# Chapter 5
# Developmental Expression of Krüppel-like Factors

**Yizeng Yang and Jonathan P. Katz**

**Abstract** Krüppel-like factors (KLFs) are members of an emerging family of DNA-binding transcriptional regulators with critical roles in development, differentiation, and a number of other key cellular processes. The KLF family contains at least 17 members, many with overlapping patterns of expression and function, and all linked by a similar DNA-binding element. During development, KLFs may function as transcriptional activators or repressors depending on the cell or tissue context or even the stage of development. Here, we provide a brief introduction to the expression patterns and established roles of the KLFs in development. By examining these patterns and functions, we uncover a number of themes that are explored in detail in ensuing chapters.

## Introduction

Members of the KLF family of transcription factors play an essential role during embryonic development and cell-specific lineage differentiation. In many cases, the expression of these factors during embryogenesis is spatiotemporally restricted and regulated. By binding to "CACCC" elements in the regulatory regions of specific target genes, KLFs control multiple intracellular signaling pathways important for cellular proliferation and differentiation, organogenesis, and stem cell commitment. Recently, the role of the KLFs in development has been expanded by the identification of a function for these factors in somatic cell reprogramming to induced pluripotent stem (iPS) cells (Jiang et al. 2008; Okita et al. 2007). Many of the KLFs can be either transcriptional activators or repressors depending on the cell or tissue context or even the developmental stage. In this review, we provide a brief introduction to the expression and the established roles of the KLFs during development (Table 1).

Y. Yang and J.P. Katz (✉)
Division of Gastroenterology, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA

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**Table 1** Developmental expression patterns of KLFs

| Name (alternative) | Developmental expression pattern | Major gene knockout phenotypes | References |
|---|---|---|---|
| KLF1 (EKLF) | Erythroid cells, yolk sac, fetal liver | Defective hematopoiesis and lethal β-thalassemia around E14 | Nuez et al. 1995; Perkins et al. 1995 |
| KLF2 (LKLF) | Blood vessels, lungs, T lymphocytes, erythroid cells, white adipose tissue | Death from severe hemorrhage from E11.5 to 14.5; delayed lung development; defective T-lymphocyte and adipocyte differentiation | Kuo et al. 1997a, 1997b; Wani et al. 1999; Wu et al. 2005 |
| KLF3 (BKLF) | Embryonic hematopoietic tissue, brain, limb buds | Decreased white adipose tissue; report of myeloproliferative disorders and defective hematopoesis | Sue et al. 2008; Turner and Crossley 1999 |
| KLF4 (GKLF, EZF) | Gut epithelia, thymus, skin, testes | Lethal perinatal dehydration due to defective skin barrier; abnormal differentiation of colonic goblet cells | Katz et al. 2002; Segre et al. 1999 |
| KLF5 (IKLF, BTEB2) | Gut epithelia, skin, vascular smooth muscles, heart, skeleton, white adipose tissue | Homozygous mice die at E8.5; heterozygous mice show defects of smooth muscle, arteries, cardiac hypertrophy, and fibrosis in response to stress; deficiencies in white adipose tissue development; skeletal growth retardation | Oishi et al. 2005; Shindo et al. 2002, 2008 |
| KLF6 (Zf9, CPEP) | Extraembryonic tissues, nervous system, cornea, lung buds, ureteric bud, heart, liver, intestinal mucosa; mesenchyme surrounding neural tube and developing brain | Lethal failure of hematopoiesis by E12.5 and poorly organized yolk sac vacularity | Fischer et al. 2001; Laub et al. 2001b; Matsumoto et al. 2006 |
| KLF7 (UKLF) | Predominantly in central and peripheral nervous systems; lower levels throughout embryo at later stages | Neonatal lethality by P3 with defects in selected regions of the nervous system | Laub et al. 2001a, 2005 |
| KLF8 | Placenta; otherwise, not described | – | van Vliet et al. 2000 |
| KLF9 (BTEB) | Broadly expressed; high levels in developing brain, thymus, epithelia, and smooth muscle of gut and bladder, vertebrae, and cartilage primordia | Normal lifespan but uterine hypoplasia and defects in parturition in females; impairment of specific behavioral activities; shorter small intestinal villi | Martin et al. 2001; Morita et al. 2003; Simmen et al. 2004, 2007 |

| | | | |
|---|---|---|---|
| KLF10 (TIEG1, mGIF) | Broadly expressed | Normal lifespan but osteopenia in females, cardiac hypertrophy in males, defects in the mechanical properties and healing of tendons | Bensamoun et al. 2006; Hawse et al. 2008; Rajamannan et al. 2007; Subramaniam et al. 1995, 2005; Tsubone et al. 2006; Yajima et al. 1997; |
| KLF11 (FKLF, TIEG2) | Ubiquitous in adult; expression in erythroid cells in fetal liver; other developmental expression not described | Normal development, fertility, and lifespan | Asano et al. 1999; Cook et al. 1998; Song et al. 2005 |
| KLF12 (AP-2rep) | Some expression in developing brain and kidneys; very low levels in adult liver and lung | — | Imhof et al. 1999; Suda et al. 2006 |
| KLF13 (RFLAT-1, BTEB3) | Broadly expressed with high levels temporally in heart, brain, bladder, gut, thymus, epidermis | Some decreased viability by 3 weeks of age; enlarged thymus and spleen; decreased numbers of circulating erythrocytes; increased survival and decreased apoptosis of thymocytes | Gordon et al. 2008; Martin et al. 2001; Scohy et al. 2000; Zhou et al. 2007 |
| KLF14 | Ubiquitous expression | – | Parker-Katiraee et al. 2007; Scohy et al. 2000 |
| KLF15 (KKLF) | Minimal cardiac expression during development; other developmental expression not described | Fertile, normal viability; cardiac fibrosis and hypertrophy in response to stress; fasting hypoglycemia | Fisch et al. 2007; Gray et al. 2007; Uchida et al. 2000; Wang et al. 2008 |
| KLF16 (DRRF, BTEB4) | Highly expressed in certain regions of developing brain; lesser expression in thymus, duodenum, kidney, liver, heart, bladder, and lung | — | D'Souza et al. 2002; Hwang et al. 2001 |
| KLF17 (Zfp393) | Spermatids and oocytes; other developmental expression not described | — | van Vliet et al. 2006; Yan et al. 2002 |

## KLFs in Development

### *KLF1*

Klf1 was first identified as an erythroid lineage-specific zinc finger transcription factor, named erythroid Krüppel-like factor (EKLF) (Miller and Bieker 1993). Klf1 plays a essential role in the γ-hemoglobin to β-hemoglobin switch during fetal development, and inactivation of *Klf1* in mice results in defective hematopoiesis in fetal liver and death from anemia, with a deficit in β-globin expression by E16, providing a model for β-thalassemia (Miller and Bieker 1993; Nuez et al. 1995; Perkins et al. 1995). *Klf1* is expressed in the yolk sac as early as E7.5. Following the development of the hematopoietic system, *Klf1* appears in fetal liver and the mesoderm near the hindgut toward the dorsal aorta at E10.5, and by E14.5 *Klf1* is restricted to the fetal liver. Klf1 is not required for yolk sac hematopoiesis or expansion of erythroid progenitors (Perkins et al. 1995) but is required for the last steps of erythroid differentiation (Drissen et al. 2005). Interestingly, *Klf1* is down-regulated in megakaryocytes and inhibits the formation of megakaryocytes while stimulating erythroid differentiation (Frontelo et al. 2007).

### *KLF2*

Klf2 is expressed temporally during early embryonic development and plays an important role in the development of the lungs, blood vessels, T lymphocytes, and adipocytes (Kuo et al. 1997a, 1997b; Wani et al. 1999; Wu et al. 2005). In the adult, *Klf2* is highly expressed in the lung and thus was initially identified as lung Krüppel-like factor (LKLF) (Anderson et al. 1995). Expression of *Klf2* is first seen in vascular endothelial cells throughout the developing mouse embryo at E9.5 (Anderson et al. 1995; Kuo et al. 1997a; Wani et al. 1998). *Klf2* is expressed at high levels between E9.5 and E12.5, especially in the umbilical arteries and veins, a critical time for both angiogenesis and blood vessel wall stabilization. At E14.5, *Klf2* continues to be expressed in the vasculature and appears in the lung buds, vertebral column, and the bony structures of the head and rib cage. By E18.5, *Klf2* is expressed abundantly in the lungs and in blood vessels. Mice with homozygous deletion of *Klf2* exhibit growth retardation and craniofacial abnormalities, and they die between E11.5 and 14.5 from severe intraamniotic and intraembryonic hemorrhage (Kuo et al. 1997a). Notably, blood vessels in these mice have an abnormally thin tunica media. *Klf2* null mice also have defects in their lung development (Wani et al. 1999). In addition, *Klf2* is developmentally induced during single-positive T-lymphocyte maturation, and *Klf2*-deficient T cells are spontaneously activated (Kuo et al. 1997b). *Klf2* also inhibits adipogenesis by maintaining a preadipocyte state (Wu et al. 2005).

## *KLF3*

KLF3, or basic Krüppel-like factor (BKLF), is a highly basic KLF first identified in murine yolk sac and fetal liver erythroid cells (Crossley et al. 1996). *Klf3* is highly expressed in embryonic hematopoietic tissues, brain, and several other tissues. It appears in the midbrain and anterior hindbrain at E8.5 and in the ventral anterior half of the embryo, midbrain–hindbrain junction, ventral midbrain, diencephalon, and forebrain at E9. At E10.5, expression becomes more widespread, with some staining of the developing limb buds (Crossley et al. 1996). *Klf3*-deficient mice are smaller than their littermates, and adipocyte differentiation is altered in murine embryonic fibroblasts from *Klf3* knockout mice (Sue et al. 2008). Myeloproliferative disorders and abnormalities in hematopoiesis have also been reported (Turner and Crossley 1999).

## *KLF4*

KLF4 is highly expressed in postproliferative epithelial cells of the gut and the epidermis and was thus named gut-enriched Krüppel-like factor (GKLF) and epithelial zinc finger (EZF) when it was initially characterized by two independent groups (Garrett-Sinha et al. 1996; Shields et al. 1996). *Klf4* mRNA is found in the epidermal layer of the skin and in epithelial cells in the tongue, palate, esophagus, stomach, and colon of newborn and adult mice; and it is enriched in epithelial cells of the middle to upper colonic crypts, a region of cellular differentiation (Ton-That et al. 1997). *Klf4* transcript is initially low in the whole embryo but begins to rise around E13, peaking on E17, the period in which the intestinal epithelium undergoes major transition from a pseudostratified to a columnar epithelium, before decreasing prior to birth. Klf4 is seen in mesenchymal cells of the nasal prominence and first branchial arch, mesenchymal cells surrounding the cartilaginous primordia of the skeleton, and the metanephric kidney at E11.5, and it is upregulated in thymus epithelium at E18 (Garrett-Sinha et al. 1996; Panigada et al. 1999). Strong Klf4 expression is also seen in postmeiotic germ cells undergoing final differentiation into sperm cells in postnatal mouse testis (Behr and Kaestner 2002). Mice homozygous for a null allele of *Klf4* die shortly after birth due to apparent failure to establish proper skin barrier function and have a 90% decrease in the number of goblet cells in the colon (Katz et al. 2002; Segre et al. 1999). Klf4 has been identified as a critical regulator of pluripotency in embryonic stem cells and recently has been utilized, along with several other factors, to reprogram mouse and human somatic cells directly into pluripotent cells (induced pluripotent stem cells, or iPS cells) (Li et al. 2005b; Okita et al. 2007; Takahashi et al. 2007). This function in stem cells appears to be distinct from the role of KLF4 in a number of adult tissues and cell types (McConnell et al. 2007).

## *KLF5*

KLF5 (BTEB2) was initially cloned from a human placenta cDNA library using rat BTEB cDNA as a probe (Sogawa et al. 1993). Later, the murine homologue was identified and named intestinal-enriched Krüppel-like factor (IKLF) for its high level of expression in intestinal epithelia (Conkright et al. 1999). Temporal changes of *Klf5* expression during embryogenesis indicate that this gene is developmentally regulated (Ohnishi et al. 2000). *Klf5* transcript is abundant in the embryo at E7 (Conkright et al. 1999) and is seen in the developing gastrointestinal tract by E10.5 (Conkright et al. 1999; Ohnishi et al. 2000). Klf5 mRNA is also detected in the E15.5 meninges, E16.5 epithelia of the trachea and bronchi, and the outer layer of the tongue, as well as in the developing epidermis. Progressively, Klf5 expression in the skin and gastrointestinal tract becomes localized to the proliferative compartments, such as the basal layer of the epidermis and the small intestinal crypts (Ohnishi et al. 2000). KLF5 is also abundantly expressed in embryonic vascular smooth muscles and is downregulated in adult vessels (Ogata et al. 2000). Homozygous null mice for *Klf5* die before E8.5, indicating an essential but unclear role for Klf5 in early embryonic development (Shindo et al. 2002). Heterozygotes appear grossly normal, but the arteries exhibit diminished levels of arterial wall thickening, angiogenesis, cardiac hypertrophy, and interstitial fibrosis in response to external stress. In addition, neonatal mice heterozygous for *Klf5* deletion exhibit a marked deficiency in white adipose tissue (Oishi et al. 2005) and show skeletal growth retardation with impaired cartilage matrix degradation (Shinoda et al. 2008). Klf5 also appears to be involved in the maintenance of self-renewal in embryonic stem cells and is expressed in mouse embryonic stem cells, blastocysts, and primordial germ cells (Parisi et al. 2008).

## *KLF6*

KLF6, also known as ZF9 or CPBP, was originally isolated from a cDNA library of human placenta (Koritschoner et al. 1997). Human KLF6 is expressed ubiquitously with a high level in the placenta and adult liver, lung, intestine, and prostate (Blanchon et al. 2001; Narla et al. 2001; Ratziu et al. 1998). KLF6 is also seen in the developing cornea of the 7-week-old fetus, mostly in the cytoplasm, becoming more nuclear after birth (Nakamura et al. 2007). In the mouse, *Klf6* is expressed in extraembryonic tissues at E10.5 and in undifferentiated mesenchyme surrounding the neural tube and brain vesicles by E11.5, with strong expression in the nervous system by E12.5 and low levels in the heart, ureteric bud, and lung buds (Fischer et al. 2001; Laub et al. 2001b). By E14.5, *Klf6* is nearly undetectable except in the ventral horn at the level of the forelimbs. Subsequently, very strong *Klf6* expression is seen between E16.5 and E18.5 in the intestinal mucosa and in the fetal liver between E14 and E20 (Laub et al. 2001b; Ratziu et al. 1998). Like some of the other KLFs, expression of KLF6 plays a role in preadipocyte differentiation, in this case promoting differentiation by inhibiting delta-like 1 (Li et al. 2005a).

Homozygous null mice for *Klf6* die by E12.5; they are small and pale with no obvious liver, have thin, poorly organized yolk sacs, and show significant defects in hematopoiesis (Matsumoto et al. 2006).

## *KLF7*

KLF7 was initially cloned from human vascular endothelial cells by the polymerase chain reaction (PCR) using degenerate oligonucleotides corresponding to the DNA-binding domain of KLF1 (Matsumoto et al. 1998). Given its broad, low-level expression in adult tissues, KLF7 was termed ubiquitous Krüppel-like factor (UKLF). However, the predominant developmental expression of mouse *Klf7* is in postmitotic neuroblasts of the developing central and peripheral nervous systems (Laub et al. 2001a). *Klf5* mRNA is first seen at E9.5 and is maximum around E11.5, with intense expression in the forebrain, midbrain, and hindbrain; the eye; and the trigeminal, geniculate, vestibulocochlear, petrosal, superior, jugular, nodose, accessory, and dorsal root ganglia. *Klf7* expression is maintained in the dorsal root ganglia from E11.5 to E18.5, whereas expression declines in the neural tube and low levels of expression are seen diffusely throughout the embryo. *Klf7* is also expressed in the olfactory epithelium at E16.5 and the neural retina at E17.5. Postnatally, *Klf7* expression is observed in a few regions of the brain but is later confined to the adult cerebellum, olfactory system, and dorsal root ganglia (Laub et al. 2001a). Loss of *Klf7* in mice leads to neonatal lethality, with 98.5% of pups dying within 3 days of birth (Laub et al. 2005). *Klf7* null mice have hypoplastic olfactory bulbs, with defects of axonal projections in the olfactory and visual systems, cerebral cortex, and hippocampus, as well as abnormalities of dendritic organization.

## *KLF8*

Human KLF8 (ZNF741) was first cloned by PCR from K562 cells, a human hematopoietic cell line (van Vliet et al. 2000). KLF8 is broadly expressed in human tissues, with greatest expression in kidney, heart, and placenta. Multiple KLF8 transcripts have been identified, and the relative levels of transcript expression appear to be similar in the various tissues. Little is known to date about *Klf8* expression during development, and a *Klf8* knockout has not been described.

## *KLF9*

*Klf9* (BTEB) was initially isolated from a rat liver cDNA library (Imataka et al. 1992). *Klf9* is widely expressed throughout mouse embryonic development, at least as early as E8 (Martin et al. 2001). By E11, *Klf9* is highly expressed in the

cephalic mesenchyme of the developing brain, the epithelia and smooth muscle of the gut and bladder, and the skin epidermis. At E16, high levels of *Klf9* are also observed in the thymus and vertebrae cartilage primordia. In the developing cerebral hemispheres, *Klf9* is undetectable from E16 until birth and then rises dramatically into adulthood, suggesting a possible role in neurite outgrowth (Denver et al. 1999). In addition, in mice, *Klf9* expression increases dramatically in Purkinje cells of the cerebellum and in the pyramidal cells of the hippocampus at postnatal day 7, a time when synapses in the brain begin to form (Morita et al. 2003). *Klf9* null mice show a normal lifespan, are fertile, and exhibit no overt pathological defects; their general behavioral activities are unaffected (Morita et al. 2003). However, *Klf9* null mice do show impairments in specific behavioral testing, such as rotorod tests and contextual fear conditioning tests. Ablation of *Klf9* in female mice results in uterine hypoplasia, reduced litter size, and increased incidence of neonatal deaths in offspring, with parturition defects involving the progesterone receptor (Simmen et al. 2004; Zeng et al. 2008). In addition, *Klf9* loss results in an intestinal phenotype, with short small intestinal villi, reduced crypt cell proliferation, decreased migration along the villi, and altered cell lineage allocation (Simmen et al. 2007).

## *KLF10*

KLF10 was identified by differential display PCR from normal human fetal osteoblasts following transforming growth factor-β (TGF-β) treatment and thus is also called TGF-β-inducible early gene 1 (TIEG1) (Subramaniam et al. 1995). Human KLF10 is expressed in keratinocytes; epithelial cells of the placenta, breast, and uterus; osteoblasts and other cells of the bone marrow and cerebellum; skeletal muscle; and pancreas with some cells showing cytoplasmic staining and others a nuclear localization (Subramaniam et al. 1995, 1998). Mouse *Klf10*, also called mGIF, is widely distributed in the adult with high levels in kidney, lung, brain, liver, heart, and testis (Yajima et al. 1997). During development, murine *Klf10* is broadly expressed, including in the cerebral cortex, cerebellar primordium, kidney, intestine, liver, lung, bones, and the differentiating mesenchyme surrounding the nasal cavity and some of the skull (Yajima et al. 1997). *Klf10* null mice initially appeared to be phenotypically normal, with no evidence of alterations in bone formation despite an increase in the number of osteoblasts (Subramaniam et al. 2005). These *Klf10* null osteoblasts display reduced expression of key differentiation markers and a decreased ability to support osteoclast differentiation in vitro. Subsequent analyses revealed that loss of *Klf10* results in severe osteopenia in female animals only, with reduced cancellous and cortical bone and reduced bone strength (Hawse et al. 2008). Conversely, male but not female *Klf10* null mice develop cardiac hypertrophy at 16 months of age (Rajamannan et al. 2007). *Klf10* null mice also show defects in the mechanical properties and healing potential of tendons (Bensamoun et al. 2006; Tsubone et al. 2006).

## *KLF11*

Human KLF11 was first described as TIEG2, another TGF-β-inducible gene that inhibits growth in cultured cells (Cook et al. 1998). Another homologue, FKLF, was cloned from fetal globin-expressing human fetal erythroid cells (Asano et al. 1999). KLF11 is ubiquitously expressed in adult human tissues, with the highest levels in the pancreas and skeletal muscle (Cook et al. 1998). KLF11 is also enriched in erythroid cells, with much higher expression in fetal liver than adult bone marrow (Asano et al. 1999). *Klf11* null mice appear normal at all stages of development, are fertile, and show no abnormalities of hematopoiesis (Song et al. 2005).

## *KLF12*

Klf12, formerly named AP-2rep, is a transcriptional repressor of the AP-2α gene identified by screening a mouse brain cDNA library (Imhof et al. 1999). Overall, *Klf12* is seen in the adult kidney and at very low levels in the adult liver and lung but not in most other adult and embryonic tissues. Some *Klf12* transcripts are seen in brain and kidney at E15.5 and E19.5 (Imhof et al. 1999), and *Klf12* expression in the developing kidney rises at postnatal day 15 (Suda et al. 2006). A knockout mouse for *Klf12* has not been reported.

## *KLF13*

KLF13 (RFLAT-1) was identified as an activator of RANTES (regulated upon activation normal T-cell expressed and secreted), a chemokine for T-cell activation (Song et al. 1999). KLF13 is ubiquitously expressed in human tissues, with two distinct transcripts, and the greatest abundance is seen in peripheral blood lymphocytes and thymus. In the mouse, *Klf13* is widely distributed in adults (Scohy et al. 2000) and embryos (Martin et al. 2001), beginning by at least E8. *Klf13* is expressed in primitive heart at E8 and in atria and ventricles of the developing heart at E11; it is seen less prominently at E13 and E16. *Klf13* is also expressed at high levels in the cephalic mesenchyme of the developing brain, the thymus, vertebrae cartilage primordia, gut, bladder, and epidermis. Whereas *Klf13* in the gut and bladder are expressed throughout the muscle and epithelia at E11 and E13, by E16 the expression is localized to the epithelia. Inactivation of *Klf13* in mice results in decreased viability by 3 weeks after birth, with reduced numbers of circulating erythrocytes, an increase in less mature erythroblasts, prolonged survival of thymocytes due to decreased apoptosis, splenomegaly, and an enlarged thymus (Gordon et al. 2008; Zhou et al. 2007). *Klf13* null mice also show a trend toward reduced numbers of granulocytes and monocytes, suggesting abnormalities in pathways affecting differentiation or survival of hematopoietic cells (Gordon et al. 2008). Although

one report indicates an increase in the number of thymocytes, another reports a 30% decrease in thymocyte numbers (Gordon et al. 2008; Zhou et al. 2007). Knockdown of *Klf13* in *Xenopus* embryos leads to atrial septal defects and hypotrabeculation (Lavallee et al., 2006).

## *KLF14*

*Klf14* was identified together with mouse *Klf13* using the sequence of the Sp1 zinc finger DNA-binding domain as a probe to screen a mouse EST database (Scohy et al. 2000). Klf14 is ubiquitously expressed in adult tissues. Human *KLF14* has been described as an imprinted gene with monoallelic maternal expression in all embryonic and extraembryonic tissues studied in humans and the mouse (Parker-Katiraee et al. 2007). Expression is seen in placenta and fetal heart, liver, lung, and colon, as well as adult skeletal muscle, colon, stomach, and brain but not the liver or lymphoblasts. A gene knockout of KLF14 has not been described.

## *KLF15*

KLF15 was cloned from a human kidney cDNA library as kidney Krüppel-like factor (KKLF) (Uchida et al. 2000). In human and rat tissues, KLF15 is expressed most abundantly in liver, with moderate levels in kidneys, heart, and skeletal muscle and no expression in bone marrow or lymphoid tissues. *Klf15* is highly expressed in adipocytes and myocytes in vivo and is induced when preadipocytes differentiate into adipocytes (Gray et al. 2002). *Klf15* shows minimal cardiac expression during embryonic development and is barely detectable in the rat heart at postnatal day 3 but reaches adult levels by postnatal day 30 (Fisch et al. 2007). *Klf15* null mice are viable, fertile, and born in expected Mendelian ratios. In response to pressure overload, *Klf15* null mice develop cardiac fibrosis and an eccentric form of cardiac hypertrophy (Fisch et al. 2007; Wang et al. 2008). *Klf15* null mice also develop severe fasting hypoglycemia (Gray et al. 2007).

## *KLF16*

KLF16, also known as dopamine receptor regulating factor (DRRF), was initially cloned from a mouse neuroblastoma cell line (Hwang et al. 2001). In mice, *Klf16* is expressed in multiple adult tissues, including brain, heart, spleen, lung, liver, kidney, and testis. The highest levels of *Klf16* are seen in multiple regions of the brain, including the olfactory tubercle, olfactory bulb, nucleus accumbens, striatum, hippocampal CA1 region, cerebral cortex, dentate gyrus, and amygdala (Hwang et al. 2001). During embryogenesis, the pattern of *Klf16* in brain overlaps that

found in the adult and with the expression profile of dopamine receptors (Hwang et al. 2001). *Klf16* is expressed at E12 in regions of the brain and skull and in muscles of the tongue and tail, with moderate expression in the heart and liver (D'Souza et al. 2002). At E14, KLF16 is highly expressed in the olfactory lobe and other regions of the brain, moderately expressed in the liver, and minimally expressed in the lung. At E16, KLF16 expression is seen in the brain, thymus, duodenum, and kidney, with lesser expression in the liver, heart, bladder, and lung. A KLF16 knockout has not yet been described.

### *KLF17*

Human KLF17 is a recently described member of the KLF family, which appears to be the human orthologue of the mouse gene Zfp393 (van Vliet et al. 2006; Yan et al., 2002). Human KLF17 and murine Zfp393 have 54.8% identity at the protein level but have significantly higher similarity in their zinc finger regions (81.5% similarity). Zfp393 is expressed exclusively in the testis and ovary, with specific expression in steps 3–8 spermatids and growing oocytes (Yan et al. 2002). The expression of human KLF17 has not been extensively studied, but based on the sources of human *KLF17* ESTs it appears to be present in testis, brain, and bone, although likely at low levels (van Vliet et al. 2006). A knockout of *Klf17* has not been reported.

## Conclusion

The expression patterns of the individual KLFs vary during development and adulthood. A careful examination of the overlapping patterns of expression and function suggest a number of themes for the members of the KLF family. These themes, involving processes such as adipogenesis, cardiac hypertrophy, hematopoiesis, and the pluripotency of stem cells, are explored thoroughly in the ensuing chapters.

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