cell activation, growth, and proliferation might include its ability to inhibit expression of *c-Myc* (44,168) and stimulate expression of *p21^{Cip1/Waf1}* (462).

Although studies had demonstrated that KLF2 is downregulated upon T cell activation, its expression appears to be dynamic. For example, expression of KLF2 is re-induced in antigen-activated CD8⁺ T cells in the presence of certain cytokines, including IL-7 (124,360). The ability of IL-7 to induce KLF2 expression in activated T cells is mediated by the MEK5/ERK5 pathway and depends on the transcription factor MEF2 (124,391). Prolonged culture of activated CD8⁺ T cells in the presence of IL-7 causes them to acquire characteristics of memory CD8⁺ T cells, which maintain stable levels of KLF2 (360); stable expression of KLF2 has been reported in memory T cells (160,360). In activated T cells, KLF2 might upregulate transcription of *IL-2* (160,360,463). Specific cytokines might therefore induce expression of KLF2 in activated T cells, possibly to regulate factors required for long-term survival and development of the memory T-cell phenotype.

In addition to regulating T cell proliferation and survival, KLF2 controls T cell migration and trafficking. Compared to *Klf2^{+/-}* cells, *Klf2^{-/-}* thymocytes have reduced expression of several receptors required for emigration and peripheral trafficking, including the sphingosine-1-phosphate receptor (S1P₁), CD62L (L-selectin), CCR7, and integrin subunit β 7 (51). As a consequence, *Klf2^{-/-}* thymocytes have abnormal tissue distribution following adoptive transfer; they are absent from blood and lymphoid organs and accumulate in the spleen (51). Pulse-labeling experiments showed impaired emigration of *Klf2^{-/-}* thymocytes into the periphery (51). Conversely, primary T cells that express ectopic Klf2 are more efficient in homing to lymphoid organs (16). KLF2 accomplishes these activities by directly activating expression of CD62L (L-selectin) (16), a receptor required for T cells to enter lymphoid nodes (439); and S1P₁ (51), which allows T cells to exit the thymus (266). Interestingly, KLF2 and S1P₁ have similar patterns of expression in T cells—they are upregulated in mature thymocytes, downregulated upon T cell activation, and re-expressed in memory T cells (51). The PI3K signaling pathway regulates KLF2. PI3K and its downstream nutrient sensor, the mammalian target of rapamycin (mTOR), determine the repertoire of adhesion and chemokine receptors expressed by T cells and are required for T-cell trafficking (128,387). PI3K regulates the transcription factor forkhead box O1 (FOXO1), which regulates KLF2 expression (128). KLF2 then directly regulates the expression patterns of chemokine receptors that induce T cell migration (366,457); KLF2 thereby controls the regulatory network that controls T cell migration and trafficking.

KLF10 has an important role in the development of CD4⁺CD25⁺ regulatory T (Treg) cells, which maintain self-tolerance and immune suppression (138). The transcription factor Foxp3 regulates the Treg cell lineage (138) and TGF- β converts CD4⁺CD25⁻ naïve T cells into Foxp3⁺CD4⁺CD25⁺ Treg cells *in vitro* and maintains Treg cells *in vivo* (63,129,247). KLF10 induces expression of Foxp3 in T cells following exposure to TGF- β (50,438). KLF10 cooperates with Itch to induce Foxp3 expression (438); both *Klf10^{-/-}* and *Itch^{-/-}* T cells are resistant to the effects of TGF- β and have reduced TGF- β (438). Following incubation with TGF- β converted *Klf10^{-/-}* Treg cells are unable to suppress airway inflammation in mice (438). Moreover, CD4⁺CD25⁻ T cells that overexpress KLF10 increase TGF- β 1 expression, compared with those that do not overexpress KLF10, and have reduced expression of Th1 and Th2 markers (50). Conversely, *Klf10^{-/-}* CD4⁺CD25⁻ T cells increase expression of Th1 and Th2 cytokines and cannot be suppressed by wild-type Treg cells (50). Because KLF10 transactivates *TGF- β 1* and *Foxp3* in response to TGF- β , it is involved in a positive feedback loop that controls T cell activation (50).

KLF13 was initially identified as a transcription factor that regulates expression of regulated upon activation normal T cell expressed and secreted (RANTES or CCL5), a chemokine that generates inflammatory infiltrates and is expressed late after T cell activation (393,394). Although levels of *KLF13* mRNA are similar between naive and activated T cells, only KLF13 protein is abundant in the late stage of T cell activation, so KLF13 is likely to be regulated at the level of translation (393). Studies have shown that KLF13 expression is translationally regulated through the 5'-untranslated region of its mRNA in a cell type-specific manner (309). Overexpression of the translation initiation factor eIF4E and Mnk1 (which phosphorylates eIF4E) increase KLF13 protein levels (309). These events are regulated by ERK1/2 and p38 MAPKs and allow T cells to rapidly adjust levels of RANTES expression in response to changes in the cellular environment, such as stress or exposure to growth factors (309). The ability of KLF13 to activate *RANTES* transcription requires the recruitment of several transcription co-activators and the serine/threonine protein kinase PRP4, which phosphorylates KLF13 (4,187). *Klf13*^{-/-} mice have enlarged thymuses and spleens because of decreased thymocyte apoptosis; KLF13 inhibits expression of the anti-apoptotic factor BCL-XL (506). In addition, KLF13 influences multiple stages of B- and T-cell development *in vivo* (322). KLF13 therefore appears to regulate T cell activation, survival, and development.

2. B Lymphocytes—The most extensively studied KLF in B cell function is KLF4. KLF4 is expressed in early-stage B cell precursors, at the time of immunoglobulin gene rearrangement (433); its expression continuously increases until B cells are mature (220). Upon B cell activation, levels of KLF4 are rapidly reduced. *Klf4*^{-/-} mice have modest reductions in numbers of pre-B cells and mature B cells in the bone marrow and spleen, respectively. B cells isolated from *Klf4*^{-/-} mice have reduced DNA synthesis and delayed entry into the cell cycle in response to B-cell receptor (BCR) activation, a result of decreased cyclin D2 expression (220). KLF4 binds directly to the *cyclin D2* promoter and activates *cyclin D2* expression (220). KLF4 is therefore a positive regulator of BCR-mediated B cell proliferation. However, overexpression of KLF4 in pre-B cells transformed by the *ABL* oncogene induces arrest in the G₁ phase of the cell cycle and apoptosis (216). Transformed B cells that overexpress KLF4 increase expression of p21^{Cip1/Waf1} and reduce expression of c-Myc and cyclin D2 (216). Moreover, the anti-proliferative effect of KLF4 on B cells requires its activation by FOXO1 (484).

KLF4 also mediates the proliferative response of memory B cells. Ectopic expression of KLF4 in memory B cells delays cell division and thereby reduces the number of proliferating cells (156). It is not clear what accounts for the discrepancies observed in the effects of KLF4 on B cell proliferation but differences could arise from variations in physiologic contexts, genetic backgrounds, or experimental methodologies.

3. Monocytes and Macrophages—KLFs regulate inflammatory responses in both endothelial and SMCs (172,233,369). KLFs regulate signaling following activation of macrophages, and could thereby mediate the development of acute and chronic inflammatory disorders. KLF4 mediates macrophages signaling in response to inflammatory cytokines, such as IFN- γ , LPS, or TNF- α , and anti-inflammatory factors such as TGF- β 1 (130). KLF4 is rapidly induced in macrophages incubated with IFN- γ , LPS, or TNF- α and reduced in response to TGF- β 1 (130). In combination with the p65 (RelA) subunit of NF- κ B, overexpression of KLF4 in macrophages induces iNOS, a marker of cell activation (130). However, KLF4 overexpression also inhibits *PAI-1* (a TGF- β 1-regulated gene) without binding to it (130).

KLF4 regulates monocyte differentiation *in vitro* and *in vivo* (6,131). Although overexpression of KLF4 in HL-60 cells confers characteristics of mature monocytes, KLF4 inhibition blocks phorbol ester-induced monocyte differentiation (6,131). Ectopic expression of KLF4 in common myeloid progenitors or hematopoietic stem cells induces differentiation of only

monocytes in clonogenic assays, whereas inhibition of KLF4 increases differentiation of granulocytes, at the expense of monocytes (131). Hematopoietic *Klf4*^{-/-} chimeras (generated by transplantation of *Klf4*^{-/-} fetal liver cells into irradiated wild-type mice) completely lack circulating inflammatory cytokines (6). KLF4 is therefore an important promoter of monocyte differentiation.

Whereas KLF4 activates macrophages to promote inflammation, KLF2 has the opposite effect (106); its expression is reduced upon monocyte activation and differentiation into macrophages. Ectopic expression of KLF2 inhibits monocyte activation and their phagocytic capacity, whereas KLF2 inhibition increases expression of inflammation genes. Reconstitution of immunodeficient mice with KLF2-overexpressing monocytes significantly reduces carrageenan-induced acute paw edema formation (106). KLF2 inhibits the transcriptional activity of both NF- κ B and AP-1 by recruitment of co-activator P/CAF, thereby preventing activation of inflammatory genes (106). These results demonstrate that KLF2, as opposed to KLF4, is a negative regulator of monocytic activation.

E. The Digestive System

1. Small Intestine and Colon—The mammalian intestinal epithelium is a continuously renewing system in which cell proliferation, differentiation, migration, and apoptosis are carefully orchestrated to achieve homeostasis. The epithelium of the small and large intestines consist of a crypt/villus and crypt/surface epithelium compartment, respectively. The bulk of the villus and surface epithelium of the small and large intestine, respectively, is composed of differentiated columnar epithelial cells that are divided into absorptive (primarily enterocytes) and secretory (including goblet, enteroendocrine and Paneth cells) classes. Paneth cells are unique to the small intestine under normal conditions. The differentiated epithelial cells are descendants of the crypt progenitor cells, which themselves are derived from the multi-potent stem cells, also located in the crypt compartment (19,342,365). Intestinal epithelial homeostasis is regulated by signaling mechanisms that include the Wnt, Notch, Hedgehog, BMP, and PI3K pathways (19,342,365).

Both KLFs 4 and 5 control and maintain intestinal epithelial homeostasis (151,272). Expression of KLFs 4 and 5 in the intestines is developmentally regulated, with higher levels of expression occurring towards the later stage of fetal development and adulthood (315,422). The temporal pattern of expression of *Klf4* during fetal development correlates with the transition of a pseudo-stratified epithelial cell layer into a simple columnar monolayer at approximately E15–E17 of development (422). In the adult, KLF4 and KLF5 are highly expressed in the intestinal epithelial cells but have different distribution—KLF4 is found primarily in the terminally differentiated cells in the villi and surface epithelium of the small intestine and colon, respectively, whereas KLF5 is present primarily in the proliferating crypt epithelial compartment (89,272,375). This is demonstrated in Figure 3, which shows the distribution of *Klf4* and *Klf5* in the mouse colon in conjunction with the proliferation marker, *Ki67*. The biological activities of KLFs 4 and 5 are reflective of their cellular distribution; KLF4, when overexpressed, inhibits cell proliferation, whereas KLF5 promotes it (54,151,272,375). The cytostatic effect of KLF4 is mediated by induction of the gene that encodes the cell cycle inhibitor p21^{Cip1/Waf1} (66) and by inhibition of the genes that encode cyclin D1 and ornithine decarboxylase (ODC) (71,373); this combination blocks the G₁/S transition of the cell cycle. KLF4 also mediates the cytostatic effect of p53 following DNA damage and by blocking the G₁/S and G₂/M phases of the cell cycle (479,481,493). Transcriptional profiling studies have shown that many of the genes upregulated by KLF4 inhibit the cell cycle and many of those that are downregulated promote the cell cycle (68).

In non-transformed cells, such as NIH3T3 and several intestinal epithelial cell lines, overexpression of KLF5 stimulates proliferation and in some cases, leads to anchorage-

independent growth (22,54,410). This is consistent with the findings that KLF5 expression is upregulated by mitogens such as serum, phorbol ester, and the oncogenic HRAS (214,297, 301,410). A common mechanism by which these stimuli induce KLF5 expression is through activation of the MAPK/early growth response gene (EGR)-1 signaling pathway (214,301), which activates *KLF5* transcription (214). KLF5 subsequently stimulates expression of cyclin D1 and cyclin B1/Cdc2, accelerating cell cycle progression (297,301). Conversely, KLF5 expression in intestinal epithelial cells is inhibited by ATRA, an inhibitor of epithelial cell proliferation; constitutive expression of KLF5 blocks the growth inhibitory effect of ATRA (54). KLF5 also mediates the induction of proliferation of colon cancer cells by lysophosphatidic acid (LPA) (486). The effects of KLF5 on cell proliferation require post-translational regulation including protein-protein interaction and modifications. Interaction with PIAS1 and modification by SUMO increase KLF5's pro-proliferative activity (119, 120). Interestingly, whereas KLF4 activates its own promoter, KLF5 inhibits the *KLF4* promoter (104,262). This result is reminiscent to the opposing activity and cellular distribution of these KLFs in the intestinal epithelium.

The *in vivo* functions of KLFs 4 and 5 in the intestine have been partially determined through studies of knockout mice. *Klf4*^{-/-} mice die shortly after birth with a defect in skin barrier function (367). Newborn *Klf4*^{-/-} mice also have a 90% reduction in the number of goblet cells in their colon, compared to wild-type controls (211), so KLF4 might regulate intestinal epithelial differentiation. This finding is consistent with results of *in vitro* studies demonstrating that KLF4 regulates expression of intestinal epithelial markers, including intestinal alkaline phosphatase and keratins (68,181,381). Expression of KLF4 increases with differentiation of colon cancer cell lines of goblet and absorptive cell lineages (136). Short-chain fatty acids such as sodium butyrate, which regulates colonic epithelial differentiation, induce KLF4 expression (70,136), whereas Notch signaling inhibits KLF4 expression. Inhibition of Notch induces KLF4 expression and increases the number of goblet cells in the intestine (148,345,504). These results indicate that in the intestinal tract, KLF4 controls epithelial differentiation.

Klf5^{-/-} mice die *in utero* whereas *Klf5*^{+/-} mice are born with intestinal phenotypes such as misshapen villi and intestinal fibrosis (378). When *Klf5*^{+/-} mice are infected with *Citrobacter rodentium* (a murine bacterial pathogen that causes colonic epithelial hyperplasia), they have significantly reduced colonic hyperproliferation, compared with wild-type mice (273). These results indicate that KLF5 mediates colonic crypt cell proliferation in response to bacterial infection (Figure 4). Expression of KLF5 in intestinal epithelial cells is induced by the bacterial endotoxin, LPS. LPS-mediated induction of KLF5 increases the transcriptional activity of NF- κ B, leading to induction of inflammatory cytokines such as TNF- α and IL-6, as well as intercellular adhesion molecule-1 (ICAM-1) (53). *Klf5*^{+/-} mice are more susceptible to dextran sodium sulfate (DSS)-induced colitis than wild-type mice—additional evidence that KLF5 regulates epithelial restitution following injury (McConnell and Yang, unpublished observations).

KLF9 also regulates intestinal morphogenesis. In contrast to KLFs 4 and 5, KLF9 is predominantly expressed in the SMCs of the small intestine and colon (383). The jejunum of *Klf9*^{-/-} mice have shorter villi, reduced proliferation of crypt cells, and alterations in lineage determination (383). KLF9 therefore directs the production of mediators of crypt cell proliferation, lineage determination, and migration from intestinal SMCs.

2. Esophagus and Stomach—Several KLFs function in the esophagus and stomach. KLF4 is expressed in the squamous epithelial cells of the esophagus, where it activates the promoters of two genes that are highly expressed in the esophageal squamous epithelium: the Epstein-Barr virus *ED-L2* and *keratin 4* (196). Keratin 4 is also regulated by KLF9 (319). Together,

Sp1 and KLF4 activate transcription of *keratin 19* in esophageal epithelial-derived cell lines (41).

The esophageal squamous epithelium contains a proliferating layer and a differentiated suprabasal layer. KLF4 is expressed in the suprabasal layer while KLF5 is expressed in the basal layer. Overexpression of KLF4 or KLF5 modulates proliferation, apoptosis, and invasion of human esophageal squamous cancer cell line TE2 (472). Expression of KLF5 coincides with that of the epidermal growth factor (EGF) receptor (EGFR) (473). Overexpression of KLF5 in primary esophageal keratinocytes increases proliferation, EGFR levels and MAPK signaling (473). KLF5 activates EGFR expression by directly binding to a regulatory element of the *EGFR* promoter (473). Overexpression of KLF5 also increases migration of primary esophageal keratinocytes, via its upregulation of integrin-linked kinase (ILK) (474) and increases proliferation of the basal, but not suprabasal, esophageal epithelial cells (155). KLF5 therefore regulates proliferation and migration of squamous esophageal epithelial cells.

Conditional deletion of *Klf4* from mouse stomach (using Cre recombinase, regulated by the *Foxa3* promoter) (210) results in mice that survive to adulthood but have increased proliferation in the gastric epithelium without evidence of dysplasia or cancer. The *Klf4* mutant mice also have altered differentiation of gastric epithelia, including a dramatic increase in the number of trefoil factor 2-positive cells—a characteristic of premalignant conditions of the stomach (210). KLF4 therefore also regulates gastric epithelial homeostasis.

3. Liver and Pancreas—KLF6 regulates the early stages of the fibrotic response during liver injury. Hepatic stellate cells (HSCs) are the major source of extracellular matrix during liver fibrosis; they are often activated upon liver injury and during subsequent wound healing (142). Using a rat model of liver fibrosis, Friedman and colleagues found that KLF6 is induced during the early phase of HSC activation (238,344). In fibrotic liver, KLF6 transactivates the promoters of several genes involved in fibrotic injury and repair, such as collagen $\alpha 1(I)$ and TGF- β receptors (218,344). *In vivo*, KLF6 slows proliferation; mice that overexpress KLF6 specifically in liver have reduced liver size, whereas *Klf6*^{+/-} mice have increased liver size (306). Several alternatively spliced forms of KLF6 exist in human and rodents that have dominant-negative activities (303). A specific, germ-line, single-nucleotide DNA polymorphism results in a splice variant of KLF6 that is associated with increased risk of prostate cancer and advanced fibrosis in patients with nonalcoholic fatty liver disease (278, 303).

KLFs 10 and 11 are expressed in the pancreas. KLF10 is expressed in the acinar and ductular epithelial cell populations of the exocrine pancreas (414). KLFs 10 and 11 belong to the TGF- β -induced early gene subfamily and mediate the anti-proliferative effect of TGF- β on pancreatic epithelial cells—a process that involves its downstream effector Smad4 (91,92). Overexpression of KLF10 in TGF- β -sensitive pancreatic epithelial cells causes apoptosis (414). KLFs 10 and 11 share an amino-terminal transcription repressive domain called the SID, which is also required for the growth suppressive effect of KLF11 (90,133,488). KLF11 potentiates TGF- β signaling and transcription in normal epithelial cells by suppressing expression of Smad7, which normally inhibits TGF- β signaling (122). Transgenic mice that express KLF11 under the control of a pancreas-specific promoter have smaller pancreases, compared with the non-transgenic control mice, and down-regulate expression of the oxidative stress scavengers SOD2 and catalase 1 (133). KLF11 expression renders cells more sensitive to oxidative drugs, an effect that is rescued by overexpression of SOD and catalase 1 (133).

KLF11 regulates β cell function in the pancreas. It is expressed in human pancreatic islets and in pancreatic β cell lines (308). β cells cultured in high levels of glucose have higher levels of KLF11, which activates the insulin promoter (308). KLF11 regulates expression of pancreatic-

duodenal homeobox-1, which is required for pancreatic organogenesis and activity of insulin-secreting β cells in adults (434). Genetic analysis of *KLF11* among North European populations revealed the presence of several rare variants that impair KLF11's transcriptional activity and are associated with early onset of type 2 diabetes (308). A variant of the promoter of *KLF11* has also been linked to insulin sensitivity in a Danish population (167). However, similar studies failed to demonstrate an association of any genetic variants of KLF11 with type 2 diabetes in Japanese or native American populations (236,260,418).

F. The Role of KLFs in Metabolic Regulation

No fewer than eight KLFs are involved in metabolism, primarily by regulating differentiation of fat cells (adipocytes) (see (42) for a recent review). The adipose tissue is the major site of energy storage and determines energy homeostasis, the perturbation of which can lead to pathological conditions including obesity and diabetes. The differentiation of precursor adipocytes (pre-adipocytes) into mature adipocytes is regulated by an intricate network that is best modeled in cell culture systems (348–350). Genes that mediate adipocyte differentiation are controlled by the transcription factor families C/EBP, PPAR, and sterol regulatory element binding proteins (SREBP)/adipocyte differentiation and determination factor (349,350). C/EBPs β and δ are activated in the early phase of adipogenesis, followed by sustained expression of C/EBP α and PPAR γ in the late phase of differentiation and the eventual expression of adipocyte-specific genes (349,350). KLFs are an important part of the regulatory cascade that leads to adipogenesis (42). The roles of various KLFs as positive and negative regulators of adipocyte differentiation are summarized in Figure 5.

1. KLFs 2 and 3—KLFs 2 and 3 inhibit adipocyte differentiation. In a well-characterized 3T3-L1 model of differentiation (161), levels of KLFs 2 and 3 are high in undifferentiated pre-adipocytes and reduced upon differentiation into adipocytes (18,409,464). Overexpression of KLF2 or 3 blocks adipocyte differentiation (18,409,464), partly through KLF2's ability to repress PPAR γ expression (18) and KLF3's ability to inhibit C/EBP α expression (409).

Mouse embryonic fibroblasts (MEFs) that lack *Klf2* (*Klf2*^{-/-}) or *Klf3* (*Klf3*^{-/-}) are more prone to differentiate into adipocytes, indicating that KLFs 2 and 3 inhibit adipogenesis *in vivo* (409,464). Recent studies in *Caenorhabditis elegans* have implicated a role for the *C. elegans* Klf3 homolog in regulation of fat metabolism (487).

2. KLFs 4 and 5—KLFs 4 and 5 promote adipogenesis. KLF4 is expressed very early in the course of 3T3-L1 differentiation with a pattern similar to that of previously described transcription factors, Krox20, C/EBP β , and C/EBP δ (32). KLF4, in conjunction with Krox20, activates expression of the C/EBP β gene (32). Importantly, knockdown of KLF4 inhibits adipogenesis and reduces C/EBP β levels (32). Interestingly, knockdown of C/EBP β increases levels of KLF4 and Krox20, indicating that C/EBP β normally controls KLF4 and Krox20 expression via a negative feedback loop (32).

Similar to KLF4, KLF5 is also induced at an early stage of 3T3-L1 differentiation that requires C/EBPs β and δ (318). Then, KLF5 activates expression of PPAR γ 2 (318). Overexpression KLF5 spontaneously induces adipocyte differentiation, whereas expression of a dominant-negative form of KLF5 inhibits adipogenesis (318). *Klf5*^{+/-} have defects in development of white adipose tissue and MEFs obtained from *Klf5*^{+/-} mice have attenuated adipocyte differentiation (318). These results indicate that KLF5 is a key regulator of adipocyte differentiation *in vitro* and *in vivo*. Furthermore, *Klf5*^{+/-} mice are resistant to high fat diet-induced obesity, hypercholesterolemia, and glucose intolerance, despite their consumption of more food than wild-type mice (317). Instead, *Klf5*^{+/-} mice have increased energy expenditure, in part from increased expression genes that encode lipid oxidation in the soleus muscle such

as carnitine-palmitoyl transferase-1b (Cpt1b) and uncoupling proteins 2 and 3 (Ucp2 and Ucp3) (317). KLF5 must be sumoylated to repress these oxidizing genes, which allows it to interact with co-repressors such as nuclear receptor co-repressor and SMRT, as well as unliganded PPAR δ (317). PPAR δ agonists stimulate desumoylation of KLF5; KLF5 then associates with transcriptional activation complexes containing ligand-bound PPAR δ and CBP (317). This activation complex subsequently activates expression of the lipid oxidizing genes (317). Sumoylation is therefore a molecular switch that controls KLF5 function and the transcriptional machinery that governs lipid metabolism.

3. KLF6—Delta-like 1 (Dlk1), also called pre-adipocyte factor-1 (Pref-1), regulates adipogenesis by preventing differentiation of 3T3-L1 cells into adipocytes (390). KLF6 represses Dlk-1 expression and thereby stimulates 3T3-L1 differentiation (390). Conversely, knockdown of KLF6 prevents adipogenesis (390). The repressive effect of KLF6 on the *Dlk-1* promoter requires HDAC3 activity (390).

4. KLF7—A search for single nucleotide polymorphisms (SNPs) in 12 KLF genes identified a SNP in *KLF7* that was significantly associated with type 2 diabetes in Japanese subjects (209). Although the same SNP is not associated with diabetes in a Danish population, a minor allele of a different *KLF7* locus protects against obesity in the same population (510). These studies provided evidence that KLF7 is involved in fat metabolism. Expression of KLF7 is decreased upon 3T3-L1 adipocyte differentiation and overexpression of KLF7 inhibits adipogenesis (209). Similarly, overexpression of KLF7 in human pre-adipocytes inhibited their differentiation into adipocytes and reduced expression of genes involved in adipogenesis, including C/EBP α and PPAR γ (215). Overexpression of KLF7 in differentiated adipocytes significantly reduces the levels of adipocytokines such as leptin and adiponectin (215). When overexpressed in an insulin-secreting pancreatic β cell line, KLF7 inhibits expression of insulin and glucose-induced secretion of insulin (215). In addition, KLF7 inhibits expression of hexokinase 2 in a skeletal muscle cell line and of glucose transporter 2 in a liver-derived cell line (215). KLF7 might therefore contribute to the pathogenesis of diabetes by impairing insulin biosynthesis and secretion in pancreatic β cells and reducing insulin sensitivity in peripheral tissues. These results are consistent with the observation that (-)-catechin, a component of the green tea polyphenols, promotes adipogenesis by inhibiting expression of KLF7 and activating that of adiponectin in 3T3-L1 cells (81)

5. KLF11—The role for KLF11 in regulating pancreatic β cell functions was addressed in section E3. Liver and Pancreas. KLF11 also regulates cholesterol-mediated gene expression. Following exposure of vascular endothelial cells to cholesterol, KLF11 represses the gene that encodes caveolin-1 gene, in which is involved in cholesterol homeostasis (49). Upon depletion of cholesterol, KLF11 is displaced from a Sp1-site that flanks a sterol-response element in the *caveolin-1* promoter, allowing the binding of SREBP and Sp1 and activation of the *caveolin-1* promoter (49). In response to cholesterol, KLF11 therefore represses genes that SREBP/Sp1 otherwise activate.

6. KLF15—KLF15 also regulates adipogenesis; its expression is highly upregulated during differentiation of 3T3-L1 pre-adipocytes into adipocytes (288). Dominant-negative forms or RNA interference of KLF15 reduce expression of PPAR γ and block adipogenesis of 3T3-L1 pre-adipocytes (288). KLF15 and C/EBP α act synergistically to increase the activity of PPAR γ 2 in 3T3-L1 adipocytes (288). In non-adipocyte cell lines such as NIH3T3 and C2C12, ectopic expression of KLF15 increases PPAR γ levels and lipid accumulation (288). Moreover, KLF15 expression is increased by ectopic expression of C/EBP α , β , or γ in NIH3T3 cells (288). KLF15 therefore plays an essential role in regulating adipocyte differentiation through its regulation of PPAR γ expression.

In addition to its role in adipogenesis, KLF15 is involved in energy metabolism in the liver, skeletal muscle, and adipocytes. KLF15 regulates expression of the insulin-sensitive glucose transporter GLUT4 in both adipose and muscle tissues (158). KLF15 also contributes to the transcriptional activation of mitochondrial acetyl-CoA synthetase 2 in skeletal muscle during fasting (469). In the liver, expression of KLF15 is increased by fasting and reduced by refeeding (421). In cultured hepatocytes, KLF15 expression is increased by cAMP and decreased by insulin (421). Ectopic expression of KLF15 in cultured hepatocytes increases expression of phosphoenolpyruvate carboxykinase (*PEPCK*), which is required for gluconeogenesis (421). Consistent with a role for KLF15 in gluconeogenesis, *Klf15*^{-/-} mice have severe hypoglycemia after an overnight fast (159). Interestingly, instead of a reduction in *PEPCK* levels, *Klf15*^{-/-} mice have defects in amino acid catabolism that arise from reduced expression of enzymes required for amino acid degradation in the liver and skeletal muscle; reductions of these enzymes limit the substrates available for gluconeogenesis (159). The activity of alanine aminotransferase (*ALT*), which helps convert the amino acid alanine into the gluconeogenic substrate pyruvate, is reduced by 50% in the livers of *Klf15*^{-/-} mice (159). These studies implicate KLF15 as a critical regulator of gluconeogenesis.

G. KLFs and Bone Metabolism

KLF 10 is the only family member known to be associated with bone metabolism. It was initially identified as a TGF- β -induced cDNA from a human fetal osteoblast (hFOB) library (406). Expression of KLF10 is rapidly and significantly induced in hFOB cells incubated with TGF- β 1 and BMP-2, and to a less extent, EGF (406). Other TGF- β superfamily members such as BMP-4, BMP-6, and activin, also induce KLF10 in hFOB cells but are less potent than TGF- β 1 (178). In addition, KLF10 is rapidly induced by the estrogen 17 β -estradiol (E2), in estrogen receptor (ER)-positive hFOB cells—this induction is antagonized by parathyroid hormone (419). E2-induced KLF10 inhibits DNA synthesis (419) and proliferation of hFOB cells incubated with TGF- β (177). In fact, human osteosarcoma cells (MG-63) that have been stably transfected with a vector that encodes KLF10 display changes similar to those following incubation with TGF- β (177). KLF10 increases TGF- β signaling through transcriptional activation of Smad2 and inhibition of Smad7, (202,203).

KLF10's role in bone physiology has been studied in knockout mice. *Klf10*^{-/-} mice have a greater number of osteoblasts, but not osteoclasts, during bone formation than wild-type mice (405). Following exposure to BMP-2, osteoblasts differentiate, but osteoblasts from *Klf10*^{-/-} mice fail to mineralize or support differentiation of osteoclasts (405). As a consequence, *Klf10*^{-/-} mice have defects in bone and tendon strength and microarchitecture (25,26). The defects in bone mineral content, density, and area in *Klf10*^{-/-} mice appear to be sex-specific (175). *KLF10* was one of five genes whose expression was associated with volumetric bone density in a SNP study of bone metabolism genes (476).

H. The Nervous System and Neuronal Morphogenesis

Several KLFs participate in neuronal morphogenesis. *Klf7* exhibits three phases of expression in the nervous system of the developing mouse (239). During embryogenesis, *Klf7* is highly expressed in the spinal cord, dorsal root ganglia, and sympathetic ganglia. During early postnatal development, *Klf7* is expressed in the cerebral cortex and is subsequently downregulated. In adult mice, *Klf7* is localized to the cerebellum and dorsal root ganglia. These phases of expression correspond with establishment of the neuronal phenotype in the embryonic spinal cord, development of synaptic circuitry in the postnatal cerebral cortex, and survival and function of adult sensory neurons and cerebellar granule cells. Deletion of *Klf7* in mice results in neonatal lethality which is associated with deficits in neurite outgrowth and axonal misprojection (241). Axonal pathways affected include the olfactory and optic systems, the cerebral cortex and the hippocampus.

Klf9 is expressed in dentate granule neurons of the dentate gyrus (DG), a region of the mammalian brain in which neurogenesis occurs in adulthood (363). Klf9 is upregulated during the early postnatal period and is expressed in dentate granule neurons during the late stage of maturation, when the cells are integrated into the hippocampal network. Dentate granule neurons from *Klf9*^{-/-} mice show delayed maturation, and adult *Klf9*^{-/-} mice exhibit impaired differentiation of adult-born neurons. Thus, Klf9 is necessary for late-phase maturation of dentate granule neurons both in DG development and during adult hippocampal neurogenesis.

KLF4 was recently identified as an important factor regulating the regeneration potential of neurons in the central nervous system (CNS) (286). Gene expression profiling was used to identify factors that are upregulated in retinal ganglion cells (RGCs) during postnatal loss of axon growth ability. Of the candidate genes identified, KLF4 is the most effective suppressor of neurite outgrowth when overexpressed in RGCs. Conversely, RGCs lacking KLF4 exhibit increased axon growth both *in vitro* and after optic nerve injury *in vivo*. Other KLFs are also developmentally regulated in postnatal RGCs—KLFs 6 and 7 which have growth-enhancing effects are downregulated, whereas KLF9 which is growth-suppressive is highly upregulated. In agreement with this study, Klf6 and Klf7 are required for regeneration of RGCs in zebrafish (437). Thus, KLFs that act as positive and negative regulators of axon outgrowth are coordinated to control the regenerative capacity of CNS neurons.

I. The Role of KLFs in Tumor Biology

Numerous KLFs are involved in the pathobiology of cancer (33,46,121,126,152,355,384,453). Here we review the role of representative KLF family members in tumor biology.

1. KLF4—As discussed in Section E.1. Small Intestine and Colon, KLF4 was initially identified as a growth arrest-associated gene in the intestinal epithelium that suppresses DNA synthesis when expressed ectopically (375). In RKO colon cancer cells, induction of KLF4 leads to G₁/S cell cycle arrest, which correlates with an increase in the level of p21^{Cip1/Waf1} (66). Using cell culture models in which DNA damage is elicited by γ irradiation or methyl methanesulfonate, KLF4 is transcriptionally activated by the tumor suppressor p53 and mediates subsequent G₁/S and G₂/M cell cycle checkpoints by activating transcription of *p21^{Cip1/Waf1}* (479,481,493). KLF4 is necessary for and sufficient to prevent centrosome amplification following γ -irradiation-induced DNA damage; it does so by inhibiting expression of the gene encoding cyclin E, which promotes centrosome amplification when overexpressed (480). KLF4 also represses expression of cell cycle-promoting genes such as cyclin D1 and ODC in the human colon cancer cell line HT29 (71,373). Agents that have anti-proliferative agents in colon cancer cells, including IFN- γ (72), sulforaphane (424,425), sodium butyrate (70), 15-deoxy- Δ 12,14-prostaglandin J₂ (73), and certain phytochemicals (79,80), increase levels of KLF4.

The checkpoint function of KLF4 in colon cancer-derived cell lines suggests that it is a tumor suppressor. Induced KLF4 expression in RKO cells, which do not express endogenous KLF4, reduces colony formation, cell migration, invasion, and *in vivo* tumorigenicity (102). KLF4 is regulated by adenomatous polyposis coli (APC), the most frequently mutated tumor suppressor gene in colon cancer (103). APC is part of the Wnt signaling pathway responsible for maintaining intestinal epithelial homeostasis by modulating cellular levels and localization of β -catenin (19,342,365). Either the presence of Wnt ligands or mutational inactivation of APC leads to nuclear translocation of β -catenin; formation of nuclear β -catenin/T cell factor 4 (TCF4) transcriptional complex increases cell proliferation (228,289). KLF4 inhibits Wnt signaling by downregulating β -catenin protein and mRNA levels (404), interacting physically with β -catenin, and repressing β -catenin/TCF4 transcriptional activity (492). KLF4 therefore

assists the tumor suppressive activity of APC via regulation of the Wnt/ β -catenin signaling pathway in colon cancer cells.

The tumor suppressor activity of KLF4 in colon cancer has been investigated in primary tumor samples. The levels of *KLF4* mRNA are reduced, compared with control tissues, in the respective intestinal and colonic adenomas from the *Apc^{Min}* mice and patients with familial adenomatous polyposis—both carrying germ-line *APC* mutations (101). Similarly, *KLF4* mRNA levels are lower in adenocarcinoma of the colon compared to normal colon (374). In a panel of 30 colorectal cancer specimens, the mean level of *KLF4* mRNA was reduced by 50% compared with paired normal colon samples (501). *KLF4* mRNA levels are also reduced in cultured colon cancer cell lines, compared to non-transformed colonic epithelial cells (501). Reductions in KLF4 expression arise through several mechanisms often involved with tumor suppressor inhibition, including loss of heterozygosity (LOH), promoter hypermethylation, and mutations that disrupt protein activity (501). Several studies have validated the loss of KLF4 expression in colorectal cancer, including those showing that *KLF4* mRNA levels are inversely correlated with Duke stages (86,356,465). Moreover, KLF4 has tumor suppressive activity in cancers of other regions of the gastrointestinal tract, including the esophagus (259, 443), stomach (85,208,452), and pancreas (454). Expression of KLF4 is also reduced in tumors that arise outside the gastrointestinal tract, such as in lung (30,186), prostate (139), and urinary bladder (316).

The tumor suppressive function of KLF4 has been examined *in vivo*. Between 10 and 20 weeks of age, *Apc^{Min}/Klf4^{+/-}* mice develop on average 55% more intestinal adenomas than *Apc^{Min}* mice (150). The levels of Klf4 protein in the normal-appearing mucosa of the *Apc^{Min}/Klf4^{+/-}* mice are lower than in that of wild-type, *Apc^{Min}*, or *Klf4^{+/-}* mice. In contrast, the levels of β -catenin and cyclin D1 are higher in the intestinal tissues of *Apc^{Min}/Klf4^{+/-}* mice, compared with the other genotypes (150). Klf4 levels are further decreased in adenomas derived from *Apc^{Min}/Klf4^{+/-}* and *Apc^{Min}* mice compared to their respective normal surrounding mucosa (150). There is an inverse correlation between the size of adenoma and *Klf4* transcript levels and a correlation between LOH at *Apc* and adenoma size (150). Haploinsufficiency of *Klf4* therefore promotes *Apc*-dependent intestinal tumorigenesis, consistent with the observations that KLF4 is regulated by APC (103) and that KLF4 inhibits Wnt/ β -catenin signaling (404, 492). MEFs isolated from *Klf4^{-/-}* embryos and maintained in culture are genetically unstable—they show aneuploidy, DNA damage, chromosome aberrations, and centrosome amplification (169). These results support a role for KLF4 as a tumor suppressor that maintains genetic stability (169).

An additional mechanism by which KLF4 suppresses intestinal tumor formation involves Notch signaling, which suppresses goblet cell differentiation in the intestinal epithelium and is upregulated in intestinal tumors (197,430). KLF4 is required for goblet cell differentiation (211); overexpression of Notch in HT29 cells suppresses KLF4 expression and increases proliferation (148). Conversely, inhibition of Notch by pharmacological or genetic means increases KLF4 expression and reduces proliferation (148). *Apc^{Min}* mice given the Notch inhibitor dibenzazepine (DBZ) have a 50% reduction in numbers of intestinal adenomas, compared with mice given vehicle alone (controls) (148). Importantly, the normal-appearing intestinal mucosa and adenomas from DBZ-treated *Apc^{Min}* mice have increased levels of Klf4 and numbers of goblet cells, as well as reduced cyclin D1 and Ki67 levels, compared with controls (148). These results were subsequently replicated (504) and suggest that KLF4 mediates the anti-tumor effect of Notch inhibitors such as DBZ (148).

Although there is much evidence that KLF4 is a tumor suppressor, contradictory data exist. For example, KLF4 mRNA and protein are present in a relatively high proportion of breast tumor samples, compared with the adjacent uninvolved epithelium (139). Furthermore, nuclear

localization of KLF4 in early-stage ductal carcinoma of the breast is associated with an aggressive phenotype that includes shortened survival time (324). The mechanism by which KLF4 promotes breast carcinogenesis might involve its ability to repress transcription of p53 and Mucin 1, which are often overexpressed in breast tumors (456). KLF4 activates transcription of *Notch1* in mammary epithelial cells and promotes signaling through a non-canonical Notch1 pathway (257). However, the role of KLF4 as a putative oncoprotein in breast tissue is controversial. A search of gene expression databases showed that *KLF4* mRNA levels are lower in breast tumor tissues, compared with normal tissues, in 9 of 11 data sets and that the levels are inversely correlated with tumor grade (5). *KLF4* mRNA levels are also correlated with ER-positive breast tumors (5). In breast cancer cells, KLF4 physically interacts with ER to inhibit its transcriptional activity and ER-dependent proliferation (5). Exposure of breast cancer cells to okadaic acid (OA) induces c-Myc and subsequent c-Myc-mediated apoptosis (489). KLF4 is also induced by OA and is responsible for OA-dependent induction of c-Myc (489). KLF4 also regulates transcription of the gene encoding laminin α 3A (*LAMA3A*) chain, a component of the extracellular matrix protein laminin-5, which is produced by normal mammary epithelial cells but markedly down-regulated in breast cancer cells (280). This loss of laminin-5 expression is associated with progression of breast cancer (179,264). Notably, KLF4 protein and DNA binding at the *LAMA3A* promoter are found in normal mammary epithelial cells but not in any of the breast cancer cell lines analyzed (280). Further studies are required to determine whether KLF4 is oncogenic or tumor suppressive in the breast.

KLF4 is also involved in the pathogenesis of squamous cell carcinoma. KLF4 is expressed in the normal squamous cell epithelium of the skin and oral cavity, in the differentiated suprabasal layer but not the basal layer (139). KLF4 staining is increased in dysplastic epithelium or squamous cell carcinoma of the oral cavity (69,139). Conditional expression of KLF4 in basal keratinocytes of transgenic mice blocks the proliferation-differentiation switch between the basal and parabasal epithelial cells and leads to hyperplasia, dysplasia, and squamous cell carcinoma *in situ* (140). In normal squamous epithelium or hyperplastic epithelium derived from the skin of KLF4 transgenic mice, expression of KLF4 and the proliferation marker PCNA are mutually exclusive (188). In contrast, KLF4 and PCNA co-localize in dysplastic or carcinoma-like lesions epithelium (188). These results indicate that successive increases of KLF4 in the nuclei of basal keratinocytes increases cell turnover and progression through the different stages of squamous cell tumorigenesis (188). KLF4 also activates expression of several retinoic acid receptors, including retinoid acid receptor- γ (RAR- γ) and retinoid X receptor- α (RXR- α). Exposure of mice to RXR-selective agonists such as 9-cis UAB-30 or rexinoid prevents formation of skin tumors that arise via induction of KLF4 in the basal keratinocytes and the appearance of hyperplastic, dysplastic, and squamous cell carcinoma-like lesions (200).

The mechanisms by which KLF4 could function as a tumor suppressor or oncoprotein are presented in Figure 6. In untransformed cells, KLF4 inhibits cell proliferation, but KLF4-induced arrest is bypassed by oncogenic RAS^{V12} due to the upregulation of cyclin D1 (351). Inactivation of p21^{Cip1/Waf1}-induced cell cycle arrest by the upregulated cyclin D1 overcomes the suppressive effects of KLF4 and contributes to cell transformation (351). Overexpression of KLF4 suppresses expression of p53 at the promoter level, allows RAS^{V12}-mediated transformation, and prevents DNA damage-induced apoptosis (351). In a similar study, KLF4 was identified in a functional screen as a transforming protein in adenovirus E1A-immortalized rat kidney RK3E cells (141). Cells that lack KLF4 exhibit a greater degree of apoptosis following γ irradiation (149). KLF4's anti-apoptotic effects are mediated through activation of p21^{Cip1/Waf1} and inhibition of p53 activation of the pro-apoptotic gene, BAX (149). KLF4 levels are determined by the extent of DNA damage and different levels of KLF4 determine the outcome of p53 response to DNA damage (507). Thus, KLF4 is activated after cytostatic, low-level DNA damage, leading to cell cycle arrest, but is repressed after severe DNA damage,

leading to apoptosis (507). These studies indicate that KLF4 regulates whether a cell will undergo cell cycle arrest or apoptosis depending on the level of genetic damage.

2. KLF5—KLF5 promotes proliferation of different cell types. In intestinal epithelial cells, expression of KLF5 coincides with that of Ki67, a marker of proliferation (273). *In vivo*, KLF5 mediates the hyperproliferative response of the colonic epithelium following pathogenic infection by *Citrobacter rodentium* (273) and the regenerative response in chemical colitis caused by DSS (McConnell and Yang, unpublished observations). Similarly, nanoparticles that contain siRNA against KLF5 have anti-tumor activity (467), and ATRA inhibits proliferation of untransformed intestinal epithelial cells, IEC6, and several colon cancer cell lines by inhibiting expression of KLF5 (54). Conversely, LPA facilitates proliferation of intestinal epithelial cells and colon cancer cells by inducing KLF5 (252,486). A recent high-throughput screening approach identified several novel and potent small molecular inhibitors of KLF5 that inhibit proliferation of several colon cancer cell lines (29). Moreover, overexpression of KLF5 in NIH3T3 fibroblasts (410), COS-7 (120), intestinal epithelial cells (22,54), and colon cancer cells (119) increases rates of proliferation, and in some cases, anchorage-independent growth. Finally, KLF5 mediates the transforming activity of oncogenic HRAS and KRAS in NIH3T3 fibroblasts (297,301) and IEC6 cells (299), respectively. Consistent with these findings, intestinal tumors derived from KRAS^{V12}-expressing transgenic mice and human colon cancer samples with oncogenic KRAS mutations contain increased levels of KLF5, determined by immunohistochemical analysis (299).

Apc^{Min}/*Klf5*^{+/-} mice have a 96% reduction in the number of intestinal adenomas compared with *Apc*^{Min} mice (271). This reduction in tumor formation correlates with decreased nuclear localization of β -catenin and reduced expression of the β -catenin targets cyclin D1 and c-Myc (271). In cultured cells, KLF5 physically interacts with β -catenin, facilitates its nuclear localization, and modulates β -catenin's transcriptional activity (271). KLF5 is therefore required for the tumor-initiating activity of β -catenin during intestinal tumorigenesis in *Apc*^{Min} mice. The tumor-promoting effects of KLF5 are supported by the observation that *Klf5* haploinsufficiency reduces intestinal burden in *Apc*^{Min} mice with the *KRAS*^{V12} mutation (298).

The involvement of KLF5 in cancers of the extra-intestinal tissues of the gastrointestinal tract has been investigated. As addressed in Section E.2. Esophagus and Stomach, overexpression of KLF5 in esophagus squamous epithelial cells (keratinocytes) regulates proliferation, migration, and signal transduction (155,473,474). In tumor samples from 247 patients with gastric cancer, KLF5 expression is correlated with early-stage cancers that are small in size and have not metastasized to the lymph nodes (237). In several pancreatic cell lines, KLF5 levels are increased independently of MAPK signaling, but increased KLF5 expression do depend on IL-1 β and hypoxia-inducible factor 1- α (HIF1- α) (287). Downregulation of KLF5 expression in pancreatic cancer cells by siRNA reduced expression of the KLF5 targets survivin and PDGF-A, which promote pancreatic tumor growth (287). The chromosome region that contains *KLF5*, 13q22.1-22.2, is frequently amplified in salivary gland tumors, so KLF5 might also be involved in the pathogenesis of this tumor type (287).

The role of KLF5 in the pathogenesis of breast cancer is somewhat unclear—with some studies showing that it promotes breast tumor formation. *KLF5* frequently undergoes hemizygous deletion and loss of expression in breast tumors, indicating a possible tumor suppressive role (57). In addition, KLF5 is actively degraded by the hyperactive E3 ubiquitin ligase, WWP1, in some breast cancer cell lines (59,74). Conversely, several studies demonstrate that KLF5 promotes breast cancer cell proliferation and survival by upregulating transcription of fibroblast growth factor binding protein 1 and stabilizing the dual-specificity phosphatase, MAPK phosphatase 1 (255,505). KLF5 is also induced upon overexpression of *ERBB2* (also

known as *HER1* or *NEU*), which is amplified in some breast tumors (23). In tumor samples from 90 patients with breast cancer, those that express higher levels of *KLF5* have shorter disease-free survival and overall survival times, compared to those that express lower levels of *KLF5* (423). *KLF5* expression is correlated with that of *HER2* and the proliferation marker *Ki67* (423). It is not clear why *KLF5* is upregulated in some breast tumors and downregulated in others, but the status of the ER might be a factor—*KLF5* inhibits the proliferative action of estrogen in ER-positive, but not ER-negative, cells (165).

The role of *KLF5* in prostate cancer pathogenesis is also unclear. The *KLF5* locus is frequently deleted and downregulated in prostate cancer and overexpression of *KLF5* in prostate cancer cell lines inhibits their growth (58). *KLF5* is often degraded by ubiquitin-mediated proteolysis in prostate cancer cells, as in breast cancer cells (59). However, gene expression profiling experiments showed that *KLF5* transcript levels were consistently increased in prostate cancer samples, relative to normal prostate epithelium (52). Furthermore, *KLF5* increases the expression of fatty acid synthase and the chemokine receptor, *CXCR4* (143,244), which are involved in prostate cancer proliferation and migration. Further studies are needed to identify the role of *KLF5* in prostate cancer pathogenesis.

The studies described here indicate that *KLF5* has a context-dependent proliferative or anti-proliferative function, sometimes in the same cell types. A number of recent studies explored the mechanism by which this can be achieved. In an *in vitro* epidermal epithelial cell system, proliferative *KLF5* becomes anti-proliferative, in the presence of TGF- β (163). *KLF5* inhibits the expression of the cell cycle inhibitor, p15, in the absence of TGF- β , but when TGF- β is added to cells, *KLF5* becomes acetylated and co-activates p15 transcription (163). In a similar manner, although *KLF5* activates c-Myc expression in the absence of TGF- β , it inhibits c-Myc in the presence of TGF- β (164). These findings suggest that *KLF5* activates cell proliferation in response to TGF- β , which has well-recognized pleiotropic effects on cell proliferation.

3. *KLF6*—An association between *KLF6* and cancer was made by Narla *et al.* who found that one allele of *KLF6* is deleted and the remaining allele is mutated in most primary prostate tumors (305). Wild-type *KLF6* upregulates p21^{Cip1/Waf1} and inhibits prostate cell proliferation but mutant forms of *KLF6* do not (305), indicating that *KLF6* is a prostate tumor suppressor. LOH and somatic mutations in *KLF6* are detected in another study of prostate cancer specimens, although at a lower frequency than that of Narla *et al.* (58). More recent studies confirmed that overexpression of *KLF6* in prostate cancer cells reduces proliferation and induces apoptosis (75,189). Conversely, reduced expression of *KLF6* is associated with poor prognosis in gene expression profiling studies of patients with prostate cancer (154). Expression of *KLF6* is decreased in aggressive, androgen-independent, metastatic prostate tumors (402). Other studies, however, report that *KLF6* mutations are rare events in sporadic or inherited-forms of prostate cancer (3,224,291).

Numerous studies demonstrated that loss of *KLF6* expression or activity, due to LOH, mutation, or promoter methylation, occur in many other types of cancer, including hepatocellular (45,182,229,230,306), colorectal (82,83,282,292,346), gastric (84,359), lung (193,508), head and neck (420), ovarian (114), and brain (47,478) cancers. However, other studies failed to establish an association between *KLF6* and some of these cancer types (38, 222,225,250,285,397).

A large cohort study of men with prostate cancer identified a germ-line SNP in *KLF6* that increases the relative risk of familial and sporadic prostate cancer (303). This polymorphism occurs in the first intron of *KLF6* (denoted as the intervening sequence (IVS) 1–27 G>A or IVS $\Delta\Delta$ allele) and generates a functional binding site for the splicing factor SRp40 that increases transcription of three alternatively spliced forms of *KLF6*: *KLF6*-SV1, -SV2 and -

SV3 (303). The KLF6-SV1 and -SV2 splice variants mislocalize to the cytoplasm, antagonize wild-type KLF6, and decrease p21^{Cip1/Waf1} expression (303); expression of these variants is increased in prostate tumors compared with normal prostate tissues (303) and targeted inhibition of the KLF6-SV1 variant suppresses prostate cancer cell proliferation, colony formation, and invasion (304). Conversely, overexpression of KLF6-SV1 accelerates prostate tumor progression and metastasis in humans and mice (302). These results demonstrate that dominant-negative KLF6 splice variants contribute to prostate cancer pathogenesis.

KLF6-SV1 has been detected in hepatocellular (475), ovarian (112,114), lung (111,358), pancreatic (174), and gastric tumors (359), and glioblastoma (47). In hepatocellular carcinoma, oncogenic RAS signaling stimulates alternative splicing of KLF6 and increases proliferation (475). In ovarian cancer cells, KLF6-SV1 promotes degradation of the anti-apoptotic protein NOXA, increasing cell survival (112). KLF6-SV1 also has anti-apoptotic effects in lung cancer cells (111). Indeed, KLF6-SV1 represents the first therapeutically targeted KLF and inhibitors of KLF6-SV1 slow tumor growth and progression in several model systems (111–113,359).

4. KLF8—Tumors acquire invasive phenotypes via the epithelial–mesenchymal transition (EMT) (162), which is mediated by many factors, including focal adhesion kinase (FAK) (87,354). FAK regulates expression of KLF8, which controls the cell cycle by activating cyclin D1 expression (500). In human ovarian epithelial and cancer cells, FAK regulates transcription of *KLF8* by activating the PI3K–AKT pathway (444). KLF8 expression is increased in several types of human cancer cells and tissues and ectopic expression of KLF8 induces transformation (445). Stable expression of KLF8 in immortalized normal human breast epithelial cells induces the EMT, repressing transcription of E-cadherin and thereby increasing the motility and invasiveness of cancer cells (446). (446)

5. KLF9—KLF9 is associated with endocrine-responsive cancers of the female reproductive tissues such as endometrial cancer (384). Stable expression of KLF9 in the human endometrial carcinoma cell line Hec-1-A increases DNA synthesis and cell cycle kinetics by inducing genes involved in cell cycle control (386,497). KLF9 physically interacts with the progesterone receptor; together, they co-regulate expression of progesterone-responsive target genes (435, 485,498). KLF9 is a negative regulator of ligand-dependent ER α signaling in endometrial carcinoma cells (436). KLF9 might therefore function in the progesterone and ER signaling pathways to control endometrial cell proliferation. Human endometrial cancer is associated with unopposed estrogen activity. Levels of KLF9 mRNA are reduced in endometrial tumor of higher grades, compared with normal endometrium and low-grade endometrial tumors (382).

6. KLFs 10 and 11—KLF10 is a TGF- β -inducible early gene that is normally expressed in the acinar and ductular epithelial cells of the exocrine pancreas; its over-expression causes apoptosis in pancreatic epithelial cell lines, so KLF10 has tumor suppressive effects (414). The induction of KLF10-mediated apoptosis increases the sensitivity of pancreatic cancer cells to gemcitabine; this effect is mediated by suppression of stathmin expression (199). However, a mutational screen of the KLF10 gene in 22 pancreatic cell lines revealed no sequence alterations (11).

KLF10 has anti-proliferative effects, promotes apoptosis (7,201,281), and is involved in the pathogenesis of cancers in addition to pancreatic cancer. Expression of KLF10 is progressively lost during the transition of normal breast epithelium into invasive carcinoma (347,407). KLF10 is regulated by estrogen in breast cancer and is part of a gene expression signature that can be used to discriminate ER-positive from ER-negative tumors (398). In colon cancer cells, KLF10 expression is increased by 15-hydroxy-eicosatetraenoic acid (15S-HETE), an endogenous ligand for PPAR γ , and induces apoptosis (61). Colon tumors have decreased levels

of KLF10 and 15-lipoxygenase, the enzyme responsible for 15S-HETE formation, compared with normal mucosa; colonic tumorigenesis is therefore associated with decreased 15S-HETE levels (61). In acute lymphoblastic leukemia (ALL), KLF10 inhibits proliferation in response to stimulation by TGF- β or BMP-6 derived from bone marrow stromal cells (117). However, the anti-proliferative effect of KLF10 protects the ALL cells against chemotherapy-induced cell death (117). KLF10 might therefore mediate signals from the microenvironment to leukemia cells. KLF10 is upregulated in renal clear cell carcinoma as a result of mutation in the tumor suppressor von-Hippel Lindau protein (194), but further studies are required to determine the exact role of KLF10 in cancer pathogenesis.

Like KLF10, KLF11 mediates the effect of TGF- β on cell growth and has a role in pancreatic tumor progression. KLF11 potentiates TGF- β signaling by binding to the mSin3A co-repressor and terminating the inhibitory Smad7 loop (122). These events are inhibited in pancreatic cancer cells with oncogenic KRAS mutations—ERK/MAPK phosphorylates KLF11, leading to disruption of the interaction between KLF11 and mSin3A (122). Expression of an ERK-insensitive, mutant form of KLF11 restores mSin3A binding and Smad7 repression and increases TGF- β signaling in pancreatic cancer cells (122). In response to TGF- β stimulation, KLF11 and Smad3 bind the TIE and inhibit transcription of *c-Myc*; this silencing is required for TGF- β -mediated inhibition of epithelial cell proliferation (43). In pancreatic cancer cells with oncogenic mutations in KRAS, hyperactive forms of ERK counteract TGF- β -induced repression of *c-Myc* and induce proliferation by disrupting the KLF11/Smad3 complex and inhibiting its binding to the TIE in the *c-Myc* promoter (43). ERK signaling thereby antagonizes the tumor suppressor activity of TGF- β , blocking ability of KLF11 to inhibit *c-Myc* expression (43).

7. KLF12—KLF12 was initially identified as a repressor of the transcription factor AP-2 α (192). *KLF12* is located on chromosome region 13q21-q22, which houses a putative breast cancer susceptibility gene and is the site of somatic deletions in different malignant tumors (353). In contrast, this chromosome region is frequently amplified in salivary gland and gastric tumors (153,296). Knockdown of KLF12 induces growth arrest of HGC27 gastric cancer cells (296). Overexpression of KLF12 in NIH3T3 and AZ-521 cells increases their invasive potential (296). *KLF12* mRNA levels are increased in 11 of 28 samples of gastric tumors from patients, compared to normal gastric epithelium (296), and correlate with tumor size (296). These results suggest that KLF12 has an important role in the progression of gastric cancer.

J. KLFs and Somatic Cell Reprogramming

The ability to reprogram somatic cells into pluripotent, ES-like cells has many potential clinical applications in regenerative medicine. The importance of KLF proteins in somatic cell reprogramming was revealed by Takahashi and Yamanaka, who identified four transcription factors that could reset the fate of somatic cells: Klf4, Oct3, Sox2, and c-Myc (415,416). One mechanism by which KLF4 participates in ES cell self-renewal is through its upregulation in ES cells by leukemia inhibitory factor (LIF), which maintains pluripotency of ES cells (248). ES cells that overexpress KLF4 have a greater capacity to self-renew based on secondary embryoid body (EB) formation. Furthermore, EBs transduced with KLF4 express higher levels of Oct4, consistent with the notion that KLF4 regulates ES cell self-renewal (248). Global analysis of promoter occupancy by the four somatic cell reprogramming factors (Klf4, Oct4, Sox2 and c-Myc) and five additional factors important for pluripotency (217) revealed an integral role for KLF4 in a transcriptional hierarchy regulating ES cell pluripotency. Klf4 was identified as an upstream regulator of a large, feed-forward transcription factor loop that contains Oct4, Sox2, and c-Myc, as well as other common downstream factors such as Nanog (217) (see Figure 7). The study also indicated that c-Myc has a distinct role in regulating cell

proliferation and chromosomal accessibility in ES cells, based on the identification of c-Myc promoter targets that were independent of the other pluripotency-inducing factors.

The ability of KLF4 to maintain immortality of iPS cells may arise from its cooperation with c-Myc. In a manner similar to the cooperation between KLF4 and RAS to affect transformation (352) (Figure 6), KLF4 and c-Myc may cooperate to promote iPS cell self-renewal, with KLF4 suppressing apoptosis induced by c-Myc and c-Myc neutralizing the cytostatic effect of KLF4 by suppressing p21^{Cip1/Waf1} (470). In this way, the balance between KLF4 and c-Myc may establish the immortalized state of iPS cells.

To identify additional factors that can generate iPS cells, Nakagawa *et al.* substituted the different factors used in somatic reprogramming with their respective homologs (295). They reported the successful generation of iPS clones upon substitution of Klf2 for Klf4 or L-Myc for c-Myc. Other substitutions, including Klf5 for Klf4, Sox1 for Sox2, and N-Myc for c-Myc resulted in positive clones, although fewer in number. No iPS clones developed when only three factors, devoid of Klf4, were used for reprogramming. The requirement for Oct4 and Klf4 in reprogramming somatic cells has been substantiated (110,372).

Jiang *et al.* examined the contribution of KLFs 2, 4, and 5 to ES cell self-renewal (198). These KLFs are downregulated in ES cells induced to differentiate with retinoic acid. Depletion of Klf2, 4, or 5 in mouse ES cells does not affect ES self-renewal, and pair-wise depletion of the three factors likewise has no effect. In contrast, depletion of all three factors results in ES cell differentiation. The authors used chromatin immunoprecipitation studies to show that Klf2, 4, and 5 share gene targets with Nanog, including a number of genes that regulate pluripotency such as *Esrrb*, *Pou5f1*, *Sox2* and *Tcf3*. Furthermore, these Klf2s bind two upstream regions in the *Nanog* promoter, including a *Nanog*-enhancer element, and promote *Nanog* expression. These findings indicate that KLFs and Nanog work in concert to provide a core circuitry that regulates ES cell self-renewal (198).

Oct4 and LIF have additive effects that induce KLFs to sustain ES cell self-renewal, providing further support for the role of KLFs in ES cell maintenance. Oct4 primarily induces Klf2, whereas LIF/STAT3 signaling selectively increases Klf4 expression (171). Induction of both KLFs is necessary to maintain ES cell pluripotency, identity, and self-renewal (171).

KLF5 also plays a key role in self-renewal of mouse ES cells (123,327). Parisi *et al.* reported that Klf5 is present in undifferentiated ES cells and co-localizes with Oct3/4 and Nanog. They also found that nuclear Klf5 localization correlates with that of Oct3/4 and Nanog in the pre-implantation embryos and in blastocysts at E3.5. *In vitro* depletion of Klf5 results in the morphological differentiation of ES cells, with a concomitant reduction in *Oct3/4* and *Nanog* mRNA levels. Interestingly, *Klf4* or *Klf2* mRNA levels are unchanged upon *Klf5* depletion. Overexpression of Klf5 prevents ES cell differentiation following removal of LIF, but the cells retain expression of Oct3/4 and Nanog. Furthermore, Klf5 was shown to regulate transcription of *Oct3/4* and *Nanog*. Parisi *et al.* concluded that Klf5 is important for ES cell self-renewal and cannot be completely substituted by either Klf4 or Klf2 (327).

Ema *et al.* studied *Klf5*^{-/-} ES cells and made similar observations (123). *Klf5*^{-/-} embryos fail to develop past E6.5 because of their failure to implant, which results from trophoectoderm defects—this time frame is earlier than what had been reported previously (378). *Klf5*^{-/-} ES cells carried in culture exhibit expression of several differentiation marker genes and spontaneously differentiated at a high frequency. Overexpression of Klf5 in ES cells, on the other hand, decreases expression of differentiation markers and maintained pluripotency in the absence of LIF. To investigate the redundancy of KLFs in ESC self-renewal, Ema *et al.* examined whether Klf4 could rescue the differentiation defects observed in the *Klf5*^{-/-} ES cells. Overexpression of Klf4 maintains *Klf5*^{-/-} ES cells in an undifferentiated state, but the

cells proliferate more slowly. *Klf4* and *Klf5* therefore suppress differentiation, but have opposing effects on proliferation (123).

A great deal of work remains to fully understand the molecular mechanisms of somatic reprogramming. KLFs are clearly key factors in self-renewal and pluripotency of ES cells, but it will be important to determine the redundant and non-redundant features of individual KLFs in promoting a self-renewing, pluripotent state. Additional work is also required to elucidate the interactions between KLF proteins and other factors that control the stepwise transition in gene expression from somatic cell to pluripotent cell.

Chapter V. Conclusion

Since the initial characterization of KLF1 over 15 years ago, a large body of knowledge has been compiled regarding the biochemical and physiological functions of KLF family members. Studies of KLF proteins in mouse model systems and human diseases have elucidated the normal biological roles of the KLFs as well as their involvement in disease processes. However, further studies are needed to identify factors that determine the specific functions of individual KLFs, given the redundancy of family members and their common transcriptional targets. One factor contributing to KLF specificity may be post-translational modifications of KLFs, such as acetylation, sumoylation, and phosphorylation. These modifications have been shown to “switch” the transactivating or repressor functions of KLFs by altering their binding partners and changing affinities for target promoters. Structural analyses of KLF proteins will also help elucidate their specific functions—especially studies of their diverse amino-terminal regions. Finally, continued identification of novel KLF-binding proteins and co-factors in transcriptional complexes will provide information about their specific actions.

In defining functional processes in which KLFs participate, mouse models with disruptions of individual *Klf* genes are providing significant information about *Klf* expression patterns and functions during embryonic development and cell-specific lineage differentiation. Analyses of mice with tissue-specific deletion or inducible disruptions of *Klfs* are also helping to define tissue-specific functions. Furthermore, treatment of *Klf* KO mice with various stressors is yielding a more complete understanding of the participation of KLFs in stress responses. Another model system, *C. elegans*, provides an elegant tool for studying the role of KLFs in biological processes. KLF activity can be disrupted in *C. elegans* by expression of mutant forms or through RNA interference. Thus, this organism has been used to explore the participation of KLFs in fat storage and energy metabolism (42). The genetics of *C. elegans* also makes this system useful for the investigation of conserved regulators and downstream targets of KLF proteins.

Involvement of KLFs in the pathogenesis of cardiovascular disease and cancer have been recognized for some time; however, new activities await discovery, such as the participation of KLFs in regulating fat metabolism—currently an area of intense research. The participation of KLFs in somatic cell reprogramming has also generated much excitement for their possible application to regenerative medicine. Opportunities for development of targeted therapies will arise as we continue to expand our understanding of the normal biological functions of KLFs and their contribution to disease.

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Abbreviations

ALL	Acute lymphoblastic leukemia
APC	Adenomatous polyposis coli
ASM	Airway smooth muscle
ATRA	All- <i>trans</i> retinoic acid
AP-1	Activator protein-1
BCR	B cell receptor
BMP	Bone morphogenetic protein
BTEB	Basic transcription element binding protein
CBP	CREB-binding protein
CCL5	Chemokine C-C motif ligand 5
C/EBP	CCAAT/enhancer-binding protein
CNS	Central nervous system
CtBP	C-terminal binding protein
CTGF	Connective tissue growth factor
DBZ	Dibenzazepine
DG	Dentate gyrus
DSS	Dextran sodium sulfate
EB	Embryoid body
EGF	Epidermal growth factor
EMT	Epithelial mesenchymal transition
eNOS	Endothelial nitric oxide synthase
ER	Estrogen receptor
ERK	Extracellular signal-regulated kinase
ES	Embryonic stem
EZF	Epithelial zinc finger
FAK	Focal adhesion kinase
Fbw7	F-box and WD40 domain protein 7
FOXO1	Forkhead box O1
HAT	Histone acetyltransferase
HDAC	Histone deacetylase
hFOB	Human fetal osteoblast
HSC	Hepatic stellate cell
IEC6	Intestinal epithelial cell 6 (rat)
IFN-γ	Interferon- γ
IL	Interleukin
iNOS	Inducible nitric-oxide synthase

iPS	Induced pluripotent stem
IVS	Intervening sequence
KLF	Krüppel-like factors
LAMA3A	Laminin α 3A
LCR	Locus control region
LIF	Leukemia inhibitory factor
LOH	Loss of heterozygosity
LPA	Lysophosphatidic acid
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase
MEF	Mouse embryonic fibroblast
MEF2	Myocyte enhancer factor 2
MEK	MAPK/ERK kinase
MEP	Megakaryocyte erythroid progenitor
MMP-9	Matrix metalloproteinase-9
OA	Okadaic acid
ODC	Ornithine decarboxylase
PAI-1	Plaminogen activator inhibitor-1
P/CAF	p300/CBP-associated factor
PDGF	Platelet-derived growth factor
PEPCK	Phophoenolpyruvate carboxykinase
PI3K	Phosphatidyloinositol-3-kinase
PIAS	Protein inhibitor of activated STAT1
POVPC	1-Palmytoyl-2-(5-oxovaleroyl)-sn-glycero-3-phosphocholine
PPAR	Peroxisome proliferation-activated receptors
RANTES	Regulated upon activation, normal T cell expressed and secreted
RAR	Retinoid acid receptor
RGC	Retinal ganglion cell
RXR	Retinoid X receptor
S1P₁	S1P receptor
SBE	Smad binding element
15S-HETE	15-Hydroxy-eicosatetraenoic acid
SNP	Single-nucleotide polymorphism
SID	Sin3-interacting domain
siRNA	Small interfering RNA
α-SMA	α -Smooth muscle actin

SMC	Smooth muscle cell
SMRT	Silencing mediator of retinoid and thyroid receptor
SNP	Single nucleotide polymorphism
SP	Single-positive
SREBP	Sterol response element binding protein
SUMO	Small ubiquitin-like modifier
TCE	TGF- β control element
TCF4	T cell factor 4
TIE	TGF- β -inhibitory element
TGF-β	Transforming growth factor- β
TNF-α	Tumor necrosis factor α
Treg	Regulatory T cells
VCAM-1	Vascular cell adhesion molecule-1
VEGF	Vascular endothelial growth factor

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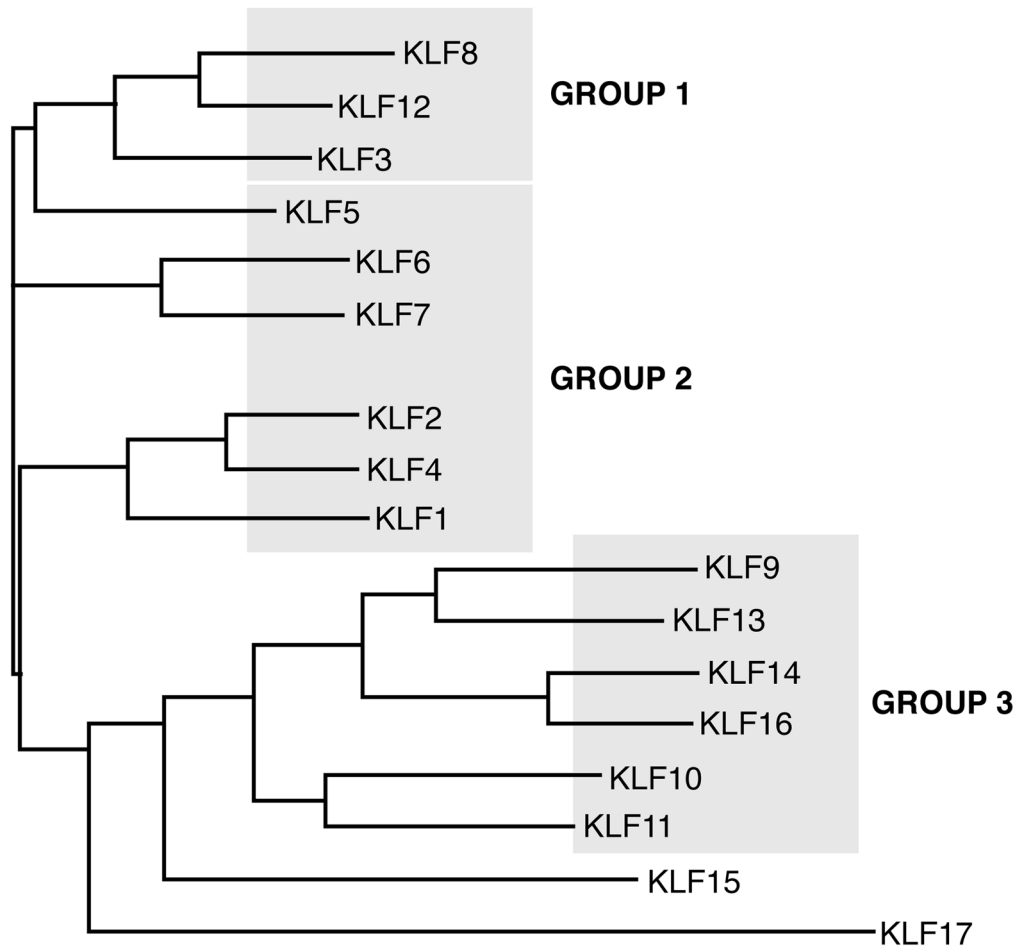


Figure 1. Phylogenetic tree of human KLFs

Multiple sequence alignment and phylogenetic analysis were performed using the ClustalW tool, Version 2.0.12. Analysis was conducted on full-length protein sequences of the 17 human KLF proteins. Structural analysis corresponded with the division of KLFs into distinct groups that have functional similarities.

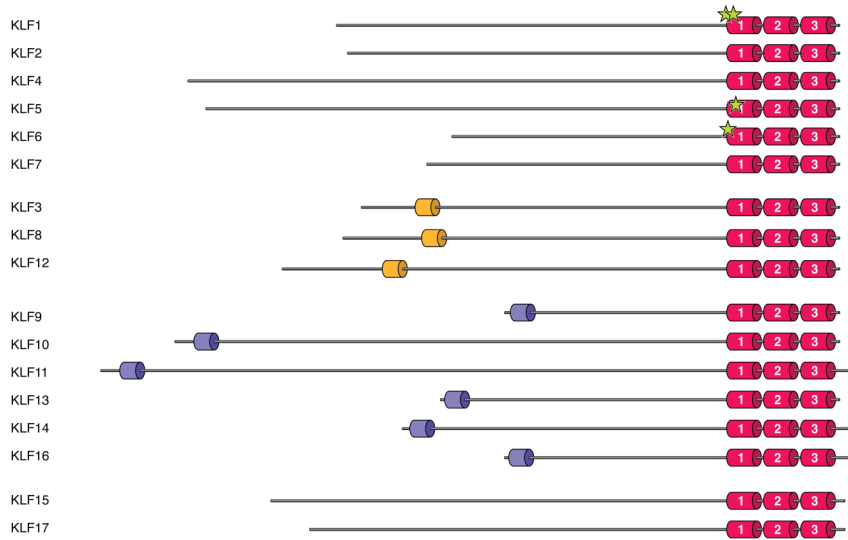


Figure 2. Protein structure of human KLF family members
 KLF proteins are grouped according to common structural and functional domains. KLFs are highly homologous in their carboxyl-terminal DNA-binding regions, which contain three C₂H₂ zinc finger motifs. The family members were grouped based on: (1) the ability to bind acetylases (KLFs 1, 2, 4, 5, 6, and 7); (2) the presence of a CtBP-binding site (KLFs 3, 8, and 12); or (3) the presence of a Sin3A-binding site (KLFs 9, 10, 11, 13, 14, and 16). Established sites of acetylation are marked by stars.

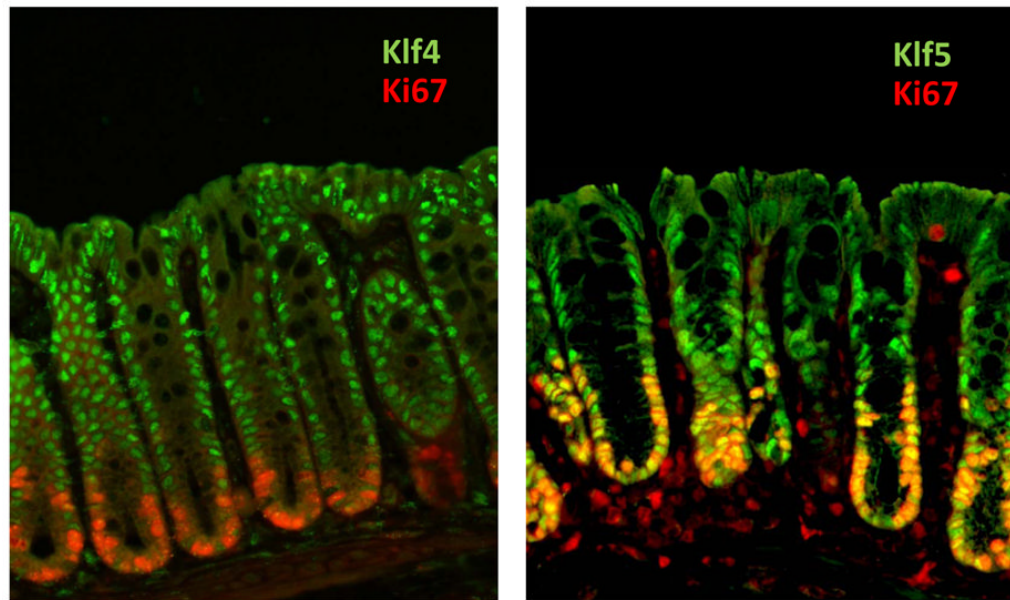


Figure 3. Localization of Klf4 and Klf5 in the mouse colon

Immunofluorescence staining of Klf 4 or 5 (green) with the proliferation marker, Ki67 (red), was conducted on mouse colon. Klf4 (green) is present in the nuclei of terminally differentiated epithelial cells in the upper regions of colonic crypts. In contrast, Klf5 is localized to nuclei of proliferating epithelial cells at the base of the crypts. Ki67 highlights regions of active proliferation. Although Klf4 and Ki67 staining patterns do not overlap, Klf5 and Ki67 exhibit considerable co-localization, indicated by yellow staining.

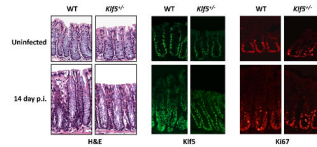


Figure 4. Reduced mucosal hyperplasia in *Klf5*^{+/-} mice following infection with the enteric pathogen, *Citrobacter rodentium*

In these experiments, C57BL/6 (WT) and *Klf5*^{+/-} mice were infected with the rodent-specific pathogen, *Citrobacter rodentium*. Colonic tissues from uninfected and *C. rodentium*-infected mice were isolated at 14 days post-infection (p.i.) and were subjected to histological staining with hematoxylin and eosin (H&E) or immunofluorescence staining for expression of *Klf5* (green) or the proliferation marker, Ki67 (red). Hyperplasia induced by infection was significantly reduced in the *Klf5*^{+/-} mice [from McConnell, *et al.* (273)].

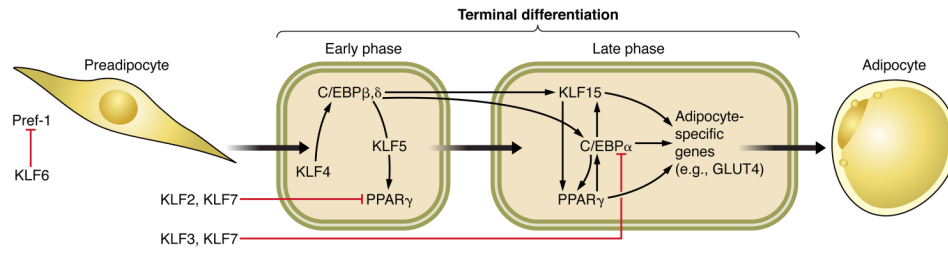


Figure 5. Contribution of KLFs in regulating adipocyte differentiation

Pre-adipocytes progress through an early stage of differentiation in which they become committed to their fate, followed by a late stage of terminal differentiation into mature adipocytes. Various members of the KLF family contribute to transcriptional control of this process and have positive and negative effects on adipogenesis [Adapted from Nagai, Friedman and Kasuga, Editors (294)].

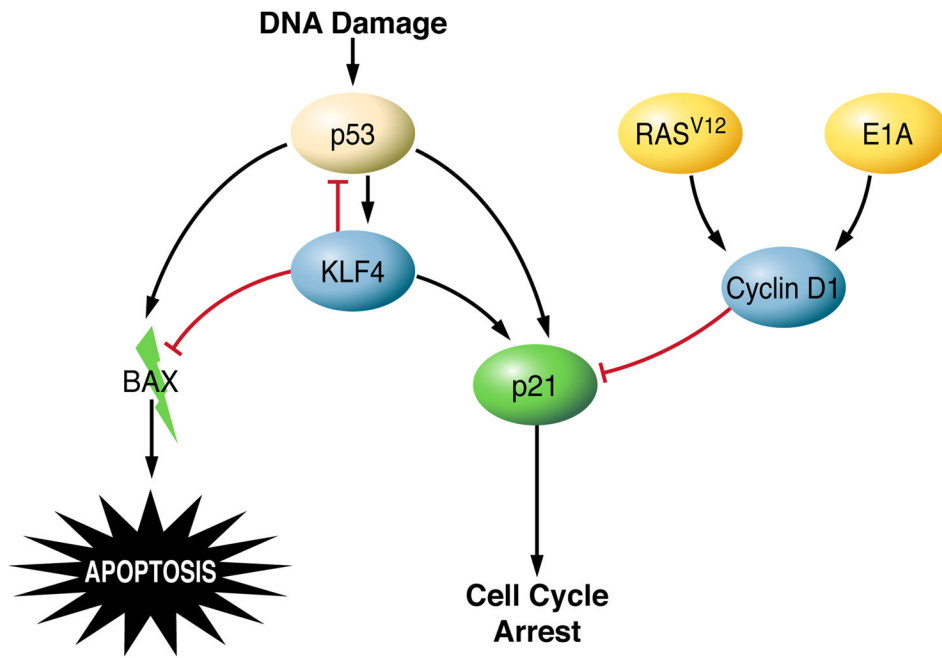


Figure 6. A model for the role of KLF4 in tumor suppression and oncogenesis

Following DNA damage, expression of KLF4 is activated in a p53-dependent manner. Increased levels of KLF4 lead to increased expression of *p21^{Cip1/Waf1}* and decreased expression of *BAX*, with the net effect being to tip the balance away from apoptosis towards cell cycle arrest. However, in the presence of activated RAS or E1A, the growth inhibitory effects of *p21^{Cip1/Waf1}* are negated by high levels of cyclin D1. The combination of high levels of KLF4 expression in the presence of oncogenic RAS or E1A lead to active proliferation and suppressed apoptosis, which contribute to carcinogenesis. KLF6 likewise acts as a tumor suppressor through induction of *p21^{Cip1/Waf1}*. The growth-suppressing activity of KLF6 can be offset by oncogenic RAS which induces alternative splicing of KLF6, generating a mutant form that promotes cell proliferation and suppresses apoptosis [Adapted from Ghaleb, *et al.* (149)].

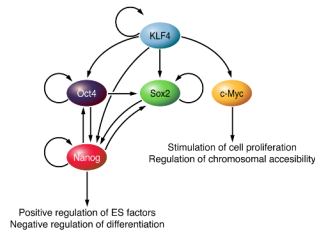


Figure 7. Klf4 as part of a transcriptional regulatory circuit for somatic cell reprogramming
 A model of the transcriptional hierarchy of the reprogramming transcription factors: Klf4, Sox2, Oct4, c-Myc. Klf4 is shown as an upstream regulator of feed-forward transcription loops—it binds the promoters of Oct4, Sox2, c-Myc and the downstream target Nanog. Klf4s 2 and 5 can substitute for Klf4 in somatic cell reprogramming [Adapted from Kim, *et al.* (217)].

Table 1

Expression, Function, and Pathobiology of Mammalian KLF Family Proteins

Name	Also known as	Expression pattern	Tissue function/disease association	Gene knockout phenotypes	References
KLF1	EKLF (Erythroid Krüppel-like factor)	Erythroid cells, fetal liver, adult bone marrow and spleen	Erythropoiesis; megakaryocyte differentiation	Defective hematopoiesis and lethal β -thalassemia at E14.5	(144,311,335)
KLF2	LKLF (Lung Krüppel-like factor)	Lungs, erythroid cells, vascular endothelial cells, T lymphocytes, white adipose tissue	Erythropoiesis; regulator of hemodynamics; lung development; T cell survival, migration and trafficking; inhibitor of adipogenesis; important in generating induced-pluripotent stem (iPS) cells	Embryonic lethality due to compromised vessel integrity/rupture; delayed lung development; defective T-lymphocyte and adipocyte differentiation	(21,51,234,235,243,295,448,464)
KLF3	BKLF (Basic Krüppel-like factor)	Widely expressed; abundant in erythroid cells	Inhibits adipocyte differentiation	Decreased white adipose tissue	(95,409)
KLF4	GKLF (Gut-enriched Krüppel-like factor); EZF (Endothelial zinc finger protein)	Epithelia of gut, skin and lungs; endothelial cells; early precursor B cells	Intestinal epithelial homeostasis; tumor suppressor in colon cancer; oncogene in breast cancer and squamous cell carcinoma; promotes adipogenesis; critical factor in generating iPS cells	Perinatal lethal due to dehydration with skin barrier defect; abnormal differentiation of goblet cells in the colon	(151,211,272,367,415,416,433)
KLF5	IKLF (Intestinal-enriched Krüppel-like factor); BTB2 (Basic transcription element binding protein-2)	Enriched in gut epithelia; expressed in epidermis, vascular smooth muscle and white adipose tissue; also developing/perinatal skeleton and lung	Intestinal homeostasis; cardiac remodeling; lung maturation and morphogenesis; promotes adipogenesis; important in generating iPS cells; dysregulated expression in colon, breast, prostate cancer and other solid tumors	Embryonic lethal at E8.5; heterozygous and tissue-specific deletions show: reduced cardiac fibrosis and hypertrophy in response to stress, deficiencies in white adipose tissue development, skeletal growth retardation, defective perinatal lung morphogenesis; heterozygous deletion drastically reduces intestinal tumor formation in Apc^{Min} mice and $Apc^{Min}/KRAS^{V12}$ mice	(52,57,58,89,271,272,295,298,299,318,378,379,417,423,440)
KLF6	ZF9 (Zinc-finger transcription factor-9); CPBP (Core promoter binding protein); GBF (G-box binding factor)	Strongly expressed in placenta and developing hindgut, heart, lung and kidney; adult endothelial cells, heart, liver, lung, kidney, intestine	Promotes vascular remodeling; stimulates adipogenesis; tumor suppressor in prostate cancer; silenced or mutated in a variety of other cancers	Embryonic lethal at E12.5, with reduced hematopoiesis and poor yolk sac vascularization	(13,113,135,240,267,268,305,389)
KLF7	UKLF (Ubiquitous Krüppel-like factor)	High expression in brain and developing spinal cord; expressed in peripheral nervous systems;	Inhibits adipocyte differentiation; single-nucleotide polymorphisms (SNPs) associated with type 2 diabetes	Neonatal lethality by P3 associated with defects in neurite outgrowth and axonal misprojection	(209,239,241,268)
KLF8	-	Low, ubiquitous expression	Elevated in ovarian and other human cancers	-	(432,445)
KLF9	BTB (Basic transcription element-binding protein)	Broadly expressed; high in developing brain, thymus, epithelia and smooth muscle of gut and bladder	Endocrine-responsive cancers, including endometrial cancer	Normal lifespan, but specific behavioral abnormalities; subfertility and parturition defects in females; shorter small intestinal villi	(265,290,383-385)

Name	Also known as	Expression pattern	Tissue function/disease association	Gene knockout phenotypes	References
KLF10	TIEG1 (TGF-inducible gene-1); mGIF (murine glial cell-derived neurotrophic factor (GDNF)-inducible factor)	Broadly expressed, including pancreas, kidney, lung, brain, liver, heart and testis	T eg cell differentiation and T cell activation; bone development; SNPs associated with volumetric bone mineral density; implicated in breast cancer	Normal lifespan, but osteopenia in females; cardiac hypertrophy in males; defects in structure and healing of tendons	(26,50,175,343,405,406,468,476)
KLF11	FKLF (Fetal-like globin gene-activating Krüppel-like factor); TIEG2 (TGF--inducible gene-2); MODY7 (Maturity-onset diabetes of the young-7)	Erythroid cells in fetal liver; ubiquitous in adult including pancreas	Tumor suppressor in pancreatic cancer; variants associated with early-onset type 2 diabetes	Normal development, lifespan, fertility	(12,43,91,122,308,396)
KLF12	AP-2rep (Activator protein-2a repressor)	Expression in developing brain and kidney; adult kidney, very low in liver and lung	Implicated in breast and gastric cancer	-	(192,296,353,408)
KLF13	BTEB3 (Basic transcription element-binding protein-3); FKLF2 (Fetal -like globin gene-activating Krüppel-like factor-2); RFLAT-1 (RANTES factor of late-activated T lymphocytes 1)	Broadly expressed; high temporal expression in developing heart, brain, thymus, epidermis, gut and bladder epithelia	Cardiac development; B and T cell development	Splenomegaly and aberrant erythroblast differentiation; abnormal T and B cell development; increased T cell survival	(157,242,265,322,506)
KLF14	-	Ubiquitous	Variants associated with basal cell carcinoma	-	(328,364,401)
KLF15	KKLF (Kidney-enriched Krüppel-like factor)	Low cardiac expression during development; adult kidney, liver, pancreas, heart, skeletal muscle, lung, ovary	Regulator of gluconeogenesis; negative regulator of cardiac hypertrophy and fibrosis	Normal viability, fertility; exaggerated cardiac fibrosis and hypertrophy in response to stress; defective amino acid metabolism resulting in hypoglycemia	(134,159,428,441)
KLF16	BTEB4 (Basic transcription element-binding protein-4); DRRF (Dopamine receptor regulating factor)	Highly expressed in regions of developing brain; lower expression in thymus, duodenum, kidney, liver, heart, bladder and lung	-	-	(99,191)
KLF17	Zfp393 (Zinc finger protein 393)	Spermatids and oocytes	-	-	(431,471)