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Krüppel-like factors in mammalian stem cells and development

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ABSTRACT

Krüppel-like factors (KLFs) are a family of zinc-finger transcription factors that are found in many species. Recent studies have shown that KLFs play a fundamental role in regulating diverse biological processes such as cell proliferation, differentiation, development and regeneration. Of note, several KLFs are also crucial for maintaining pluripotency and, hence, have been linked to reprogramming and regenerative medicine approaches. Here, we review the crucial functions of KLFs in mammalian embryogenesis, stem cell biology and regeneration, as revealed by studies of animal models. We also highlight how KLFs have been implicated in human diseases and outline potential avenues for future research.

KEY WORDS: Krüppel-like factors, Stem cells, Mammalian development, Cellular regeneration, Human disease

Introduction

Krüppel-like factors (KLFs) are evolutionarily conserved zinc-finger transcription factors that share homology with the *Drosophila melanogaster* protein Krüppel, which regulates body segmentation during fly embryogenesis (Preiss et al., 1985). Members of the KLF family also share structural homology and DNA-binding capacity with specificity proteins (SPs) and are thus often referred to as SP/KLF transcription factors. Recent studies have shown that specific KLFs are expressed across many species, spanning from single-celled to multicellular organisms (Presnell et al., 2015). Importantly, since their discovery, KLFs have been implicated in a variety of physiological processes, acting to regulate key cellular functions such as proliferation, differentiation and apoptosis. Furthermore, the identification of KLF4 as a crucial factor in reprogramming somatic cells into induced pluripotent cells has garnered great interest in KLFs in the stem cell biology and regeneration community.

Here, we describe the role of KLFs in mammalian development, highlighting how and when individual KLFs act during early embryogenesis and organogenesis. We also discuss the varied roles of KLFs in stem cell biology, reprogramming and regeneration, and review their roles in human diseases.

An introduction to KLFs: from structure to function

All KLFs possess three highly conserved C2H2 zinc finger domains in their carboxyl-terminal regions (Fig. 1) that mediate transcriptional activation and/or repression by interacting with GC-rich consensus, including 5'-CACCC-3', DNA sequences (Lomber and Urrutia, 2005; Suske et al., 2005). Conversely, the

amino-terminal regions of KLFs are divergent and modulate the specificity of protein-protein and protein-DNA interactions (Nagai et al., 2009). Recently, comprehensive evolutionary studies of SP/KLF family members using zinc finger sequences as well as transactivation/repression domains for phylogenetic analysis confirmed the existence of this family in 48 species within Eukaryota (Presnell et al., 2015); the evolutionary relationships between KLFs of murine and human origin based on their zinc finger domains is outlined in Fig. 2

The specificity of KLF-mediated transcriptional activation is defined mostly by their N-terminal sequences. KLF1, 2, 4, 5, 6, 8 and 15 (the latter by homology only) possess a transactivation domain (TAD) within their N-terminal regions (Chen and Bieker, 1996; Conkright et al., 1999, 2001; Kojima et al., 1997; Koritschoner et al., 1997; Lahiri and Zhao, 2012; Mas et al., 2011; Ratzu et al., 1998; van Vliet et al., 2000; Wani et al., 1999a). KLF1 has a very well-defined and essential TAD in its first 100 amino acids (Chen and Bieker, 1996). It has been shown that the KLF1 TAD can be divided into two regions – TAD1 and TAD2 – and that the latter is also conserved in KLF2, 4, 5 and 15 (Mas et al., 2011). In addition, a repression domain adjacent to the activation domain has been identified in KLF2 and KLF4 (Conkright et al., 2001; Geiman et al., 2000; Wani et al., 1999a). Furthermore, two KLF subgroups have been identified based on their respective interacting partners – CtBP and Sin3: KLF3, 8 and 12 possess an N-terminal repression domain (Fig. 1) that contains a CtBP recognition motif (Lahiri and Zhao, 2012; Schuierer et al., 2001; Turner and Crossley, 1998; van Vliet et al., 2000), and KLF9, 10, 11, 13, 14 and 16 contain a C/EBP domain in their N-terminal section (Fig. 1) that encompasses a Sin3 interaction domain (SID) and is referred to as a transcriptional regulatory repression domain (Cook et al., 1999; Daftary et al., 2012; Kaczynski et al., 2001, 2002; Lomber et al., 2013; Truty et al., 2009; Zhang et al., 2001a). Nuclear localization signals (NLSs) have also been identified in several KLFs (Fig. 1). For example, KLF1 contains two NLSs: NLS1, which is adjacent to the first zinc finger domain, and NLS2, which spans through three zinc finger domains (Quadri and Bieker, 2002). In comparison, KLF2 and KLF4 harbor NLSs adjacent to their first zinc finger domain (Shields and Yang, 1997), and KLF6 has a single NLS localized within its first and second zinc finger domains (Rodriguez et al., 2010). Furthermore, KLF15 has two NLSs located within its second and third zinc finger domains (Leenders et al., 2012), whereas the two NLSs of KLF8 flank the ends of its zinc finger domains (Lahiri and Zhao, 2012; Mehta et al., 2009). Finally, KLF7 has a putative NLS motif adjacent to the zinc finger domains (Matsumoto et al., 1998) and KLF13 possesses two putative NLSs, one adjacent to and one within its zinc finger domain (Song et al., 2002). Interestingly, two KLFs – KLF5 and KLF6 – also include nuclear export signal (NES) sequences (Fig. 1), which regulate their cellular localization (Du et al., 2008; Rodriguez et al., 2010). Although NLS or NES signals have not been identified within the KLF16 sequence, it has been shown *in vitro* that serum levels in the media regulate the nuclear-cytoplasm shuttling of

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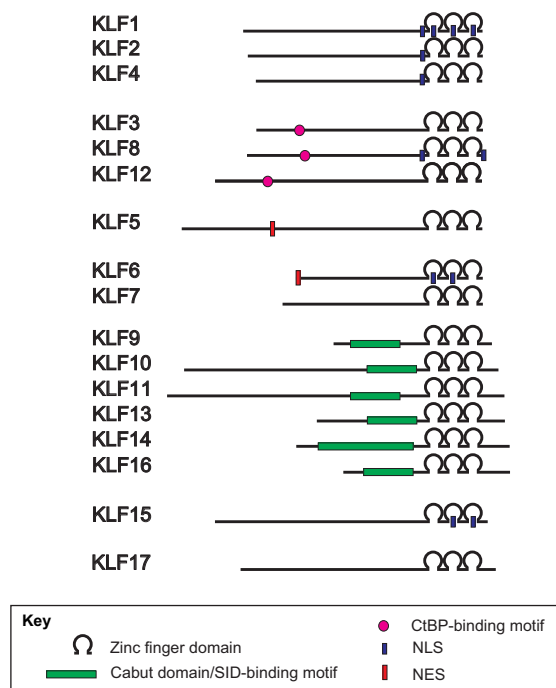


Fig. 1. Schematic of the domain structure of human KLF proteins. All KLFs possess three highly conserved C2H2 zinc finger domains in their carboxyl-terminal regions that mediate transcriptional activation and/or repression. By contrast, their N-terminal regions are less conserved, harboring additional motifs, such as CtBP-motifs and Cabut domains/SID-binding motifs, that are implicated in protein-protein and protein-DNA interactions. Some KLFs also contain nuclear localization signals (NLSs) and nuclear export signals (NESs) that regulate their subcellular localization. Proteins are drawn to scale.

KLF16 and that interactions with Sin3-HDAC complexes impact its chromatin localization (Daftary et al., 2012).

KLFs also display key differences in their temporal, spatial and cell-specific modes of expression, their post-translational modifications (phosphorylation, acetylation, methylation, SUMOylation and ubiquitylation), as well as their interactions with co-activators or co-repressors, which add additional layers of specificity and governance over these factors (summarized in Table 1).

The role of KLFs in early embryogenesis

The early mammalian post-fertilization embryo undergoes cleavage divisions without growth, eventually giving rise to a structure known as a blastocyst, which contains a distinct inner cell mass (ICM) and an outer layer of trophoblast (TE) cells. Notably, the ICM – which later separates out into epiblast (EPI) and primitive endoderm (PE) – is the source of mouse embryonic stem cells (ESCs; discussed in detail below), which are pluripotent, self-renewing and have the ability to give rise to all three types of primary germ layers (Keller, 2005). A large body of evidence has demonstrated crucial roles for various KLFs during early mouse embryonic development (Fig. 3). For instance, several laboratories have shown that *Klf5*^{-/-} embryos die at embryonic day (E) 8.5, *Klf2*^{-/-} at E12.5, *Klf6*^{-/-} at E12.5, and *Klf4*^{-/-} mice soon after birth (Katz et al., 2002; Kuo et al., 1997a; Matsumoto et al., 2006; Segre et al., 1999; Shindo et al., 2002). Further analyses showed that KLF5 is expressed early in the pre-implantation mouse embryo, starting at the two-cell stage, with persistent expression occurring during the morula and blastocyst stages (Lin et al., 2010). Although KLF5 is not detected at the epiblast stage between E5.5 and E6.5, it is present in primordial germ cells at E11.5 (Lin et al., 2010).

Importantly, KLF5 regulates the formation of the three distinct cell lineages that arise during pre-implantation development, promoting TE and EPI formation, and repressing PE development (Lin et al., 2010). Abnormalities within all three lineages were also observed in *Klf6*^{-/-} ESCs, suggesting some redundancy between KLFs in ESC differentiation (Matsumoto et al., 2006). In contrast, the expression of KLF2 and KLF4 is not required for the development of these cell lineages (Ema et al., 2008; Lin et al., 2010). Recently, comparative analyses of mouse and human blastocysts using single-cell RNA sequencing (Blakeley et al., 2015) demonstrated the expression pattern of KLF4 during pre-implantation development. It was observed that mouse embryos express *Klf4* at the two-cell stage until the blastocyst stage, whereas *KLF4* is upregulated at the eight-cell stage in human embryos. By contrast, *Klf2* was highly expressed in the ICM and at very low levels in the TE in mouse embryos. Interestingly, *KLF2* was completely absent from the EPI, PE and TE of human embryos. Finally, it was also demonstrated that *KLF17* is highly expressed in EPI cells in human embryos, but is absent from the ICM and TE of mouse embryos (Blakeley et al., 2015). Combined, these findings highlight key roles for KLFs during early embryogenesis but also suggest that there are fundamental differences in the regulatory circuits that regulate lineage development in early mouse and human embryos. As we move on to discuss below, KLFs have also been implicated in later stages of development, in endoderm-, mesoderm- and ectoderm-derived lineages (as summarized in Table 2).

KLFs in the development of endoderm-derived lineages Lung development

During mouse embryogenesis, normal lung development begins at E9.5 and can be divided into structural (growth) and functional (maturation) development with four histological stages: pseudoglandular, canalicular, terminal saccular and alveolar. The first two stages are restricted to embryonic development, whereas the terminal saccular stage extends from embryogenesis to the postnatal period, and the final alveolar maturation stage occurs in the postnatal (P) 5-P30 period (Warburton et al., 2010). Studies have shown that KLF2 is essential for lung development (Wani et al., 1999b). Because *Klf2*^{-/-} mice die *in utero* at approximately E12.5, the role of KLF2 in lung development was studied using *Klf2*^{-/-} ESCs in chimeric animals (Wani et al., 1999b). These *Klf2*^{-/-} mice exhibit multiple abnormalities: lack of lung expansion with arrest in the late canalicular stage, with undilated acinar tubules and buds in peripheral regions of the lung. These findings suggest that KLF2 is vital for the later stages of embryonic lung development (Wani et al., 1999b).

KLF5 is also important for lung development. Immunohistochemistry analyses demonstrated that KLF5 is expressed in pulmonary epithelial cells throughout lung development in mice (Wan et al., 2008). At E18.5, KLF5 is expressed in a subset of cells in the alveolar compartment expressing surfactant protein C, a type II alveolar epithelial cell marker (Wan et al., 2008). KLF5 is also present in conducting airways, ciliated bronchiolar cells and non-ciliated cells expressing the bronchiolar cell marker CCSP (also known as SCGB1A1) (Wan et al., 2008). Because *Klf5*^{-/-} mice are embryonically lethal at E8.5, well before lung development occurs, the conditional deletion of *Klf5* in respiratory epithelial cells in the fetal lung was used to investigate KLF5 function in lung development (Wan et al., 2008). This study showed that ablation of *Klf5* in respiratory (Lin et al., 2010) epithelial cells inhibits lung maturation during the saccular stage of development and causes death due to respiratory distress immediately after birth. Lung maturation and morphogenesis in the

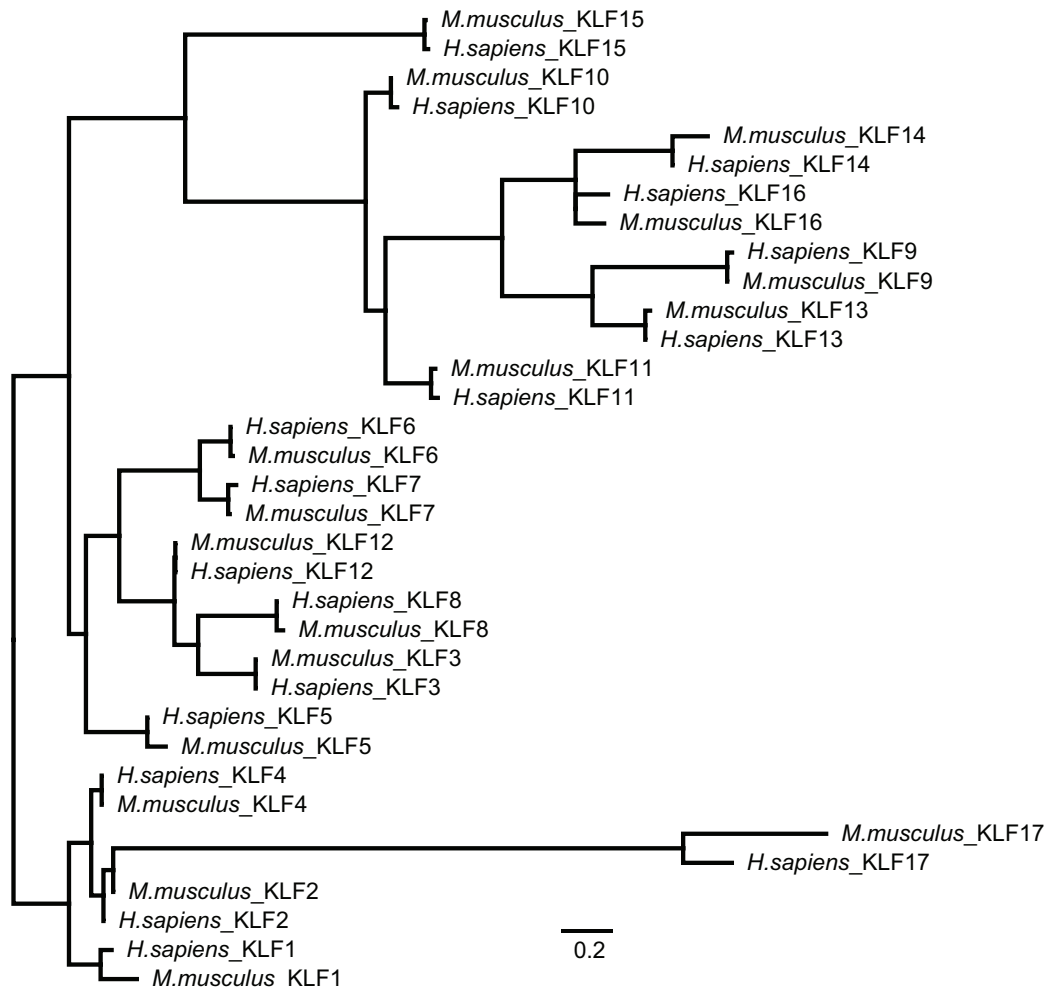


Fig. 2. Phylogenetic relationship between human and mouse KLF family members. An amino acid alignment was produced from full-length mouse and human KLF family members using MAFFT (Katoh et al., 2002) employing the L-INS-i algorithm and BLOSUM45 scoring matrix. As KLF family members share little homology outside of the C-terminal ZNF region, the alignment was trimmed 22 residues N-terminal of the first ZNF domain and one residue C-terminal of the third ZNF domain. Phylogenetic analysis of the ZNF region was performed via RAxML 7.2.8 (Stamatakis, 2006) using the Gamma LG model, and node support in the ML tree was sampled via 100 bootstrap replicates. Both alignment and phylogenetic analyses were performed in Geneious version 8.1.8 (Kearse et al., 2012). Scale bar: 0.2 amino acid changes per site.

respiratory epithelium, the bronchiolar smooth muscle, and the pulmonary vasculature are also affected (Wan et al., 2008). Further analyses also demonstrated that KLF5 modulates the expression of key genes regulating surfactant lipid and protein homeostasis, vasculogenesis, and smooth muscle cell differentiation (Wan et al., 2008). In addition, *Klf6* is also detected in the lung buds of mice at E12.5 (Laub et al., 2001b), but its function in lung development has not been explored. Nonetheless, these data demonstrate the crucial role of KLFs in lung development.

Gut development

Previous studies have demonstrated the expression of *Klf4* and *Klf5* in the intestine during mouse embryogenesis (Ohnishi et al., 2000). *Klf4* is abundantly expressed at E15.5, but nearly absent by E17.5 (Ohnishi et al., 2000; Ton-That et al., 1997). Furthermore, the level of *Klf4* expression in newborn mice is higher in the colon in comparison with the small intestine, but increases in both tissues with age (Ton-That et al., 1997). *Klf5* transcripts are detected early in the primitive gut at E10.5, with increased expression observed at E15.5 and peaking at E16.5 until a decrease at E17.5. Interestingly, *Klf5* expression is eventually confined to the crypt part of the mature

intestinal epithelium (Ohnishi et al., 2000). Mice with intestinal-specific deletion of *Klf5* (driven by the villin promoter) show high levels of mortality within the first 48 h after birth (McConnell et al., 2011). These mice, which display variegated expression of *Klf5* in the gut, survive to 8 weeks of age but eventually exhibit defects in epithelial differentiation and migration resulting in impaired barrier function and inflammation (McConnell et al., 2011).

Other endoderm-derived organs

Unfortunately, the precise role of KLFs during the development of other endoderm-derived organs is not very well-defined. Previous studies have demonstrated that *Klf6*^{-/-} mice exhibit failed hepatogenesis (Matsumoto et al., 2006). In addition, *Klf13* is expressed in endothelial cells of the liver vasculature at E14.5 in mice (Lavalley et al., 2006). However, their function during hepatogenesis and development of liver vasculature remains unclear.

KLFs in the development of mesoderm-derived lineages

Development of the hematopoietic system

During embryogenesis, hematopoiesis is initiated independently at two sites: the extra-embryonic mesoderm of the yolk sac and the

Table 1. Pattern of expression, regulation and functions of KLFs

Name	Expression pattern	Downstream pathways/cellular processes/function	Regulatory pathways	References
KLF1	Erythroid cells; fetal liver; adult spleen and bone marrow	Megakaryocyte differentiation; erythropoiesis	Acetylated by CBP/p300 and p/CAF; phosphorylation at serine and threonine residues by casein kinase II aids the activity; interaction with PPM1b increases KLF1 activity; ubiquitylation; sumoylation (K74) inhibits activity	(Frontelo et al., 2007; Nuez et al., 1995; Ouyang et al., 1998; Perkins et al., 1995; Siatecka et al., 2007; Zhang et al., 2001b)
KLF2	Erythroid cells; endothelial cells; lungs; adipose tissue; T lymphocytes	Erythropoiesis; lung and vasculature development; T-cell migration, trafficking and differentiation; generation of iPSCs; adipocyte differentiation	Stability mediated by GSK3 β -phosphorylation and FBW7 (FBXW7) degradation; ubiquitylation by ubiquitin ligase WWP1; SMURF1 interaction leads to polyubiquitylation and degradation	(Anderson et al., 1995; Basu et al., 2005; Carlson et al., 2006; Kuo et al., 1997a; Kuo et al., 1997b; Lee et al., 2006; Nakagawa et al., 2008; Wang et al., 2013; Wani et al., 1999a,b; Wu et al., 2005; Xie et al., 2011; Zhang et al., 2004)
KLF3	Erythroid cells	Inhibit adipocyte differentiation; B-cell development; cardiac development	Phosphorylation by HIPK2 and CtBP augments KLF3 transcriptional repression; interacts with E2 SUMO-conjugating enzyme Ubc9 (Ube2i) and covalently modified by SUMO-1; sumoylation by SUMO E3 ligases PIAS1, PIASgamma (PIASG), PIASalpha and PIASbeta (PIAS2), stimulates its transcriptional repression activity	(Crossley et al., 1996; Dewi et al., 2015; Perdomo et al., 2005; Schuierer et al., 2001; Sue et al., 2008; Yien and Bieker, 2012)
KLF4	Epithelial cells (intestine, kidney, skin, lungs); endothelial cells; precursor B cells	Adipogenesis; myeloid differentiation; intestinal epithelial cell homeostasis; goblet cell differentiation; skin development; podocyte homeostasis; generation of iPSCs; tumor suppressor (colon cancer); oncogene (breast cancer, pancreatic cancer, squamous cell cancer); cardiac homeostasis; brain development and homeostasis	Phosphorylation by ERK1/2 (MAPK3/ MAPK1) negatively regulates activity and stability via β TrCP1 (BTRC) or β TrCP2 (FBXW11); acetylation enhances transcriptional activity; ubiquitylation under serum starvation; sumoylated by SUMO E3 ligase PIAS1 inhibits activity and promotes degradation; methylation stabilizes and leads to increased activity	(Chen et al., 2005b; Evans et al., 2007; Ghaleb et al., 2005; Hu et al., 2015; Katz et al., 2002; Kawai-Kowase et al., 2005; Kim et al., 2012b; McConnell et al., 2007; Segre et al., 1999; Takahashi et al., 2007; Takahashi and Yamanaka, 2006; van Zelm et al., 2005)
KLF5	Epithelial cells (intestine, kidney, skin); vascular smooth muscle; adipose tissue	Formation of cell lineages during pre-implantation stage; cardiac remodeling; intestinal homeostasis; lung maturation and morphogenesis; myeloid differentiation; adipogenesis; vasculogenesis; skeletal growth; skin development; generation of iPSCs; increased expression in colon, breast and prostate cancer	Phosphorylated by ERK and PKC; acetylation by CBP/p300 enhances transcriptional activity; deacetylation by HDAC and SET negatively regulates activity; ubiquitylation by ubiquitin ligase WWP1; stability mediated by GSK3 β -phosphorylation and FBW7 degradation; sumoylation by SUMO E3 ligase PIAS1 enhances activation of cell cycle genes; sumoylation of KLF5 mediates lipid metabolism; deubiquitylation by ATXN3L or BAP1 stabilize KLF5 protein levels	(Chaib et al., 2001; Chen et al., 2002; Chen et al., 2005a; Conkright et al., 1999; Du et al., 2007; Ge et al., 2015; He et al., 2009; Liu et al., 2010; McConnell et al., 2009; McConnell et al., 2007; Nakagawa et al., 2008; Nandan et al., 2010; Nandan et al., 2008; Oishi et al., 2008; Oishi et al., 2005; Qin et al., 2015; Shindo et al., 2002; Shinoda et al., 2008; Takeda et al., 2010; Tong et al., 2006; Wan et al., 2008; Zhang and Teng, 2003; Zhao et al., 2010; Zhao et al., 2015)
KLF6	Epithelial cells (heart, liver, intestine, kidney, lungs); endothelial cells; placenta; developing hindgut, heart, lung and kidney	Formation of cell lineages during pre-implantation stage; hematopoiesis; yolk sac vascularization; hepatogenesis; adipogenesis; vascular remodeling; regulation of mitochondrial function; neural tube closure; wild-type tumor suppressor (prostate cancer); splice variants in prostate cancer	Acetylation by CBP/p300 enhances transcriptional activity; GSK3 β phosphorylation augments its transactivation; ubiquitylation after DNA damage	(Atkins and Jain, 2007; Banck et al., 2006; Chen et al., 2003; Difeo et al., 2009; Fischer et al., 2001; Lang et al., 2013; Laub et al., 2001b; Li et al., 2005; Matsumoto et al., 2006; Matsumoto et al., 1998; Miyamoto et al., 2003; Narla et al., 2001; Slavin et al., 1999; Wang et al., 2016)

Continued

Table 1. Continued

Name	Expression pattern	Downstream pathways/cellular processes/function	Regulatory pathways	References
KLF7	Brain, spinal cord; developing CNS and peripheral nervous system	Neurite outgrowth and axonal misprojection; single nucleotide polymorphisms in type 2 diabetes mellitus; inhibit adipocyte differentiation	Acetylation in DNA-binding domain mediates stem cells' quiescence	(Kanazawa et al., 2005; Laub et al., 2001a; Laub et al., 2005; Matsumoto et al., 1998)
KLF8	Ubiquitous expression	Increased in ovarian cancer	Regulated by CtBP (N-terminal); phosphorylation by ERK2 maintains stability; sumoylation by SUMO E3 ligase family inhibits activity	(Lahiri et al., 2016; Turner and Crossley, 1998; van Vliet et al., 2000; Wang and Zhao, 2007; Wei et al., 2006)
KLF9	Smooth muscle (intestine, bladder); developing brain, thymus and epithelia	Increased in endometrial cancer; fertility and parturition defects in females; neuronal differentiation	Regulated by Sin3A (N-terminal)	(Martin et al., 2001; Morita et al., 2003; Simmen et al., 2007; Simmen et al., 2004; Simmen et al., 2010; Zhang et al., 2001a)
KLF10	T lymphocytes; kidney; pancreas; lung; brain; liver; testis; heart	Bone development; T-cell activation and differentiation; cardiac homeostasis	Regulated by Sin3A (N-terminal); phosphorylated by aPKC, which augments its nuclear localization (two phosphorylation sites have opposite effects on the activity); phosphorylation at N terminus by PIN1 promotes degradation; mono-ubiquitylation by E3 ligase Itch in response to TGF β signaling in naive T cells	(Bensamoun et al., 2006; Cao et al., 2009; Hawse et al., 2008; Hwang et al., 2013; Rajamannan et al., 2007; Subramaniam et al., 2005; Subramaniam et al., 1995; Venuprasad et al., 2008; Yajima et al., 1997; Yerges et al., 2010; Zhang et al., 2001a)
KLF11	Pancreas; erythroid cells in fetal liver	Tumor suppressor (pancreatic cancer); variants in type 2 diabetes mellitus	Regulated by Sin3A (N-term); phosphorylation by ERK/MAPK inhibits activity	(Asano et al., 1999; Buck et al., 2006; Cook et al., 1998; Ellenrieder et al., 2004; Neve et al., 2005; Song et al., 2005; Zhang et al., 2001a)
KLF12	Kidney epithelial cells; developing kidney and brain	Urea transport in the kidney	Regulated by CtBP (N-terminal)	(Imhof et al., 1999; Nakamura et al., 2009; Rozenblum et al., 2002; Suda et al., 2006; van Vliet et al., 2000)
KLF13	Developing heart, thymus, brain, skin, intestine, bladder	B- and T-cell development; cardiac development	Regulated by Sin3A (N-terminal); acetylation enhances transcriptional activity; phosphorylation by serine/threonine kinase PRP4 (PRPF4) increases transcriptional activity; stability mediated by GSK3 β -phosphorylation and FBW7g degradation	(Gordon et al., 2008; Huang et al., 2007; Kim et al., 2012a; Lavallee et al., 2006; Martin et al., 2001; Song et al., 2002; Zhang et al., 2001a; Zhou et al., 2007)
KLF14	Ubiquitous expression	Variants in basal cell carcinoma	Regulated by Sin3A (N-terminal)	(Parker-Katiraei et al., 2007; Scohy et al., 2000; Stacey et al., 2009)
KLF15	Endothelial cells; epithelial cells (kidney, liver, pancreas, skeletal muscle, lung, ovary); developing heart	Podocyte differentiation; nephrocyte development; gluconeogenesis; cardiac homeostasis	Regulated by retinoic acid and glucocorticoid signaling	(Fisch et al., 2007; Gray et al., 2007; Uchida et al., 2000; Wang et al., 2008)
KLF16	Thymus, intestine, kidney, liver, heart, bladder, lung, developing brain	–	Regulated by Sin3A (N-terminal)	(D'Souza et al., 2002; Hwang et al., 2001)
KLF17	Oocytes, spermatids	–	–	(van Vliet et al., 2006; Yan et al., 2002)

intra-embryonic site. The primitive hematopoiesis that occurs in the yolk sac generates erythrocytes that are necessary for embryo survival and distinct from fetal and adult erythrocytes (which express γ - and α -, and β -globin, respectively). By contrast, definitive hematopoiesis originating from the intra-embryonic site establishes myeloid, lymphoid and erythroid lineages as well as fetal and adult hematopoietic stem cells (HSCs). Several KLFs are expressed in these hematopoietic tissues and thus have been implicated in hematopoiesis. For example, the mouse yolk sac, fetal

liver and adult spleen express ample levels of KLF1, 2, 3, 4, 5, 8, 11, 12 and 13 (Zhang et al., 2005). The expression pattern of these KLFs has also been confirmed in human erythroid cell line models (Zhang et al., 2005).

KLF1 is uniquely expressed in erythroid cells of the yolk sac, fetal liver, spleen and bone marrow in both mice and humans (Zhang et al., 2005). *Klf1*^{-/-} mice develop fetal anemia during definitive erythropoiesis and die of profound β -thalassemia between E14 and E16 due to defects in red blood cell (RBC)

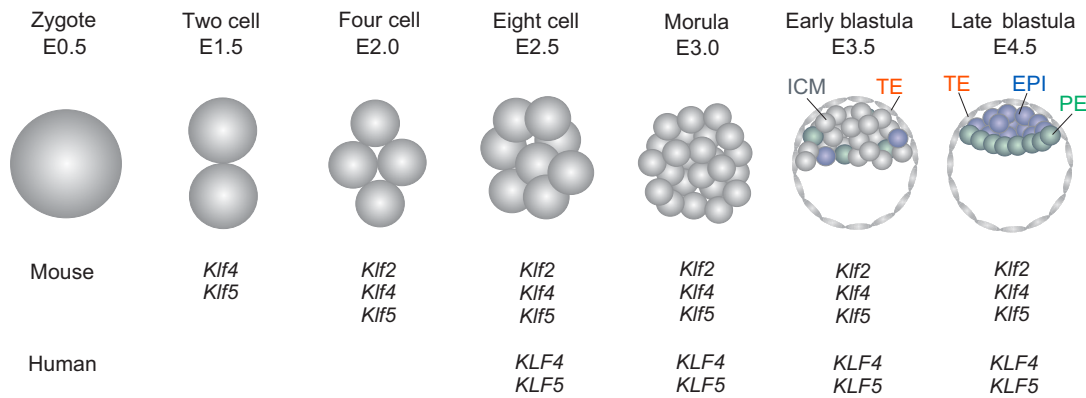


Fig. 3. The expression of KLF2, KLF4 and KLF5 during mammalian pre-implantation embryo development. Diagram of mouse pre-implantation embryo development, highlighting the stages at which KLF2, KLF4 and KLF5 genes are expressed; the expression of these factors in human pre-implantation embryos is also indicated. Patterns of expression are based on findings reported by Blakeley et al. (2015) and Lin et al. (2010). EPI, epiblast; ICM, inner cell mass; PE, primitive ectoderm; TE, trophoctoderm.

maturation (Perkins et al., 1995; Siatecka and Bieker, 2011). This is mainly caused by defects in β -globin expression whereas α -globin levels are largely unaffected. Ultimately, KLF1 has been shown to play an essential role in embryonic and adult erythropoiesis by positively regulating β -globin (Siatecka and Bieker, 2011), ϵ -globin and γ -globin genes in the mouse embryo (Alhashem et al., 2011). KLF1 has also been shown to act as a master regulator of global erythroid gene expression by controlling the heme biosynthetic pathway, RBC membrane proteins, the cell cycle, transcription factor expression patterns (Drissen et al., 2005; Hodge et al., 2006), and long noncoding RNAs that regulate RBC maturation (Alvarez-Dominguez et al., 2014). Furthermore, during hematopoiesis, *Klf1* represses megakaryocyte formation from the megakaryocyte-erythroid lineage (Frontelo et al., 2007). Finally, recent studies in mice demonstrate the existence of two KLF1 isoforms – full-length KLF1 and KLF1-SV – that are generated by alternative splicing, with the latter potentially impacting expression levels of the transcriptional targets of full-length KLF1 (Yien et al., 2015).

KLF2, by contrast, is required for the production of embryonic ϵ -globin in human and $\epsilon\gamma$ -globin and β h1-globin in mouse erythroid cells, but not adult β -globin (Alhashem et al., 2011; Basu et al., 2007). Consequently, *Klf2*^{-/-} mice are embryonically lethal between E12.5 and E14.5 due to defects in the development of vascular endothelial cells, leading to intra-embryonic and intra-amniotic hemorrhage (Kuo et al., 1997a). Studies in mice show that KLF2 also regulates T-cell differentiation, quiescence and survival (Kuo et al., 1997b). Recently, it was also postulated that KLF2 alternatively regulates thymocyte and T-cell trafficking in mice (Carlson et al., 2006). Interestingly, *Klf1/Klf2* double knockout mouse embryos die before E11.5 as the result of deficiencies in endothelial and erythroid development (Basu et al., 2007; Vinjamur et al., 2014). KLF3, which is expressed in the fetal liver, plays a role in normal B-cell development in the bone marrow, spleen and peritoneal cavity in mice; these processes are impaired in *Klf3* null mice (Pearson et al., 2011; Turchinovich et al., 2011).

Although it was known originally for its expression in the skin and gut, *Klf4* is induced in a stage-specific manner during embryogenesis as cells transition from HSCs into granulocyte/macrophage progenitors, and is reduced in megakaryocyte/erythrocyte progenitors. Interestingly, *Klf4* deficiency within myeloid progenitors results in reduced monocyte and granulocyte formation, suggesting a potential role for KLF4 in primary myeloid

differentiation (Feinberg et al., 2007; Kurotaki et al., 2013). KLF5 is also implicated in myeloid differentiation: *Klf5* expression increases in granulocyte lineage cells during both mouse and human hematopoiesis, and the targeted, conditional ablation of *Klf5* in the hematopoietic compartment of mice revealed its novel role as a myeloid transcription factor (Shahrin et al., 2016). In these studies, KLF5 contributed to neutrophil formation and inhibited eosinophil production. Moreover, KLF5 serves as a target of C/EBP α after the formation of granulocyte-macrophage progenitors and impacts the fate of myelomonocytic precursors (Shahrin et al., 2016).

Klf6 null mice also exhibit markedly reduced hematopoiesis and poorly organized yolk sac vascularization, which probably contribute to the embryonic lethality at E12.5 of these mice (Matsumoto et al., 2006). In contrast, *Klf7* null mice do not exhibit changes in hematopoiesis despite the ubiquitous expression of *Klf7* in all hematopoietic lineages and human pluripotent stem cell subsets (Schuettpelz et al., 2012). However, the overexpression of *Klf7* was shown to inhibit the formation of all myeloid lineage cells (Schuettpelz et al., 2012), suggesting a deleterious role of excess *Klf7* in development. Furthermore, recent transcript analysis of *Klf8* demonstrated its expression in erythroid lineages: at E11.5 in the yolk sac, at E14.5 in the fetal liver, and finally in adult peripheral blood (Funnell et al., 2013). It was further shown that double mutants for *Klf3* and *Klf8* die at E14.5, whereas *Klf3*^{-/-} and *Klf3*^{-/-}/*Klf8*^{sg/sg} mice exhibit de-repression of embryonic, but not adult, globin expression (Funnell et al., 2013). These observations suggest that KLF8 might play a compensatory role upon *Klf3* ablation. KLF11 is also expressed during embryonic hematopoiesis, although *Klf11*^{-/-} mice exhibit no changes in hematopoiesis during development (Song et al., 2005). Finally, studies have shown that *Klf13* expression increases upon maturation of erythroid precursors in mice (Gordon et al., 2008). As such, *Klf13*^{-/-} mice exhibit an increase in the number of immature erythrocytes in the spleen; however, the number of committed precursors is unchanged in the bone marrow (Gordon et al., 2008). Interestingly, these immature precursors accumulate at the proerythroblast stage of development and exhibit increased expression of *Klf1* and *Klf3* (Gordon et al., 2008). Collectively, these studies highlight the crucial role of KLFs in the development of the hematopoietic system.

Cardiovascular development

The vasculature is the first organ system to develop and its development is initiated early during embryogenesis. The vascular

Table 2. Krüppel-like factor participation in lineage formation during mouse embryogenesis

Name	Endoderm-derived lineages		Mesoderm-derived lineages				Ectoderm-derived lineages	
	Lung	Hepatocytes	Hematopoietic	Cardiovascular	Adipogenesis	Cartilage formation	Skin	Central nervous system
KLF1			+					
KLF2	+		+	+	+	+		
KLF3			+	+	+			
KLF4			+	+		+		+
KLF5	+		+	+			+	
KLF6	+	+	+	+				+
KLF7			+					+
KLF8			+					
KLF9								+
KLF10								
KLF11			+					
KLF12								
KLF13			+	+				
KLF14								
KLF15								
KLF16								
KLF17								

system is formed by the differentiation of primitive mesodermal cells into endothelial cells (vasculogenesis) and by endothelial cell proliferation and migration to colonize tissues (angiogenesis). In the final stage, with the onset of a heart beat and blood flow, vessels remodel and branch out to penetrate different organs. To date, six KLFs have been implicated in cardiovascular development: KLF2, 3, 4, 5, 6 and 13.

Early studies demonstrated that *Klf2* is expressed in the mouse embryo as early as E7 in the developing vasculature, exhibits a decrease in expression at E11, but returns to high levels at E15 and remains elevated, specifically in the umbilical arteries and veins (Anderson et al., 1995). By contrast, recent experiments have highlighted that changes in *Klf2* expression during cardiovascular development might correlate with variations in fluid shear stress (Lee et al., 2006). Namely, *Klf2* expression begins at E8.5 within endothelial and endocardial compartments and rises by E10.5 as the heart tube loops and endocardial cushions form. By E11.5, *Klf2* expression is higher in the arteries (compared with veins), in the endothelium overlying the endocardial cushions, and in the common ventricular outflow tract – sites predicted to experience high fluid shear forces (Lee et al., 2006). However, *Klf2* expression becomes restricted to the flow side of developing valves as the cushions mature by E14.5 (Lee et al., 2006). In addition, *Klf2* expression is also detectable in the endocardium lining the intraventricular papillary muscles. Surprisingly, no changes in vasculogenesis and angiogenesis are observed in *Klf2*^{-/-} mice; however, these mice do exhibit impaired blood vessel maturation (Wu et al., 2008). More recent studies have shown that *Klf2* is also expressed at E9.5 in endocardial cells of the atrioventricular canal cushion region and that its deletion results in embryonic heart failure, attributable to a high cardiac output state caused by a profound loss of peripheral vascular resistance (Chiplunkar et al., 2013b; Lee et al., 2006).

KLF3 is also implicated in cardiac development. Although early observations did not report an embryonic phenotype in *Klf3*^{-/-} mice (Funnell et al., 2013), recent data show that homozygous mutant *Klf3*^{H275R/H275R} mice have significant lethality at E14.5-E16.5 (Kelsey et al., 2013). Increased mortality in these mice is likely to be due to heart failure, as the ventricular myocardium and septum are notably thinned and disorganized in these mice (Kelsey et al.,

2013). Furthermore, mice harboring heterozygous *KLF3*^{H275R} point mutants exhibit increased perinatal lethality with numerous abnormalities in heart morphology at E12.5: marked biventricular myocardial hypertrophy and aortic valve leaflet thickening with adult survivors exhibiting hypotension, aortic valvular stenosis, aortic dilatation, myocardial hypertrophy and increased chamber size (Kelsey et al., 2013). It was suggested that the cardiovascular abnormalities in these mice could be attributed to blood pressure dysregulation, because KLF3 is also expressed in the renal vasculature during development (Kelsey et al., 2013).

KLF4 is expressed in extra-embryonic tissues at E4.5, and in mesenchymal and ectodermal tissues, and the endothelium by E10.5. However, vascular abnormalities have not been reported in *Klf4* null mice (Ehlermann et al., 2003). A more recent study demonstrated that *Klf4* is expressed in the heart (in the atrium and ventricle at E18.5, but not in smooth muscle) from late embryonic development to adulthood (Yoshida et al., 2010). These findings led to further investigations using the smooth and cardiac muscle-specific conditional deletion of *Klf4* in mice (Yoshida et al., 2010). Although abnormalities were not observed within smooth muscle and vascular morphology or in the heart and great arteries at P14 and P28, five-week-old *Klf4*^{-/-} mice demonstrated decreased cardiac output that was associated with abnormal postnatal growth (Yoshida et al., 2010). It was further shown that the lack of *Klf4* in these mice decreased the expression of many cardiac genes, including myosin light polypeptide 1 (*Myl1*), cardiac/slow skeletal troponin C (*Tnnc1*), myosin binding protein C (*Mybpc2*), natriuretic peptide precursor type B (*Nppb*) and *Gata4* (Yoshida et al., 2010). An independent study showed that *Klf2/Klf4* double knockout mice die earlier than the single knockouts, possibly due to gross hemorrhaging of multiple vessels (Chiplunkar et al., 2013a). Thus, KLF4 might play a role in vasculogenesis and the maintenance of embryonic vascular integrity by interacting with KLF2.

KLF5 is also abundantly expressed in developing blood vessels, and its deletion leads to early embryonic lethality (Shindo et al., 2002). Similarly, KLF6 is important in specifying mesoderm to hematopoietic and vascular lineages, and for vasculogenesis (Matsumoto et al., 2006). As such, *Klf6*^{-/-} mice have poorly organized yolk sac vasculature and decreased levels of Flk-1 (KDR)-positive cells (vascular progenitors) (Matsumoto et al., 2006). Furthermore, initial *in situ* hybridization

studies revealed that *Klf13* is highly expressed in the heart and cephalic mesenchyme: its expression in the primitive heart can be detected as early as E11.0 in the atria and ventricles, but decreases by E13.0–E16.0 (Martin et al., 2001). Further comprehensive immunohistochemistry of developing mouse embryos (Lavalley et al., 2006) demonstrated that, at E9.5, KLF13 is detected mostly in the heart and the epidermis. At E10.5, KLF13 is localized in the atrial myocardium and endocardial layer and by E12.5 in atria and ventricles with higher atrial expression (Lavalley et al., 2006). KLF13 staining is also present in the cushions of the atrioventricular region and the truncus arteriosus (Lavalley et al., 2006). Although KLF13 is subsequently downregulated postnatally, its expression is restricted to the atrial and ventricular myocardium, with the highest expression in the valves and interventricular septum (Lavalley et al., 2006). Mechanistically, KLF13 interacts with GATA4 to regulate atrial expression of *Nppb*, which is essential for cardiac development (Lavalley et al., 2006). Consequently, *Klf13*^{-/-} mice exhibit an enlarged heart and increased susceptibility to cardiovascular injury, highlighting the importance of KLF13 in heart development (Gordon et al., 2008). Combined, these data emphasize the essential role of KLFs in cardiovascular development.

Adipogenesis

The adipocyte lineage originates from mesenchymal progenitors that form adipocyte precursor cells or preadipocytes, which then differentiate into mature, lipid-containing adipocytes. Several KLFs have been implicated in adipogenesis. For example, the analysis of embryoid bodies derived from *Klf2*^{-/-} mouse ESCs showed that they retain the ability to form functional adipocyte precursors that differentiate upon adipogenic stimuli (Wu et al., 2005). As such, *Klf2*^{-/-} cells are more prone to differentiate at the early stage of adipocyte differentiation, suggesting that KLF2 is a natural repressor of differentiation (Wu et al., 2005). In addition, *Klf3*^{-/-} mice are smaller than their wild-type littermates and exhibit reduced levels of white adipose tissue (Sue et al., 2008). Although these studies highlight that KLF2 and KLF3 play a role in adipogenesis, further studies are required to delineate the mechanisms by which they act.

KLFs and the development of ectoderm-derived lineages

Skin development

Two KLFs, namely KLF4 and KLF5, are implicated in skin development. In mice, the expression of *Klf4* and *Klf5* is observed at E15.5 in the developing skin (Ohnishi et al., 2000). A high level of *Klf4* expression is then observed in the epidermis at E16.5 with a slight reduction by E17.5 (Ohnishi et al., 2000). In contrast, *Klf5* expression persists until E17.5 (Ohnishi et al., 2000). Importantly, *Klf4*^{-/-} mice die within 24 h of birth due to improper late-stage differentiation of structures in the epidermis and loss of skin barrier function (Segre et al., 1999). Moreover, it was shown that *Klf4* overexpression (under the control of the keratin 5 promoter) during development allows for the epidermal barrier to be formed *in utero* one day earlier than in wild-type mice (Jaubert et al., 2003). Similarly, it was shown that the ectopic expression of *Klf5* during development in mice results in reduced numbers of hair follicles on the torso and a lack of hair follicles on the tail, as well as abnormal epidermal development and differentiation (Sur et al., 2006). Although KLF4 and KLF5 thus appear to be crucial for skin barrier function, future studies need to focus on their function in the formation of the epidermis.

Central nervous system development

Global gene expression analyses suggest that several KLFs are implicated in the development of the central nervous system (CNS):

Klf2, 3, 4, 6, 7, 9, 11, 12 and 13 (Qin et al., 2011). However, only a few KLFs have been well characterized during CNS development. The expression of *Klf4*, for example, is enriched in fetal hypothalamic thyrotropin-releasing hormone neurons at E15.0, peaking at the neonate stage and P7, and then decreasing in adult (Qin et al., 2011). This downregulation of *Klf4* during development and in differentiated neurons is necessary for brain development and homeostasis (Qin et al., 2011). Interestingly, the timing of *Klf4* induction during embryogenesis coincides with an increase in the biosynthesis of thyrotropin-releasing hormone (TRH), and further experiments have characterized the role of KLF4 in regulating TRH expression in hypothalamic neurons (Pérez-Monter et al., 2011). Recently, KLF4 was also shown to play an important role in cerebellar development as well as in granule cell proliferation between E13.5 and E15.5 in mice (Zhang et al., 2015). In addition, analyses of *Klf4*^{-/-} mice show that PAX6 – a marker for granule cells – is reduced at E13.5 and completely absent at E15.5, but is re-expressed at E16.5 and E18.5 (Zhang et al., 2015). KLF6, by contrast, is expressed strongly in the nervous system during embryogenesis and appears to play a role in neural tube development (Laub et al., 2001b). Consequently, one of the key anatomical anomalies in *Klf6*^{-/-} mice is incomplete neural tube closure (Matsumoto et al., 2006).

The expression of KLF7 has also been closely examined in the developing nervous system of mouse embryos. One study (Lei et al., 2001) showed that *Klf7* is expressed starting at E8.5 in the trigeminal ganglion, the VII-VIII neural crest complex, and the subventricular neuroepithelium of both forebrain and hindbrain regions. At E11.5, *Klf7* expression is detected in the neural crest-derived sensory nervous system and, at E15.5, in the brain, spinal cord, retinal neuroepithelium and the inferior XI/X complex. This study also demonstrated that *Klf7* is co-expressed with the receptor for nerve growth factor (TrkA; NTRK1) and directly regulates its expression in the peripheral nervous system. Subsequent studies demonstrated that *Klf7* expression commences at about E9.5, is maximal at about E11.5, and declines in later stages of development (Laub et al., 2001a). At E9.5, *Klf7* expression in the CNS and peripheral nervous system closely correlates with that of the neurospecific gene *Neurod1*. By E11.5, *Klf7* is intensely expressed in the fore-, mid- and hindbrain, and in the trigeminal, geniculate, vestibulocochlear, petrosal, superior, jugular, nodose, accessory and dorsal root ganglia. In the neural tube at E11.5, *Klf7* is expressed distinctly in the mantle zone, where postmitotic neuroblasts are located, and colocalizes with markers for neuronal differentiation [e.g. NeuN (RBFOX3), TuJ (TUBB3), SCG10 (STMN2)]. Between E11.5 and E18.5, *Klf7* expression gradually decreases in the neural tube, while increasing in the dorsal root ganglia. Additionally, *Klf7* is detected in the neural retina at E17.5 and the olfactory epithelium at E16.5 (Laub et al., 2001a). In postnatal and adult animals, *Klf7* expression is confined to the cerebellum and dorsal root ganglia. Importantly, it was shown that *Klf7*^{-/-} mice die within 3 days of birth and are characterized by an absence of milk in the stomach, hypopnea, cyanosis and failed response to clamp stimulation of their tails (Laub et al., 2005). Furthermore, *Klf7*^{-/-} mice also exhibit severely hypoplastic olfactory bulbs (Laub et al., 2006), suggesting that KLF7 plays a role in the development of the olfactory system. Indeed, *Klf7* was previously detected in the olfactory epithelium at E16.5 (Laub et al., 2001a), and more recent time-lapse analyses of wild-type mouse embryos show that *Klf7* transcripts can be detected in the olfactory epithelium as early as E11.5. In addition, the loss of *Klf7* activity leads to reduced formation of neurites at E11.5 and impaired axon projection in the olfactory and visual systems, cerebral cortex and hippocampus at E12.5 (Laub et al., 2005).

Mechanistically, *Klf7* deletion correlates with a significant downregulation of p21^{WAF/CIP1} (CDKN1A) and a reduction in p27^{KIP1} (CDKN1B) protein levels in olfactory sensory neurons, suggesting that interaction between these factors is important for neuronal morphogenesis in the olfactory epithelium (Laub et al., 2005). Furthermore, expression arrays of olfactory sensory neurons from wild-type and *Klf7*^{-/-} embryos revealed that KLF7 might regulate olfactory marker protein (OMP) and the neural cell adhesion protein L1 (L1CAM) (Kajimura et al., 2007), both of which are proteins that are crucial for olfactory development.

It has also been shown that *Klf9* transcripts are upregulated by mature thyroid hormone in primary neurons and astrocytes, but not oligodendrocytes, which are derived from embryonic and neonatal mice brains, respectively (Denver et al., 1999). In addition, the induction of *Klf9* regulates thyroid hormone-mediated neurite extension and branching as well as neuronal differentiation (Denver et al., 1999). Further studies also showed that *Klf9* expression is transiently induced during the early postnatal phase due to neuronal activity (Scobie et al., 2009). Finally, ablation of *Klf9* impairs the maturation of dentate granule neurons during dentate gyrus development as well as during adult hippocampal neurogenesis (Scobie et al., 2009). Although further studies are required to ascertain the mechanism, these studies highlight that KLF9 is essential for neuronal development.

The role of KLFs in stem cells and regeneration

Klf2 was the first KLF transcript identified in mouse ESCs (Carlson et al., 2006). Soon after, Takahashi and Yamanaka reported that the overexpression of *Klf4* along with *c-Myc* (*Myc*), *Oct3/4* (*Pou5f1*) and *Sox2* could reprogram somatic cells into induced pluripotent stem cells (iPSCs) (Takahashi et al., 2007; Takahashi and Yamanaka, 2006). Since this groundbreaking discovery, intense efforts have been focused on understanding how KLF4 as well as other KLFs function in stem cells and regeneration.

KLFs in ESC self-renewal and differentiation

A number of studies have shown that multiple KLFs regulate the expression of transcription factors involved in maintaining pluripotency (Fig. 4). KLF2, KLF4 and KLF5 are associated with the pluripotent state of mouse ESCs, as triple knockdown of these factors renders cells for differentiation (Jiang et al., 2008). Subsequent studies demonstrated that KLF2, KLF4 and KLF5 can maintain an undifferentiated state in mouse ESCs and can reprogram epiblast-derived stem cells (EpiSCs) into iPSCs when overexpressed (Jeon et al., 2016). In addition, KLF2, KLF4 and KLF5 were demonstrated to occupy the promoter regions of genes encoding key pluripotency factors (*Oct4*, *Sox2* and *Nanog*) and, in turn, these pluripotency factors were shown to occupy the promoters of the genes encoding these KLFs, thereby suggesting an internal regulatory circuit within mouse ESCs (Jiang et al., 2008). Further analysis showed that *Klf2* is regulated by OCT4, whereas *Klf4* and *Klf5* are regulated by OCT4 and the LIF/STAT3 pathway (Hall et al., 2009). In addition, KLF2, but not KLF4, exhibits clonogenic capacity, maintains undifferentiated ESCs in the genetic absence of STAT3, and confers resistance to bone morphogenetic protein-induced differentiation (Hall et al., 2009). In contrast, *Klf5*^{-/-} ESCs can maintain pluripotency but show increased expression of differentiation-related genes and exhibit frequent and spontaneous differentiation. The overexpression of other KLFs, with the exception of KLF9 and KLF10, in ESCs demonstrated that they exhibit increased binding affinity to downstream regulatory genes similar to those bound by KLF2, KLF4 and KLF5 (Jeon et al., 2016). Further

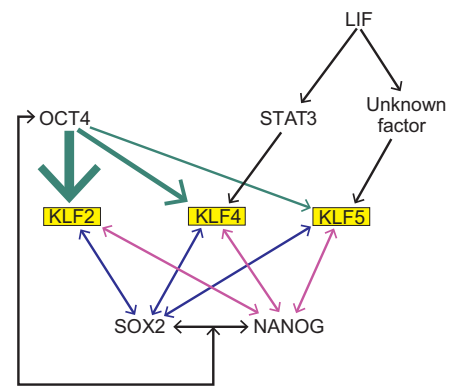


Fig. 4. KLFs and pluripotency. Schematic summarizing some of the regulatory interactions between KLF2, KLF4, KLF5 and factors involved in pluripotency in iPSCs. Interactions are based on findings reported by Jiang et al. (2008) and Hall et al. (2009). Arrows indicate induction of expression, with the thickness of arrows indicating the level of induction.

expression profiling performed during the differentiation of mouse ESCs under conditions that recapitulate differentiation *in vivo* allowed for the identification of three distinctly expressed KLF groups: (1) *Klf2*, *Klf4*, *Klf5* and *Klf9*, which show high levels of expression in the undifferentiated state and are rapidly downregulated within 3 days of differentiation; (2) *Klf1*, *Klf3* and *Klf16*, which are upregulated upon ESC differentiation; and (3) *Klf6*, *Klf7*, *Klf8*, *Klf10-Klf15*, the expression of which is unaffected by ESC differentiation (Bruce et al., 2007). Based on these data, it is postulated that competition among KLFs for occupancy of the promoter elements (CACCC boxes) probably determines self-renewal or progression towards differentiation. Interestingly, KLF1, KLF3, KLF6, KLF7 and KLF8 are not sufficient to maintain the self-renewal of mouse ESCs, despite their ability to bind to *Nanog* regulatory regions (Jeon et al., 2016).

Although most studies have focused on mouse ESCs, some approaches have attempted to understand the function of KLFs in human ESCs. In comparison with mouse ESCs, human hESCs exhibit low levels of *KLF2*, *KLF4* and *KLF5* expression that steadily increase upon differentiation (Cai et al., 2010), suggesting that mouse and human ESCs use distinct regulatory networks. This is potentially due to functional differences between these cells: human ESCs are more similar to mouse EpiSCs, which are derived from the late epiblast layer of post-implantation embryos, than to mouse ESCs, which originate from the ICM of blastocysts (Cai et al., 2010). Importantly, KLFs appear to play important roles in both the earlier 'naive' state and the 'primed' state (Kim et al., 2008). Naive mESCs are stabilized by the LIF/STAT3 pathway whereas basic fibroblast growth factor (bFGF) and TGFβ/activin signaling results in their destabilization. In comparison, bFGF and TGFβ/activin signaling are required for mouse EpiSC stabilization. Furthermore, in naive, mESCs, KLF2, KLF4 and KLF5 are expressed concurrently with NANOG and ESRRβ. However, their levels are downregulated during progression to the post-implantation epiblast ('primed') state (Hanna et al., 2010). Conversely, overexpression of *Klf2* or *Klf4* is sufficient for induction of naive pluripotency (Blakeley et al., 2015). Despite these differences between mouse and human ESCs, the generation of human iPSCs was accomplished using the same factors as for mouse iPSCs: *Oct4*, *Sox2*, *c-Myc* and *Klf4* (Kim et al., 2008; Maffioletti et al., 2015; Moad et al., 2013; Park et al., 2008; Takahashi et al., 2007).

KLFs and reprogramming

The ability to reprogram numerous somatic cell types, from both mice and humans, into iPSCs has provided exciting opportunities for

regenerative medicine, for studying diseases, and for drug discovery (Singh et al., 2015). Indeed, the *Oct3/4*, *Sox2*, *Klf4* and *c-Myc* (OSKM) ‘cocktail’ or variations of it in multiple tissues of murine and human origin (fetal, neonatal and adult fibroblasts, primary hepatocytes, adult neuronal stem cells, menstrual blood stromal cell, prostate, bladder and ureter cells) can reprogram cells into iPSCs, with possible further differentiation into specialized cells such as gastric epithelial cells, lymphocytes, erythrocytes, myeloid cells, hepatocyte-like cells, retinal cells and melanocytes (Aoi et al., 2008; Kim et al., 2008; Kitada et al., 2012; Li et al., 2011; Park et al., 2008; Seiler et al., 2011; Takahashi et al., 2007; Takahashi and Yamanaka, 2006; Yang et al., 2011). As mentioned above, KLF4 has been identified as a factor that can reprogram mouse and human fibroblasts to induce their pluripotent state (Takahashi et al., 2007; Takahashi and Yamanaka, 2006). Initially, Takahashi and Yamanaka used a genetic approach to screen 24 pre-selected factors that had previously been shown to either participate in the maintenance of pluripotency at the embryonic stage or be upregulated in tumors and contribute to the ESC phenotype. The introduction of single factors into fibroblasts did not induce pluripotency, but by using a combination of the pre-selected factors they could induce a pluripotent state. By withdrawing factors individually from the combination, they were able to identify those factors that were essential for the induction of pluripotency in somatic cells. Using this approach, they determined that OCT4, SOX2, KLF4 and c-MYC play an important role in the generation of iPSCs from somatic cells.

Their genomic analyses of iPSCs also demonstrated that they expressed *Myb*, *Kit*, *Gdf3*, *Zic3*, *Dppa3*, *Dppa4*, *Dppa5* (*Dppa5a*), *Nanog*, *Sox2*, *Esrrb*, *Rex1* (*Zfp42*), *Dnmt3a*, *Dnmt3b*, *Dnmt3l*, *Utl1*, *Tcl1*, and the LIF receptor gene, all of which are commonly expressed in mESCs (Takahashi and Yamanaka, 2006). However, the levels of expression of these genes varied between iPSCs and mESCs. Additionally, Nishimura and colleagues showed that KLF4 dosage correlates with the level of pluripotency induction (Nishimura et al., 2014); however, the precise mechanism by which KLF4 induces pluripotency is not very well understood. It has been postulated that KLF4 plays a dual role in this process, by repressing markers of differentiation and facilitating the expression of pluripotency genes. Specifically, it has been shown that during the first phase, KLF4 regulates genes associated with differentiation, such as *Tgfb1*, *Pdgfra* and *Col6a1* and, at the later stage of reprogramming, KLF4, upregulates genes associated with pluripotency (*Oct4*, *Tdgl1* and *Klf5*) (Polo et al., 2012). For instance, in iPSCs, the levels of p53 (TRP53) – a known repressor of *Nanog* – are lower in comparison with those in somatic cells, and previous studies showed that KLF4 negatively regulates p53 during differentiation. It has also been shown that KLF4 induces the expression of *Nanog* by binding to its promoter, thus preventing ESC differentiation (Zhang et al., 2010). Another study demonstrated that UTX (KDM6A; a H3K27 demethylase enzyme) interacts with OCT4, SOX2 and KLF4, and that this results in removal of the repressive H3K27me3 mark from early activated pluripotency genes such as *Fgf4*, *Sall4*, *Sall1* and *Utl1* (Mansour et al., 2012). Finally, it was demonstrated that during the reprogramming of human fibroblasts to iPSCs, OCT4, SOX2 and KLF4 bind closed chromatin with c-Myc enhancing these interactions (Soufi et al., 2012). Together, these studies highlight the importance of KLF4 in the reprogramming process and the versatility of this system for understanding KLF function.

KLFs and regeneration

Given their roles in controlling self-renewal and/or cell differentiation, it is not surprising that KLFs have been implicated in the regenerative

processes and, hence, are being targeted for use in regenerative medicine. For example, the prospect of overexpressing KLF4, SOX9 and c-MYC to direct the reprogramming of adult dermal fibroblasts into polygonal chondrogenic cells, independent of iPSCs, for cartilage regeneration has been previously proposed (Hiramatsu et al., 2011; Outani et al., 2011). In addition, it has been shown in a mouse model that epidermal multipotent stem cells express *Klf4* and that deletion of *Klf4* reduces the stem cell population and self-renewal efficiency of these stem cells (Li et al., 2012). For instance, KLF4 has been shown to contribute to skin integrity and *Klf4*^{-/-} mice have significantly delayed wound healing post-injury compared with wild-type mice, suggesting a crucial role for KLF4 in cutaneous wound healing (Li et al., 2012). Another factor, KLF6, also known as tissue remodeling factor, was shown in mice to promote vascular repair after bilateral endoluminal injury to the common femoral artery. This enhanced repair process was accompanied by increased activity of matrix metalloproteinase 14, endoglin and activin receptor-like kinase 1 (ACVRL1), which are involved in angiogenesis and vascular remodeling (Gallardo-Vara et al., 2016; Garrido-Martin et al., 2013). The potential role of KLFs in axonal regeneration has also attracted a lot of attention. For instance, studies in rats have shown that KLF4 and KLF9 are repressors of axon growth in retinal ganglion cells (RGCs), whereas KLF6 and KLF7 are capable of stimulating neurite growth in these cells (Moore et al., 2009). Furthermore, KLF7 induction in the adult rat corticospinal tract improves axon regeneration in conjunction with upregulation of Trk neurotrophin receptors (Blackmore et al., 2012), and KLF9 was revealed as a factor that contributes to myelin regeneration in the mouse cortex following cuprizone-mediated demyelination, acting via thyroid hormone pathway induction (Dugas et al., 2012). Overall, these various studies highlight the therapeutic potential of KLFs in regenerative medicine, although further studies are needed to dissect their precise roles and mechanisms of action.

The role of KLFs in mammalian diseases

Accumulating evidence in the last decade has demonstrated that KLFs play a vital role in the etiology and progression of many mammalian diseases (summarized in Fig. 5), ranging from cardiovascular disease to various types of neuronal disorders. The function of KLFs in cancer biology (Box 1) has also been well studied (reviewed by Tetreault et al., 2013), and therapeutic strategies to modulate the expression of KLFs and/or its downstream effectors are the focus of current studies. Below, we discuss how KLFs have been implicated in some of these diseases and disorders, focusing on those that are linked to the aforementioned developmental roles for KLFs.

KLFs in hematopoietic disorders

KLF1 is essential for erythropoiesis and, as such, has been implicated in disorders that involve RBC generation in adults. For example, it was demonstrated that KLF1-mediated erythrocyte differentiation is essential for RBC generation, and that the suppression of *Klf1* expression by inhibiting IL-2 (IL2) signaling in mice contributes to failed erythropoiesis and eventual anemia in mice (Chopra et al., 2015). In addition, dominant mutants and haploinsufficiency in mouse and human KLF1 contribute to altered erythropoiesis, leading to several hematological disorders such as neonatal anemia and congenital dyserythropoietic anemia (Siatecka and Bieker, 2011). Because β -globin levels are reduced and embryonic globin levels are increased in *Klf1*^{-/-} mice (Bieker, 2010), it has been postulated that the induction of human γ -globin levels by knockdown of *KLF1* could serve as a viable therapeutic strategy for individuals with sickle-cell anemia or β -thalassemia (Bieker, 2010).

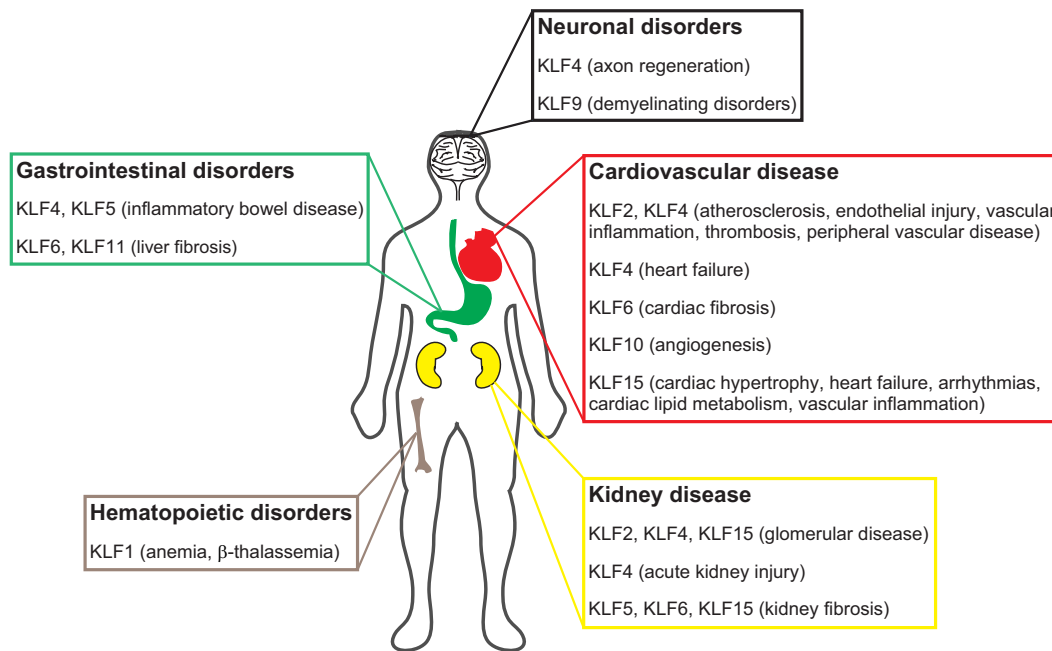


Fig. 5. Summary of the roles of KLFs in human disease. Diagram summarizing the specific roles reported for KLFs in neuronal disorders, cardiovascular diseases, kidney diseases, gastrointestinal disorders and hematopoietic disorders. It should be noted that the involvement of KLFs in various types of cancer is not included in this schematic.

KLFs in cardiovascular disease, obesity, and metabolic syndrome

As mentioned above, KLF2 is vital for endothelial cell homeostasis: it regulates leukocyte adhesion to the endothelium, thrombotic function, and endothelial proliferation, migration and angiogenesis. Based on these diverse roles, loss of *Klf2* expression has been implicated in atherosclerosis and thrombotic angiopathy (Agustian et al., 2013; Atkins et al., 2008; Boon et al., 2011). Furthermore, the pleiotropic effects of statins in preventing atherosclerosis might be directly mediated by KLF2 in endothelial cells (Tuuminen et al., 2013). Interestingly, the endothelial lineage-specific expression

of *Klf2* in bone marrow-derived mononuclear cells induces neovascularization in ischemic murine models, suggesting that KLF2 might have a therapeutic role in diseases with impaired neovascularization such as atherosclerosis (Boon et al., 2011). In addition, KLF2 was reported as an atheroprotective factor that regulates primary macrophage foam cell formation (Atkins et al., 2008).

A number of recent studies have also highlighted anti-inflammatory and anti-thrombotic roles for KLF4 in vascular biology (Hamik et al., 2007), which have direct implications for understanding the progression of atherosclerosis. The conditional knockout of *Klf4* in smooth muscle cells (SMCs), for example, specifically increases the stability of atherosclerotic plaques and fibrous cap thickness in murine models of atherosclerosis (Shankman et al., 2015), although further studies are needed to decipher the role of KLF4 in mediating potential crosstalk between SMCs and endothelial cells in atherosclerosis. Atherosclerosis and peripheral vascular disease can also lead to neovascularization due to a chronic ischemic state, and recent studies demonstrate that KLF10 mediates the TGF β 1-induced generation of bone marrow-derived proangiogenic cells in the setting of ischemic injury (Wara et al., 2011), again highlighting a potential target for therapy in these conditions.

A number of KLFs have also been associated with heart failure. For example, reduction of myocardial *Klf4* increases susceptibility to heart failure (Liao et al., 2010), which mechanistically might be due to a loss of transcriptional control of mitochondrial biogenesis (Liao et al., 2015). Furthermore, the loss of *Klf15* in mice increases susceptibility to heart failure and aortic aneurysmal formation in a p53- and p300 acetyltransferase-dependent manner (Haldar et al., 2010). In addition, recent findings have revealed that KLF15 inhibits vascular smooth muscle activation by inhibiting NF- κ B activity (Lu et al., 2013). Finally, recent studies demonstrate that KLF15 is a key regulator of cardiac lipid metabolism (Prosdocimo et al., 2014) and circadian mediated arrhythmogenesis (Jeyaraj et al., 2012).

Box 1. KLFs and cancer

As KLFs play a vital role in mammalian development, stem cell biology, and cellular regeneration, it is not surprising that they have also been implicated in cancer biology. In fact, KLFs are associated with various malignancies (reviewed by Tetreault et al., 2013). Mechanistically, KLFs have a direct impact on almost every aspect of cancer biology: regulation of the cell cycle, apoptosis, Wnt/ β -catenin signaling, RAS signaling, NOTCH signaling, oncogenic transformation, tumor metastasis, and microenvironment (Tetreault et al., 2013). For instance, KLF4, a key regulator of normal cell proliferation, inhibits tumor growth in various cancers such as pancreatic, colorectal, neuroblastoma and lung cancers by inducing the expression of CDK inhibitors and inhibiting cyclin D1 and FOXM1 expression (Kong et al., 2013; Shum et al., 2013; Wei et al., 2008; Zammarchi et al., 2011). Conversely, KLF5 promotes tumor cell growth by upregulating CCNA2, CDT1 and E2F3, all of which are key cell cycle genes (Liu et al., 2011; Takagi et al., 2012). Furthermore, loss of KLF5 expression in colon cancer cells reduces activation of Wnt/ β -catenin signaling, a key pathway in tumor cell proliferation (McConnell et al., 2009; Nandan et al., 2008). Interestingly, splice variants of KLF6 have also been implicated in the progression of non-small cell lung cancer as well as prostate cancer by reducing the expression of CDKN1A (Narla et al., 2005). Collectively, these studies suggest that specific KLFs might potentially serve as therapeutic targets when treating the progression of cancer.

Several KLFs have recently been linked to metabolic syndromes. KLF7 inhibits transcriptional inducers of human adipogenesis (Kanazawa et al., 2005) and modulates insulin sensitivity in human pancreatic β cells and skeletal muscle cells (Kawamura et al., 2006). Furthermore, it has been reported that variants in *KLF7* are protective against type 2 diabetes mellitus in Japanese and Danish patient cohorts (Kanazawa et al., 2005; Zobel et al., 2009). In addition, multiple laboratories have reported that KLF15 induces mouse adipocyte differentiation by increasing the expression of PPAR γ (Mori et al., 2005), which has direct implications when correlated with the glucocorticoid-induced effects on mouse adipogenesis (Asada et al., 2011). Interestingly, all of these findings are based on tissue-specific constitutive knockout murine models, highlighting specific and important roles for KLFs in development and disease.

KLFs in gastrointestinal disorders

The role of KLF4 and KLF5 in intestinal disorders has been well studied (McConnell and Yang, 2010). In addition, *Klf9* null mice exhibit dysregulated intestinal crypt cell proliferation and villus cell migration, which contribute to loss of intestinal barrier function in mice (Simmen et al., 2007). Furthermore, the predominant expression of KLF9 occurs in mouse intestinal smooth muscles, thereby suggesting potential crosstalk between intestinal smooth muscle and epithelial cells that might contribute to maintenance of the mouse intestinal barrier (Simmen et al., 2007).

KLFs have also been implicated in aberrant liver function. For instance, KLF6-mediated upregulation of the TGF β pathway is linked to the progression of mouse liver fibrosis (Friedman, 2000; Kawada, 2011). Furthermore, functional polymorphisms in *KLF6* are associated with progression of nonalcoholic fatty liver disease in humans (Miele et al., 2008). The modulation of PPAR α activity by KLF6 in mice contributes to hepatic glucose and lipid metabolism in fatty liver disease (Bechmann et al., 2013). In addition, KLF11 regulates collagen gene expression by silencing heterochromatin protein 1 expression and, consequently, *Klf11* null mice exhibit increased liver fibrosis due to unchecked collagen deposition (Mathison et al., 2013). Combined, these data suggest an essential role for KLFs in gastrointestinal disorders.

KLFs in kidney disease

In the last decade, several studies of the functional role of KLFs in kidney disease have been reported. Damage to the glomerular filtration barrier is the predominant consequence of kidney disease, and several recent studies demonstrate the significance of KLFs in filtration barrier maintenance in the setting of injury. For instance, the loss of endothelial-specific *Klf2* exacerbates the progression of diabetic nephropathy and chronic kidney disease (Zhong et al., 2015, 2016). In addition, the constitutive knockdown of *Klf15* in visceral epithelial cells (podocytes) of the glomerulus leads to the loss of stable differentiation markers and key actin cytoskeleton elements leading to podocyte injury and eventual kidney disease in mice (Mallipattu et al., 2016, 2012; Zhong et al., 2015). Interestingly, it was also reported that salutary benefits of glucocorticoids in the kidney are mediated by KLF15 (Mallipattu et al., 2016). Furthermore, it was recently reported that transcriptional regulation of KLF6 enhances mitochondrial cytochrome oxidase activity in the setting of podocyte stress (Mallipattu et al., 2015), and KLF4 increases the expression of genes involved in maintenance of the renal filtration barrier by reducing methylation in their promoter region (Hayashi et al., 2014). Finally, haploinsufficiency of *Klf5* in collecting duct cells exacerbates the inflammatory response in murine models of

kidney fibrosis (Fujiu et al., 2011). Although the role of KLFs in kidney disease were interrogated in the adult phase, the utilization of constitutive knockout models suggests that changes in KLF expression during kidney development might have a potential impact on the kidney phenotype in adults.

KLFs in neuronal disorders

As mentioned earlier, KLF9 is implicated in neuronal development, and recent studies have also determined that KLF9 regulates neuronal plasticity by mediating the stress-induced effects of glucocorticoids in hippocampal neurons (Bagamasbad et al., 2012; Bonett et al., 2009). In addition, thyroid hormone induced oligodendrocyte differentiation and myelin regeneration are regulated by KLF9, which has direct implications in demyelinating disorders such as multiple sclerosis (Dugas et al., 2012). Furthermore, STAT3-induced axon regeneration is crucial for promoting repair in certain neuronal disorders and, interestingly, it was shown that the loss of KLF4 results in the activation of JAK/STAT3 signaling, thereby leading to regeneration of axons in the setting of injury (Qin et al., 2013). Collectively, these studies suggest that modulating KLF expression contributes to neuronal plasticity, a finding that has implications for furthering our understanding of neuronal disorders and diseases.

Conclusions

In the last decade, there has been a dramatic rise in the number of publications that are centered on KLFs. Genetic knockouts of select members of the KLF family in various model organisms have demonstrated many interesting developmental phenotypes. In addition, several groups have highlighted essential roles for KLFs in cellular regeneration in many tissue types. Finally, as we have summarized here, KLFs have a direct impact on human diseases due to their key roles in development, highlighting potential areas that are ripe for future studies.

Although the field of KLFs has advanced dramatically in the last decade, much more work lies ahead. For instance, the mechanisms by which specific KLFs impact embryogenesis require further exploration. Moreover, the impact of changes in KLF expression during development and in the adult remains a mystery in many organ systems. Finally, as a field we need to clarify the redundant as well as the competitive functions of KLFs, both during development as well as for maintaining a differentiated phenotype in the adult state. In particular, the mechanism by which KLFs contribute to pluripotency and regeneration mandate further studies, especially for neurons and kidney cells that harbor low regenerative potential after injury. Finally, the field remains unclear on whether these transcription factors with diverse roles can serve as a viable target for therapy with minimal off-target effects. To address this, we believe efforts should focus on a system-based interdisciplinary approach combining our understanding of specific KLF functions during normal development with our knowledge of how these functions could be implicated in homeostasis, disease and the prevention of disease.

Acknowledgements

We thank Dr William E. Diehl (University of Massachusetts Medical School) for the analysis of the phylogenetic relationship between human and mouse KLF family members provided in Fig. 2.

Competing interests

The authors declare no competing or financial interests.

Funding

This work was supported by funds from the National Institutes of Health (V.W.Y. and S.K.M.), the American Heart Association (S.K.M.), and Dialysis Clinic, Inc. (S.K.M.). Deposited in PMC for release after 12 months.

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