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Role of Krüppel-like factor 4 in normal homeostasis, cancer, and stem cells

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Abstract

Krüppel-like factor 4 is a zinc finger-type transcription factor expressed in a variety of tissues, including the epithelium of intestine and the skin, where it is important in differentiation and cell cycle arrest. KLF4 can both activate and repress transcription, depending on the gene targeted. Moreover, KLF4 can function as a tumor suppressor or an oncogene, depending on the cellular context. Finally, KLF4 is important in reprogramming differentiated fibroblasts into inducible pluripotent stem cells, which highly resemble embryonic stem cells. This review will summarize what is known about the diverse functions of KLF4, as well as their molecular mechanisms.

Keywords

Krüppel-like factor 4; colorectal cancer; stem cell

Krüppel-like factor 4 (KLF4) is a transcription factor expressed in a wide variety of tissues in humans, including the intestine and the skin, and is important in many different physiologic processes, including development, differentiation, and maintenance of normal tissue homeostasis. KLF4 is a bi-functional transcription factor that can either activate or repress transcription, depending on the target gene, and utilizing different mechanisms. In addition, KLF4 can function as an oncogene or a tumor suppressor depending on the type of cancer involved. In concert with three other transcription factors, KLF4 can reprogram differentiated fibroblasts into a state resembling embryonic stem cells in every possible manner tested so far. This review will provide a detailed summary of what is currently known about KLF4 and its role in the homeostasis of tissues, in cancer, and in stem cell reprogramming.

The Krüppel-like Factor Family

Krüppel-like factors are a family of transcription factors that play an important role in many fundamental biologic processes including development, proliferation, differentiation, and apoptosis (Fig. 1). Krüppel-like factor family members contain three C-terminal C_2H_2-type zinc fingers that bind DNA, and were named “Krüppel-like” due to strong homology in this region with the *Drosophila* gene product Krüppel. Krüppel is important in segmentation of the developing embryo, and genetic deletion of Krüppel results in complete absence of the thoracic and anterior abdominal segments [1]. *KLF4* was cloned independently by two groups, and given two different names: gut-enriched Krüppel-like factor (GKLF) due to the fact that it was found to be highly expressed in the intestine [2], and epithelial zinc finger (EZF) due to its high expression in the skin epithelium [3]. GKLF/EZF was later renamed

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KLF4 to avoid confusion, as expression of KLF4 is also detectable in the lung, skin, testis [2–5], thymus [6], cornea [7], cardiac myocytes [8] and lymphocytes [9]. In addition, KLF4 is important in development, as it is detectable in the mouse embryo, with the highest expression occurring in the later stages [3,4].

Roles of KLF4 in Homeostasis of the Colonic Epithelium

The colonic epithelium consists of three major types of differentiated cells, enterocytes, goblet cells, and enteroendocrine cells. Actively proliferating cells reside at the base of the crypts and migrate towards the luminal surface as they differentiate, eventually to be sloughed off. KLF4 inhibits proliferation and promotes differentiation, and consistent with this role, expression of KLF4 is greatest near the luminal surface and gradually decreases toward the base of the crypts [2,10]. $Klf4^{-/-}$ mice lack goblet cells, without affecting the total number of enterocytes, suggesting that KLF4 may be specifically required for goblet cell differentiation [11]. In addition, KLF4 can interact with β-catenin and antagonize Wnt signaling [10], a key pathway in driving proliferation of the intestinal epithelium [12–14]. Thus, KLF4 may also be important in mediating the switch from transit-amplifying cells to the various differentiated cell types in the colonic crypts.

Butyrate is constantly produced in the colon by bacterial fermentation of dietary fiber in the intestine [15], and can induce expression of KLF4 [5,16]. In cell culture, butyrate stimulates expression of the enterocyte-specific marker intestinal alkaline phosphatase (IAP) [17], and induces colon cancer cells to acquire a more differentiated, enterocyte-like phenotype [18]. KLF4 positively regulates expression of IAP [19,20], and overexpression of KLF4 in cell culture inhibits proliferation [2,5].

Moreover, KLF4 appears to have inhibitory effect on a wide variety of cellular processes, including protein and cholesterol synthesis, transcription, cell growth, and DNA repair [21,22]. Consistent with its anti-proliferative role, KLF4 simultaneously induces the expression of cyclin-dependent kinase inhibitor proteins $p21^{Cip1/WAF1}$ [23–25] and $p57^{Kip2}$ [21], and represses the expression of cyclin D_1 [5,26,27], cyclin D_2 [28], cyclin E [29], and cyclin B_1 [30] (Fig. 2). In addition, KLF4 represses expression of ornithine decarboxylase [7,31], an enzyme involved in the production of a class of molecules known as polyamines, which are also important in proliferation. KLF4 is required for both the G_1/S-phase [32,33] and G_2/M-phase [30] checkpoints. Finally, KLF4 represses expression of p53 and may be important in determining whether cells decided to undergo apoptosis or cell cycle arrest [34].

Roles in other homeostasis of other tissues

Although the importance of KLF4 in the intestine is well characterized, increasing evidence demonstrates its importance in other organs and tissues as well. For example, $Klf4^{-/-}$ mice die soon after birth of dehydration due to defects in the epidermal barrier of the skin [35], whereas targeted overexpression of KLF4 results in early formation of the epithelial permeability barrier [36]. These data clearly implicate KLF4 as an important molecule in differentiation of the skin epithelium.

Furthermore, overexpressed KLF4 can synergize with maternally-injected corticosteroids in accelerating the formation of the skin barrier. This is likely due to overlap between the genes targeted by KLF4 and the glucocorticoid receptor [37]. The utility of glucocorticoids in lung maturation of premature infants is well-established [38], thus it might be interesting to determine whether KLF4 or possibly other Krüppel-like factors could synergize with glucocorticoids in fetal lung maturation as well. Also in the developing fetus, KLF4 synergizes with Sp1 in up-regulating expression of PSG-5, a protein secreted into the

maternal circulation by the placenta [39]. PSG-5 is thought be required for maintenance of a term pregnancy and may protect the fetus from attack by the maternal immune system. In addition, KLF4 and PSG-5 have closely overlapping patterns of expression in the placenta, suggesting an *in vivo* role for KLF4 in the regulation of PSG-5 expression [40].

Human KLF4 was isolated from a umbilical vein cDNA library and is expressed in the vascular endothelium [41]. Expression of KLF4 is induced by shear stress in endothelial cells [42], whereas KLF4 appears to block differentiation and is expressed at low levels in differentiated arterial smooth muscle cells [43]. However, expression of KLF4 is rapidly up-regulated in smooth muscle cells in response to vascular injury [44].

Overexpression of KLF4 in a pro-myelocytic cell line increases the expression of monocyte markers, whereas knockdown of KLF4 decreases TPA-induced overexpression of these same markers. In addition, $Klf4^{-/-}$ hematopoietic stem cells less frequently differentiate into monocytes [45]. When fetal liver cells from $Klf4^{-/-}$ mice were transplanted into lethally-irradiated wild-type mice, they had undetectable levels of circulating inflammatory monocytes [46]. Thus KLF4 appears to be important for both resident and inflammatory monocyte differentiation.

KLF4 is highly expressed in the corneal epithelium, where it is important in differentiation. Targeted deletion of KLF4 in the eye results in corneal fragility, edema, and a lack of goblet cells in the conjunctiva [47]. In a cell culture model of adipocyte differentiation using 3T3-L1 cells, siRNA-mediated knockdown of KLF4 completely blocked expression of several phenotypic markers of differentiated adipocytes [48]. Collectively, these data strongly implicate KLF4 as a factor involved in the differentiation of many tissues.

Roles of KLF4 in Cancers

As an anti-proliferative factor expressed in differentiated epithelia, it seems logical that KLF4 might act as a tumor suppressor, and indeed this appears to be the case in the gastrointestinal tract [49,50]. However, recent evidence suggests that KLF4 might also act as an oncogene in certain contexts [51]. This section will investigate these two contrasting roles.

KLF4 as a tumor suppressor

Increasing evidence implicates KLF4 as a tumor suppressor in the intestinal epithelium. In human colorectal carcinoma, expression of KLF4 is downregulated, with evidence of both hypermethylation and loss-of-heterozygosity [52–54]. However, no association has been found between downregulation of KLF4 and tumor staging or 5-year survival in patients with metastatic carcinoma, suggesting that loss of KLF4 in colorectal cancer may be an early event [53,54].

Examination of KLF4 expression in mouse models of colorectal cancer has yielded similar results. The $APC^{min/+}$ mouse develops hundred of intestinal adenomas early in life and is a widely-used model of intestinal tumorigenesis [55,56]. In adenomas from these mice, KLF4 is down-regulated, with expression inversely related to the size of the tumor [4,57]. As APC is a critical component of the Wnt/β-catenin pathway and $APC^{min/+}$ mice express a truncated form of the APC protein, these mice have deregulated Wnt signaling in their intestine [58,59]. Interestingly, KLF4 can interact with β-catenin in the nucleus and repress Wnt signaling *in vivo*, as well as inhibit tumor growth in tumor xenografts [10]. In addition, crossing $APC^{min/+}$ mice with $KLF4^{+/-}$ heterozygotes resulted in significantly more adenomas than in $APC^{min/+}$ mice alone [60]. Notably, this phenotype was similar to that found with another double mutant, $APC^{Min/+}/TCF1^{-/-}$. The most abundant isoform of TCF1

expressed in the intestine is also an antagonist of Wnt/β-catenin signaling, suggesting that an important effect of decreased KLF4 expression during colorectal tumorigenesis may be de-repression of Wnt signaling. In human colon cancer cell lines, several point mutations have been found in the *KLF4* gene. One mutation had a significant effect on the ability to activate a $p21^{Cip1/WAF1}$ reporter construct in NIH3T3 cells [52]. However, an investigation to identify mutations in tissue samples of human colorectal cancers has not yet been performed. In the HCT116 colorectal cancer cell line, KLF4 is required to prevent centrosome amplification after gamma-irradiation, and loss of KLF4 may promote chromosomal instability [29]. In addition, KLF4 represses expression of the enzyme ornithine decarboxylase [31], a proto-oncogene that alone is sufficient to transform NIH3T3 cells [61]. Collectively, these data strongly implicate KLF4 as a tumor suppressor in the colon. Strong evidence implicates KLF4 as tumor suppressor in the gastric epithelium as well. Similar to colorectal cancer, KLF4 is downregulated in gastric cancer, with evidence of loss-of-heterozygosity and hypermethylation [62–64]. Moreover, targeted loss of the Klf4 gene in the gastric mucosa of mice results in pre-cancerous changes in the stomach [65]. In examining both normal and cancerous gastric mucosal tissue from humans, one study found an inverse relationship between the expression of KLF4 and Sp1, a distantly related Krüppel-like factor family member (Fig. 1) [62]. In addition, the same study found that in gastric cancer cell lines, KLF4 can directly repress the expression of Sp1. Given that strong expression of Sp1 is correlated with poor survival in gastric cancer [66], loss of KLF4 may contribute to gastric cancer progression.

In addition to gastric and colorectal cancer, KLF4 is downregulated in esophageal cancer [67,68], bladder cancer [69], non-small-cell lung carcinoma [70], and leukemia [71,72].

KLF4 as an oncogene

Although these data clearly demonstrate that KLF4 can act as tumor suppressor in multiple tissues, the possibility that KLF4 might be an oncogene as well was first demonstrated almost one decade ago. Using E1A-immortalized rat kidney epithelial cells (RK3E) to screen for factors that could induce transformation, KLF4 was identified. Moreover, KLF4-transformed RK3E cells could produce tumors in xenografted mice [73]. KLF4 is overexpressed in laryngeal squamous cell carcinoma as an early event in its progression [73]. Expression of KLF4 is increased in ductal carcinoma of the breast [74] and increased nuclear staining is associated with a more aggressive phenotype and poorer prognosis [75]. In the skin, overexpression of KLF4 results in hyperplasia and dysplasia [76], eventually leading to squamous cell carcinoma [77].

Whether KLF4 acts as a tumor suppressor or an oncogene is likely due to differences in cell context, expression patterns of other genes, and the chromatin environment of individual cells, but a mechanism to fully explain these differences is lacking. Some insight was gained in a recent study where it was found that KLF4 could override Ras^{V12}-induced senescence in primary fibroblasts and induce transformation [34]. Furthermore, this study demonstrated that whether overexpression of KLF4 induced transformation or resulted in cell cycle arrest depended on the status of $p21^{Cip1/WAF1}$, a transcriptional target of KLF4. Overexpression of KLF4 alone increases expression of $p21^{Cip1/WAF1}$ and results in cell cycle arrest. However, the addition of Ras^{V12} resulted in inhibition of $p21^{Cip1/WAF1}$ expression, allowing the ability of KLF4 to repress p53 to predominate. Repression of p53 effectively blocked apoptosis and in concert with the decreased expression of $p21^{Cip1/WAF1}$, eventually led to transformation. Thus, KLF4 can be added to a growing list of genes that have multiple, context-dependent roles in cancer, including *CDKN1A* (p21), *TGF-β*, *Ras*, and *NOTCH1* [51].

Roles of KLF4 in Stem Cell Renewal and Reprogramming

Recently, it was found that overexpression of KLF4, in combination with three other transcription factors could transform mouse fibroblasts into a state resembling embryonic stem cells (ES cells). These cells have been termed “inducible pluripotent stem cells” (iPS cells) [78]. By replacing the open reading frame of *Fbx15*, a non-essential marker of embryonic stem cells, with a neomycin resistance gene, it was hypothesized that neomycin-resistant colonies might have somehow reprogrammed themselves into embryonic stem cells. After screening a short list of potential factors, it was found that the simultaneous infection of retroviruses expressing Oct3/4, Sox2, c-Myc, and KLF4 were able to produce resistant clones. These cells could form teratomas that contained differentiated tissues from all three germ layers, confirming their pluripotency. This approach was further refined by screening for neomycin resistance based on *Nanog* or *Oct4* expression instead of *Fbx15*. Unlike Fbx15-iPS cells, Nanog and Oct4-iPS could produce chimeric mice and, could generate live late-term embryos when injected into tetraploid blastocysts [79–81]. Thus, Nanog and Oct4-iPS satisfy are even more stringent tests of pluripotency than Fbx15-iPS cells.

An area currently under intense investigation is understanding the molecular events that occur during stem cell reprogramming as well as the precise role of each of the four individual factors required. The importance of Oct3/4 and Sox2 in ES cell renewal is well established [82]. What is less clear is the function of the other two factors that make up the “magic brew”: c-Myc and KLF4. One possibility is that c-Myc and KLF4 confer increased proliferative capacity on potential iPS cells, since both can function as oncogenes [83]. Since c-Myc regulates a significant number of genes, its function may be to effect global changes in the chromatin environment by recruiting histone acetyl-transferase complexes. According this model, KLF4 may then function to inhibit apoptosis induced by overexpression of c-Myc. KLF4 represses expression of c-Myc expression in colon cancer cells through inhibiting Wnt signaling [10]. Thus, c-Myc may provide a balance for KLF4. The role of Wnt signaling in iPS cells is still an open question.

Overexpression of KLF4 in ES cells inhibited differentiation into erythroid progenitors, and increased their capacity to generate secondary embryoid bodies, suggesting a role for KLF4 in self-renewal [84]. In concert with Oct3/4 and Sox2, KLF4 activates expression of *Lefty1*, a gene expressed in ES cells, but lost during differentiation [85]. In addition, KLF4-null mice survive to term and have no detectable defects during embryogenesis in their pluripotent stem cell population [11,35], suggesting that in normal ES cells, KLF4 may be dispensable. More recently, human iPS have been produced using a slightly different mix of factors, substituting c-Myc and KLF4 with Nanog and LIN28 [86], further calling into question the overall importance of c-Myc and KLF4. It has even been suggested that c-Myc and KLF4 are merely molecular catalysts, in that they might accelerate or increase the efficiency of the reprogramming process, but are otherwise not absolutely required [87].

However, a recent study has found that the function in ES cell self-renewal of KLF4 is partially redundant with KLF2 and KLF5, as knockdown of all three Krüppel-like factors, but not any one individually, resulted in spontaneous ES cell differentiation [88]. In addition, significant overlap was found between genes regulated by Nanog and the three Krüppel-like factors. Clearly, a complete understanding of the role of KLF4 in ES cell self-renewal and iPS cell reprogramming awaits further study

Molecular Mechanisms of KLF4

Human and mouse KLF4 are 470 and 483 amino acids in length, respectively, and produce a 55 kDa protein. KLF4 can be roughly divided into three separate domains: an N-terminal

activation domain [3,41,89], a central repressive domain [41], and a C-terminal DNA binding domain (Fig. 3). The DNA binding domain consists of three successive zinc fingers. Each zinc finger contains an anti-parallel β-sheet, followed by a short loop and an α-helix. Two cysteines within the β-sheet and two histidines within the α-helix work together to coordinate a single zinc ion, which acts to stabilize the fold. Each zinc finger interacts with three consecutive nucleotides on a target DNA sequence, and the sequence specificity of a zinc finger protein can be increased simply by adding additional zinc fingers [90].

In general, KLF4 interacts with GT-rich or CACCC elements on target genes [41,91]. Although one report suggests that KLF4 prefers to bind a RRGGYGY sequence (where R=A/G and Y=C/T) [92], it is still not clear whether this is a true consensus *in vivo*. KLF4 is exclusively nuclear, like many other transcription factors, and appears to contain two discrete nuclear localization sequences (NLS). The first is an basic hexapeptide sequence just N-terminal to the three C-terminal zinc fingers, whereas the second is contained within the first two zinc fingers themselves [93].

Given the large number of genes regulated by KLF4, it is not unexpected that expression of KLF4 itself should be highly regulated (Table 1). In the colon cancer cell line HCT116, KLF4 has a half-life of only 2 hours and is quickly degraded by the proteasome [94]. However, a variety of stimuli can induce KLF4 expression including serum starvation, contact inhibition [3], interferon- [31,95], sodium butyrate [5,16], cAMP [48], gastrin [96], DNA damage [24,33], and oxidative stress [8,25]. The precise mechanism of how the majority these stimuli increase the expression of KLF4 is unclear, although possibilities include increased transcription of the *KLF4* gene, increased mRNA stability, and/or increased protein stability.

Although much remains to be known about how expression KLF4 is regulated, several transcription factors have been found to regulate its promoter. For example, p53 transactivates the *KLF4* gene, and p53 is required for the induction of KLF4 after DNA damage [24,33]. CDX2, another protein important in differentiation of the intestinal epithelium, can activate a KLF4 reporter construct [97]. This suggests that KLF4 may act downstream of CDX2, although more work is necessary to demonstrate this *in vivo*. KLF4 up-regulates its own expression by binding to its promoter, whereas KLF5 inhibits KLF4 expression and blocks the binding of KLF4 to its promoter [98]. Although KLF4 and KLF5 are closely related transcription factors, expression of KLF5 is found in a completely opposite pattern in the colonic intestine, with strongest expression found in the actively proliferating cells at the base of the crypts and absent expression in differentiated cells at the luminal surface [99,100]. In fact, KLF4 and KLF5 have several antagonizing roles in the intestinal epithelium, as reviewed elsewhere [49].

Mechanism of activation

A major function of KLF4 is to activate transcription of target genes (Table 2). Consistent with this function, the N-terminus of KLF4 contains a strong transactivation domain [3,41,89]. This domain alone, when directly fused to its three C-terminal zinc fingers, is sufficient to activate a synthetic reporter construct [89]. In addition, the N-terminal domain interacts with the transcriptional co-activators p300 and CBP, and this interaction is required for its function, as point mutations that block interactions with CBP also completely abrogate its ability to activate transcription [20,89]. p300/CBP are histone acetyltransferase (HAT) proteins, and recruitment of p300/CBP results in an increase in localized histone acetylation at the promoter. Acetylation of histones facilitates the recruitment of other transcription factors as well as the basal transcriptional machinery. In addition, KLF4 itself is acetylated by p300/CBP at lysine residues 225 and 229. Mutation of these two lysines to arginine significantly decreases the ability of KLF4 to transactivate target genes, as well as

its ability to inhibit proliferation [20], suggesting that acetylation of KLF4 is important for its function.

One report found that KLF4 can interact with Tip60, a bi-functional cofactor that contains intrinsic HAT activity, but can also recruit HDAC7 [96]. Tip60 is a co-activator for several nuclear hormone receptors [101] as well as APP [102], but appears to function as a co-repressor for STAT3 by recruiting HDAC7 [103]. Another zinc finger protein Krox20, can directly interact with KLF4 and synergistically activate the *C/EBPβ*gene in 3T3-L1 cells [48]. KLF4 interacts with the NF-κB subunit p65/RelA and synergistically activates expression of iNOS [104]. Thus, the mechanisms of transactivation mediated by KLF4 may be gene-dependent.

Mechanism of repression

One mechanism for repression by a transcription factor is to simple competition with an activator for binding to a target DNA sequence. This mechanism is known as a form of passive repression. On the *CYP1A1*, *HDC*, and *SP1* genes, KLF4 binds to a sequence overlapping that recognized by the activator Sp1, displacing Sp1 from the promoter and resulting in repression of the target gene [62,105,106]. Since Sp1 is ubiquitously expressed and positively regulates many genes [107], it is likely this is mechanism is used by KLF4 to repress many of its target genes. GAL4 fusion assays demonstrate that KLF4 contains central repressive domain in addition to its more fully characterized transactivation domain [41]. This suggests that KLF might actively repress expression of some genes, in addition to, or instead of passive repression via competition with a transcriptional activator. In KLF4-mediated repression of the CD11d gene, KLF4 interacts with and recruits HDAC1 and HDAC2 [108], whereas KLF4 represses cyclin B_1 via specifically recruiting HDAC3 [20]. On the *TP53* gene, MUC1-C recruits KLF4, as well as HDAC1 and HDAC3, to mediate repression [109]. KLF4 inhibits Smad3-mediated activation of PAI-1 by directly competing with Smad3 for p300 binding [104]. Finally, KLF4 represses transcriptional targets of Wnt signaling by directly interacting with β-catenin/TCF4 [10]. These data strongly suggest that KLF4-mediated activation and repression is complex and gene-dependent.

Final Thoughts

KLF4 is complex transcription factor that can act as a transcriptional activator, a transcriptional repressor, an oncogene, and a tumor suppressor, depending on the context. A question that commonly arises when learning about such a transcription factor is how it can switch between these modes. Another important question is what molecular mechanisms govern the function of KLF4 in normal cells, in cancer, and in stem cell reprogramming. Although this review discusses much of what is already known in regards to these questions, more work is needed to fully answer them. Attaining a greater understanding of the molecular function of KLF4 will ultimately give deeper insight into these many different fundamental processes.

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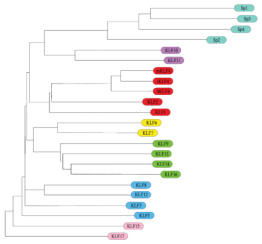

Fig. 1.

Phylogenetic tree of the Sp/KLF transcription factor family Amino acid sequence comparison between KLF/Sp family members. Note human, mouse, and rat KLF4 are included for comparison as well (hKLF4, mKLF4, and rKLF4, respectively). Horizontal distance on the tree is proportional to number of residue changes between adjacent members.

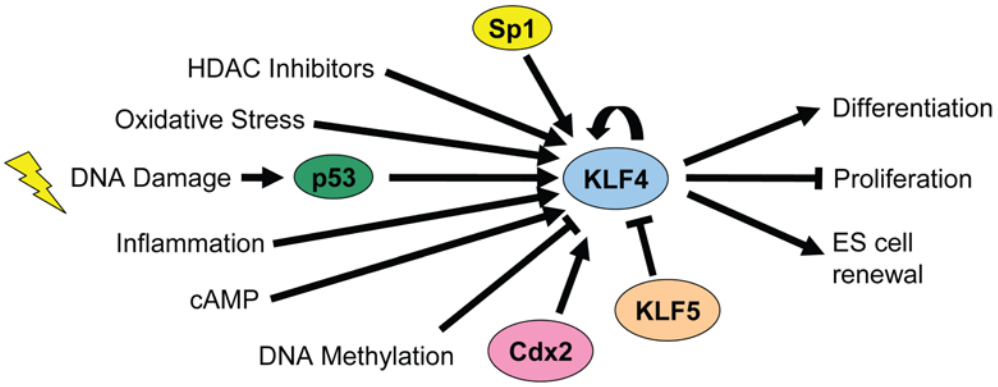

Fig. 2.

KLF4 signaling pathways Expression of KLF4 is upregulated by many stimuli, including DNA damage, inflammation, oxidative stress, and HDAC inhibitors. Sp1, Cdx2, and p53 positively regulate the KLF4 promoter, whereas KLF5 represses its expression. Overall, KLF4 functions to promote differentiation and inhibit proliferation. KLF4 is also important in ES cell renewal.

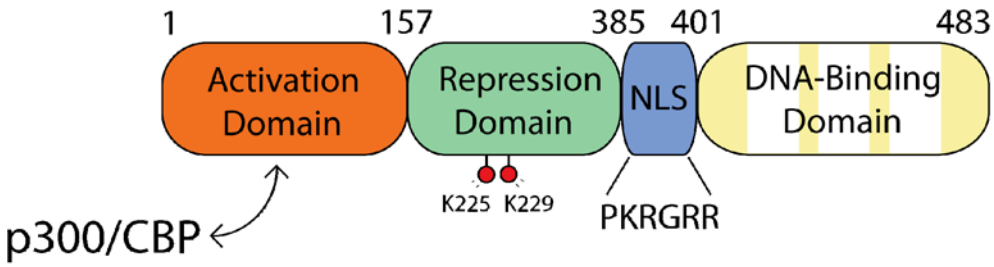

Fig. 3.

Functional domains of the KLF4 protein N-terminus of KLF4 contains a transactivation domain known to interact with the co-activators p300/CBP. The central region contains a repression domain, as well as two lysines that are acetylated by p300/CBP, followed by a hexapeptide nuclear localization sequence (NLS). Finally, the C-terminus contains the DNA binding domain, consisting of three sequential zinc fingers (each zinc finger is colored in white).

Table 1

Factors and conditions that modulate expression of KLF4

Factor/condition	References
Increase expression	
Butyrate	[5,16]
Cdx2	[23,97]
Contact inhibition	[2,3]
Endothelin-1	[8]
γ-irradiation	[33]
H_2O_2	[8,25]
Interferon-γ	[31,95,104]
IBMX	[48]
KLF4	[98]
LPS	[104]
Methyl methanesulfonate	[24]
p53	[24]
Serum starvation	[2,3]
Shear stress	[110]
Sp1	[23]
Sp3	[23]
TNF-α	[104]
Trichostatin A	[5,16]
TGF-β	[111]
Decrease expression	
KLF5	[98]
Promoter methylation	[52,57]

Table 2

Targets regulated by KLF4

Factor/condition	References	Factor/condition	References
Activation targets		Repression targets	
1200015N20Rik	[85]	Bax	[60]
A33 antigen	[112]	CD11d	[108]
B2R	[113]	Cyclin B_1	[30]
CYP1A1	[105]	Cyclin D_1	[5,26,27]
Cytokeratin 4	[67]	Cyclin E	[29]
EBV ED-L2	[114]	Fgf5	[88]
hSMVT	[115]	Histidine decarboxylase	[106]
IAP	[19,21,116]	KLF2	[85,88]
iNOS	[104]	Laminin α1	[117]
Keratin 4	[114]	Nes	[88]
Keratin 19	[118]	Ornithine decarboxylase	[31]
KLF4	[23,98]	p53	[34]
Laminin-α 3A	[119]	PAI-1	[104]
Laminin-γ 1	[120]	SM22α	[43]
Lefty1	[85]	SM α-actin	[121]
Nanog	[85,88]	Sp1	[62]
Oct4	[88]		
$p21^{Cip1}$	[23–25]		
$p27^{Kip1}$	[25]		
$p57^{Kip2}$	[21]		
PKG-Iα	[122]		
Rb	[25]		
Sox2	[88]		
SPRR1A	[67]		
SPRR2A	[67]		
Tbx3	[88]		
u-PAR	[123]		