Chapter 16
Krüppel-like Factors in Cancers

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Abstract Krüppel-like factors (KLFs) are zinc finger-containing transcription factors that play important roles in diverse physiological and pathophysiological processes. A major function of many KLFs is to regulate cell growth, proliferation, and differentiation. It is therefore not surprising that some of the KLFs are involved in tumorigenesis of various organs and tissues. This chapter reviews the pathobiological roles of KLFs in several cancers, including those of the gastrointestinal tract, breast, skin, and pancreas. Understanding the functions of KLFs in cancers may help gain insight into the pathogenesis of cancers and provide novel therapeutic approaches to their treatment.

Introduction

Krüppel-like factors (KLFs) belong to the family of zinc finger-containing transcription factors that share homology to the *Drosophila melanogaster* gap gene product, Krüppel (Bieker 2001; Black et al 2001; Dang et al 2000b; Kaczynski et al 2003; Lomberk and Urrutia 2005; Philipsen and Suske 1999). Since identification and isolation of the prototypic mammalian KLF—KLF1 or erythroid Krüppel-like factor (EKLF)—a decade and half ago (Bieker 1996; Miller and Bieker 1993), there has been an explosion of research devoted to the identification, isolation, and characterization of many additional KLF family members. To date, there are approximately 17 identified mammalian KLFs (excluding the Sp1 and Sp1-related proteins) (Kaczynski et al. 2003). Together, these KLFs have been shown to exert important regulatory functions in numerous biological and physiological processes.

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Expression or activities of the KLFs are also frequently perturbed in pathological events. One of the main roles of many of the KLFs is their involvement in the regulation of cell growth, proliferation, differentiation, and development. As such, KLF expression and activities are often abnormal in neoplastic processes including cancers. Here we review the roles played by representative KLFs in several tumors including those of the gastrointestinal tract, breast, skin, and pancreas. The functions of KLFs in cancers of the liver, prostate, and ovaries are described elsewhere in this book (see Chapters 11 and 17).

Colorectal Cancer

Colorectal cancer is a common form of cancer and one of the leading causes of cancer mortality, with more than 655,000 deaths per year worldwide (Cancer. World Health Organization, February 2006). Clinical and epidemiological evidence indicates that colorectal cancer is preceded by a benign precursor lesion, an adenoma (Levin et al. 2008). Much progress has been made in understanding the genetics and pathogenesis of colorectal cancer at a molecular level (de la Chapelle 2004; Rustgi 2007). However, recent studies point to the complex, heterogeneous nature of colorectal cancer, which involves close to 200 genes that are mutated at a significant frequency (Sjoblom et al. 2006; Wood et al. 2007).

KLF4

Several KLFs have been implicated in the pathogenesis of colorectal cancer (Ghaleb and Yang 2008; Wei et al. 2006). Among these, KLF4 is the most extensively studied. KLF4 (also called gut-enriched Krüppel-like factor or GKLF) was initially identified as a gene whose expression is enriched in epithelial tissues, including the intestine and epidermis (Garrett-Sinha et al. 1996; Shields et al. 1996). In vivo studies in transgenic mice that are null for the *Klf4* alleles indicate that KLF4 is required for the terminal differentiation of goblet cells in the colon and for the barrier function of the skin in neonates (Katz et al. 2002; Segre et al. 1999). Studies also indicate that expression of KLF4 is primarily located in the postmitotic, differentiated cells of epithelial tissues (Garrett-Sinha et al. 1996; McConnell et al. 2007; Shie et al. 2000b; Shields et al. 1996). This growth arrest-specific pattern of expression is also observed in cultured cells in vitro (Shields et al. 1996). Consequently, ectopic expression of KLF4 in cultured cells results in growth arrest (Chen et al. 2001; Shields et al. 1996). Additional conditions that are known to cause growth arrest in cultured colonic epithelial cells—such as DNA damage and treatment with interferon-γ, sodium butyrate, or 15-deoxy-Δ(12,14) prostaglandin J2 (15d-PGJ2)—all lead to the induction of KLF4 expression (Chen et al. 2000, 2004; Chen and Tseng 2005; Yoon et al. 2003; Yoon and Yang 2004; Zhang et al. 2000).

The growth-suppressive activity of KLF4 and its activation upon conditions that elicit growth arrest suggest that KLF4 may have a tumor-suppressive function. Indeed, overexpression of KLF4 in the human colon cancer cell line RKO reduces its tumorigenicity in vivo (Dang et al. 2003). The levels of *KLF4* mRNA have also been shown to be reduced in intestinal adenomas of $Apc^{Min/+}$ mice, a model of intestinal tumorigenesis (Moser et al. 1990), in colonic adenomas from patients with familial adenomatous polyposis, and in colorectal cancer when compared to the respectively matched normal tissues (Dang et al. 2000a; Ton-That et al. 1997; Zhao et al. 2004). Moreover, loss of KLF4 protein is relatively common in colorectal cancer as assessed by immunohistochemistry (Choi et al. 2006). The causes for the loss of or reduced expression of KLF4 in colorectal cancer have been shown to be mediated at different levels including loss of heterozygosity (LOH), promoter hypermethylation, and point mutations that reduce protein activity (Zhao et al. 2004), all of which are representative features of tumor suppressors. Finally, results of recent genetic studies demonstrating that haploinsufficiency of the *Klf4* alleles in mice promotes intestinal tumorigenesis in $Apc^{Min/+}$ mice are highly indicative of the tumor-suppressive nature of KLF4 in vivo (Ghaleb et al. 2007b).

A number of studies have demonstrated the mechanism by which KLF4 exerts a growth-suppressive effect (Ghaleb et al 2005, 2007a; McConnell et al. 2007). Upon its identification, KLF4 was shown to inhibit DNA synthesis when overexpressed in transfected cells (Shields et al. 1996). When examined in the context of an inducible system, induction of KLF4 inhibits cell proliferation by blocking the G_1/S progression of the cell cycle (Chen et al. 2001). This effect is correlated with the induction of the gene encoding the cell cycle inhibitor $p21^{WAF1/CIP1}$ (Chen et al. 2001). Similarly, when growth arrest is caused by serum starvation or DNA damage, expression of both KLF4 and $p21^{WAF1/CIP1}$ are concurrently induced although the increase in *KLF4* mRNA levels precedes that of $p21^{WAF1/CIP1}$ (Zhang et al. 2000). In addition, the induction of both *KLF4* and $p21^{WAF1/CIP1}$ are dependent on p53 (Zhang et al. 2000). Significantly, KLF4 activates the $p21^{WAF1/CIP1}$ promoter through a specific Sp1-like *cis*-element in the $p21^{WAF1/CIP1}$ proximal promoter (Zhang et al. 2000). This element is necessary for p53 to activate the $p21^{WAF1/CIP1}$ promoter, even though p53 does not directly bind to it (Zhang et al. 2000). Instead, KLF4 and p53 physically interact with each other and synergistically induce activity of the $p21^{WAF1/CIP1}$ proximal promoter (Zhang et al. 2000). The physiological significance of KLF4 in mediating p53-dependent activation of $p21^{WAF1/CIP1}$ is further demonstrated by the ability of antisense KLF4 oligonucleotides to block the induction of $p21^{WAF1/CIP1}$ in response to p53 activation (Zhang et al. 2000). Subsequently, the p53-dependent induction of KLF4 was shown to be essential for DNA damage-induced arrest at both the G_1/S and G_2/M checkpoints of the cell cycle (Yoon et al. 2003; Yoon and Yang 2004). These results indicate that KLF4 is an essential mediator of p53 in controlling cell cycle progression following DNA damage.

In addition to activating $p21^{WAF1/CIP1}$, KLF4 has been shown to repress a number of genes that are involved in cell cycle progression or DNA synthesis, including cyclin D1 (Shie et al. 2000a), cyclin B1 (Evans et al. 2007; Yoon and Yang 2004), cyclin E (Yoon et al. 2005), Cdc2 (Yoon and Yang 2004), and ornithine decarboxylase

(Chen et al. 2002), all of which contributing to the inhibitory effect of KLF4 on cell proliferation. The transcriptional targets of KLF4 have further been elaborated by gene profiling experiments using an inducible system for KLF4 expression (Chen et al. 2003; Whitney et al 2006). A major cluster of genes whose expression is significantly affected by KLF4 induction are those involved in cell cycle regulation. Within this cluster, many genes activated by KLF4 are inhibitors of the cell cycle. Conversely, many downregulated genes are promoters of the cell cycle. These results indicate that KLF4 controls cell proliferation by eliciting changes in expression of numerous cell cycle-regulatory genes in a coordinated manner (Chen et al. 2003; Whitney et al. 2006). Unexpectedly, several other groups of genes that are repressed by KLF4 are involved in the synthesis of macromolecules such as protein, RNA, and cholesterol (Whitney et al. 2006). These results suggest that KLF4 exerts a global inhibitory effect on macromolecular biosynthesis that is beyond its role as a cell cycle inhibitor.

The adenomatous polyposis coli (APC) tumor suppressor is the gatekeeper for colorectal carcinogenesis (Kinzler and Vogelstein 1996). APC, a crucial component of the Wnt signaling pathway that regulates cell proliferation, prevents nuclear localization of β-catenin, thus preventing its pro-proliferative activity (Dang et al. 2001). The finding that haplo insufficiency of *Klf4* in $Apc^{Min/+}$ mice promotes intestinal tumorigenesis (Ghaleb et al. 2007b) suggests that KLF4 is involved in the pathway of APC tumor suppression. Indeed, expression of KLF4 has been shown to be activated by APC (Dang et al. 2001). Conversely, overexpression of KLF4 reduces β-catenin levels (Stone et al. 2002). Moreover, KLF4 physically interacts with β-catenin and represses β-catenin-mediated gene expression (Zhang et al. 2006). These results strongly support a role for KLF4 in mediating the Wnt/β-catenin pathway that is involved in normal intestinal epithelial homeostasis and tumor suppression.

KLF5

Similar to KLF4, expression of KLF5 is developmentally regulated and is enriched in epithelial tissues of adults including the intestine and epidermis (Conkright et al. 1999; Ohnishi et al. 2000). In contrast to KLF4, KLF5 is primarily expressed in the proliferating crypt epithelial cells and basal cells of the intestine and epidermis, respectively (Conkright et al. 1999; McConnell et al. 2007; Ohnishi et al. 2000). These findings suggest that KLF5 may positively regulate cell proliferation, contrary to the antiproliferative activity of KLF4 (Ghaleb et al. 2005; McConnell et al. 2007). Results from several experimental systems support this notion. For example, expression of KLF5 is strongly upregulated in activated smooth muscle cells and myofibroblasts in the aorta following balloon injury or in vascular lesions (Hoshino et al. 2000; Watanabe et al. 1999). In response to external stress, mice with haplo insufficiency for *Klf5* exhibit diminished levels of arterial wall thickening, angiogenesis, cardiac hypertrophy, and interstitial hypertrophy, indicating that KLF5 is a key element to linking external stress and cardiovascular modeling (Shindo et al. 2002).

In the mouse, infection by the mouse pathogen *Citrobactor rodentium* results in hyperproliferation on colonic crypt epithelial cells (Luperchio and Schauer 2001), which is accompanied by induction of KLF5 expression in colonic crypt epithelial cells (McConnell et al. 2008). Infection of mice heterozygous for the *Klf5* alleles with *C. rodentium* shows attenuated induction of KLF5 that is accompanied by a reduced hyperproliferative response in the colonic crypts, suggesting that KLF5 is a key mediator of crypt cell proliferation in response to pathogenic bacterial infection (McConnell et al. 2008).

Direct evidence in support of a pro-proliferative role of KLF5 is primarily derived from in vitro studies using cultured cells. Expression of KLF5 in serum-deprived fibroblasts is rapidly activated when the cells are stimulated with serum, epidermal growth factor (EGF), or the phorbol ester phorbol 12-myristate 13-acetate (PMA) (Sun et al. 2001). Similarly, KLF5 is upregulated in vascular smooth muscle cells through the mitogen-activated protein kinase (MAPK) pathway when treated with PMA or basic fibroblast growth factor (bFGF) (Kawai-Kowase et al. 1999). Indeed, constitutive expression of KLF5 in transfected fibroblasts increases their rate of proliferation and leads to anchorage-independent growth (Sun et al. 2001). Moreover, KLF5 level is significantly increased in oncogenic HRAS-transformed fibroblasts due to elevated MAPK activity (Nandan et al. 2004). Importantly, the increased KLF5 level in HRAS-transformed cells is responsible for increased transcription of the genes encoding cyclin D1, cyclin B1, and Cdc2 and thus directly mediates the pro-proliferative and transforming activity of oncogenic HRAS (Nandan et al. 2004, 2005). Pertinent to colorectal cancer, KLF5 expression is also increased in intestinal epithelial cells containing an inducible oncogenic KRAS, which is present in approximately half of all colorectal cancers (Nandan et al. 2008). KLF5 levels are similarly elevated in intestinal tumors from mice transgenic for an intestine-specific oncogenic KRAS, human colorectal cancer cell lines containing oncogenic KRAS, and primary human colorectal cancer containing oncogenic KRAS (Nandan et al. 2008). In human colorectal cancer cell lines, inhibition of KLF5 leads to reduced proliferation and transformation, suggesting that KLF5 is a key mediator of colorectal carcinogenesis, at least in tumors containing mutated, oncogenic KRAS (Nandan et al. 2008).

In addition to the stimulatory effects on KLF5 expression by the various agonists stated above, such as serum, PMA, and bFGF, KLF5 is regulated by several other stimuli, which may also explain its role in regulating cell proliferation in intestinal epithelial cells. Among them is lysophosphatidic acid (LPA), a phospholipid that stimulates proliferation of colon cancer cells (Zhang et al. 2007a). Activation of KLF5 expression by LPA in colon cancer cells is mediated by LPA2 and LPA3 receptors (Zhang et al. 2007a). Silencing of KLF5 significantly attenuates LPA-stimulated proliferation of colon cancer cells (Zhang et al. 2007a). Conversely, expression of KLF5 in intestinal epithelial cells is inhibited by all-*trans* retinoic acid (ATRA), which inhibits cell proliferation (Chanchevalap et al. 2004). Constitutive ectopic expression of KLF5 intestinal epithelial cells abrogates the inhibitory effect of ATRA (Chanchevalap et al. 2004). Adding further relevant to tumorigenesis, KLF5 has been shown to be a target of the Wnt signaling pathway (Taneyhill and Pennica 2004; Ziemer et al 2001).

The biological functions of KLF5 can also be inferred from the target genes that it regulates and from how KLF5 is posttranscriptionally regulated. Studies cited above in HRAS-transformed fibroblasts indicate that several cell cycle-regulatory genes, including cyclin D1, cyclin B1, and Cdc2, are transcriptional targets of KLF5 (Nandan et al. 2004, 2005).

Examples of other target genes, many of which are epithelial in origin, stimulated by KLF5 include platelet-derived growth factor (PDGF)-A chain (Aizawa et al 2004; Shindo et al. 2002), lactoferrin (Teng et al. 1998), laminin α-1 (Piccinni et al. 2004), and decay-accelerating factor (DAF) (Shao et al. 2008). Interestingly, the antiproliferative KLF4 is negatively regulated by KLF5 (Dang et al. 2002). KLF5 has also been shown to regulate the proinflammatory and antiapoptotic gene NF-κB (Chanchevalap et al. 2006) and to cooperate with NF-κB in regulating target gene expression (Aizawa et al. 2004; Sur et al. 2002). Moreover, KLF5 physically interacts with a number of other regulators such as p300/CBP (Miyamoto et al 2003), retinoic acid receptor (Shindo et al. 2002), and the protein inhibitor of activated STAT1 (PIAS1) (Du et al. 2007) to modulate physiologically relevant processes. Finally, KLF5 has been shown to be posttranslationally modified by phosphorylation (Zhang and Teng 2003), SUMOylation (Oishi et al. 2008), and ubiquitination (Chen et al. 2005a,b). Given that many of the molecules or processes cited here are involved in cell proliferation, these results further support an important function of KLF5 in regulating proliferation.

KLF6

Similar to KLF4, KLF6 has been shown to be an inhibitor of cell proliferation because of its ability to activate expression of the $p21^{WAF1/CIP1}$ gene and to disrupt the cyclin D1/cyclin-dependent kinase 4 (Cdk4) complexes (Benzeno et al. 2004; Li et al. 2005; Narla et al. 2001). The first evidence that KLF6 is a tumor suppressor is derived from the study of prostate cancer (Narla et al. 2001). Here, LOH of the KLF6 alleles is frequently detected in a cohort of primary prostate cancer, and mutation of KLF6 in the remaining allele is also common. Of the mutations detected, many result in reduced ability to activate $p21^{WAF1/CIP1}$ expression (Narla et al. 2001). Since this discovery, KLF6 has been shown to function as a tumor suppressor in myriads of cancers, including colorectal cancer (this chapter), hepatocellular cancer (HCC) (see Chapter 11), brain cancer (Kimmelman et al. 2004), and lung cancer (Ito et al. 2004), to name a few. In addition to the traditional mechanisms of loss of tumor suppressor functions such as LOH, mutations, and promoter methylation, KLF6 exhibits a unique mechanism by which a gain of function is achieved due to alternative splicing (Narla et al. 2005). The clinical relevance and therapeutic implications of these findings are discussed in Chapter 17.

Reeves et al. were the first to demonstrate that inactivation of KLF6 by LOH and mutations is a common event in both sporadic and inflammatory bowel disease-associated colorectal cancer (Reeves et al. 2004). Subsequent studies in independent

cohorts of colorectal cancer samples confirmed these findings (Cho et al. 2006a,b). Another study compared the difference in the role of KLF6 LOH between sporadic and hereditary colorectal cancers and found that although KLF6 is frequently lost in sporadic cancers, especially during the late stage, its loss is relatively uncommon in hereditary cancer including familial adenomatous polyposis (FAP) and hereditary nonpolyposis colon cancer (HNPCC) (Yamaguchi et al. 2006). Finally, mutations of KLF6, along with p53, are commonly found in nonpolypoid colorectal cancer but mutations of KRAS and BRAF are not (Mukai et al. 2007).

Gastric Cancer

The first in vivo evidence that KLF4 regulates proliferation of gastric epithelial cells came from studies involving tissue-specific ablation of *Klf4* from the gastric epithelium of transgenic mice (Katz et al. 2005). *Klf4* mutant mice survive to adulthood and show increased proliferation and altered differentiation of their gastric epithelia (Katz et al. 2005). In addition, KLF4 expression is drastically decreased in both intestinal and diffuse-type human gastric cancer (Katz et al. 2005). The loss of expression of KLF4 in gastric cancer was subsequently validated by additional independent studies (Cho et al. 2007; Wei et al. 2005). It is of interest to note that loss of KLF4 expression contributes to Sp1 overexpression, which is directly correlated with the angiogenic potential of and poor prognosis for human gastric cancer (Kanai et al. 2006).

A single study examined the expression of KLF5 in human gastric cancer (Kwak et al. 2008). It showed that the expression rate of KLF5 is significantly higher in early-stage gastric cancer, in gastric cancer without lymph node metastasis, and in tumors < 5 cm in size (Kwak et al. 2008). Interestingly, the 5-year survival rate of patients with KLF5-positive tumors is higher than those of patients with KLF5-negative tumors, although the difference is not statistically significant (Kwak et al. 2008).

Esophageal Cancer

Much information on the relation between KLFs and esophageal cancer is derived from studying the role of KLF5 in squamous cell carcinoma of the esophagus. In the adult, KLF5 is expressed in basal cells of the squamous epithelium of the esophagus (Conkright et al. 1999; Ohnishi et al. 2000). A transgenic mouse model for KLF5 overexpression throughout the esophageal epithelium, developed using the ED-L2 promoter of the Epstein-Barr virus, exhibits evidence of increased proliferation in the basal layer but not the suprabasal layer of the esophageal epithelium (Goldstein et al. 2007). Subsequent studies in mouse primary esophageal keratinocytes indicated that KLF5 activates the mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK) signaling pathways via the epidermal growth factor receptor (EGFR) to stimulate proliferation

(Yang et al. 2007). KLF5 also controls keratinocyte migration by activating integrin-linked kinase (Yang et al. 2008). In contrast, overexpression of KLF5 in a poorly differentiated esophageal squamous cancer cell line, TE2, inhibits proliferation and invasion and increases apoptosis following DNA damage (Yang et al. 2005). In this regard, KLF5 may function as a context-dependent regulator of cell proliferation in a manner similar to that reported for intestinal tumor progression (Bateman et al. 2004).

Breast Cancer

KLF4 has been shown to be involved in the pathogenesis of breast cancer. However, in contrast to the tumor-suppressive role of KLF4 in colorectal cancer, studies suggest that KLF4 may be oncogenic in breast cancer. The levels of KLF4 mRNA and protein are often elevated in neoplastic breast tissues, including both ductal carcinoma in situ and invasive carcinoma, when compared to adjacent normal mammary tissues (Foster et al. 2000). In addition, nuclear localization of KLF4 in breast cancer cells is associated with an aggressive phenotype in early-stage infiltrating ductal carcinoma (Pandya et al. 2004). The mucin 1 (MUC1) protein is often overexpressed in human breast cancer and induces transformation (Li et al. 2003). MUC1 binds to KLF4 to repress transcription of p53, which may explain the oncogenic effect of MUC1 and possibly KLF4 in breast cancer (Wei et al. 2007). However, it should be noted that results contrary to the above have also been reported. KLF4 levels are low or absent in many breast cancer cell lines, which may explain the absence of laminin-5, a major extracellular matrix protein produced by mammary epithelial cells, from many breast cancer cells (Miller et al. 2001). Additionally, growth of breast cancer cells is suppressed by okadaic acid, which induces apoptosis by activating transcription of c-Myc, which is mediated in part by KLF4 (Zhang et al. 2007b). The definitive growth effect (activating or suppressing) of KLF4 on breast cancer cells therefore requires additional clarification.

The context-dependent nature by which KLF4 acts as an oncogene has been explored. KLF4 was identified in a functional screen for genes that bypass oncogenic RAS^{V12}-induced senescence (Rowland et al. 2005). Although KLF4 is a potent inhibitor of proliferation in untransformed cells, KLF4-induced senescence is bypassed by RAS^{V12} or by the RAS^{V12} target, cyclin D1. Inactivation of the cyclin D1 target, $p21^{WAF1/CIP1}$, not only neutralizes the cytostatic action of KLF4 but collaborates with KLF4 in oncogenic transformation. KLF4 suppresses expression of p53 by directly acting on its promoter, allowing RAS^{V12}-mediated transformation. Depletion of KLF4 from breast cancer cells restores p53 levels and causes p53-dependent apoptosis (Rowland et al. 2005). These studies underscore the importance of $p21^{WAF1/CIP1}$ acting as a switch that determines the outcome of KLF4 signaling (Rowland and Peeper 2006). These results are consistent with a recent report showing that KLF4 exhibits antiapoptotic activity following γ-radiation-induced DNA damage by inhibiting the ability of p53 to trans-activate the proapoptotic gene BAX (Ghaleb et al. 2007a).

A limited number of studies have been published that examined the role of KLF5 in breast cancer. Like KLF4, the results of these studies are conflicting. KLF5 is thought to be a tumor suppressor in breast cancer because its expression levels are low in breast cancer cell lines due to LOH (Chen et al. 2002). In addition, the reduced KLF5 levels are attributed to ubiquitin-mediated proteasome degradation in breast cancer cell lines (Chen et al. 2005a,b). On the other hand, as a prognostic factor in breast cancer, patients with high KLF5 expression levels have shorter disease-free survival and overall survival than patients with low KLF5 expression, suggesting that KLF5 may not be a classic tumor suppressor in breast cancer (Tong et al. 2006).

Finally, several studies has been implicated KLF6 (Guo et al. 2007), KLF8 (Wang et al. 2007), and TIEG1 (KLF10) (Subramaniam et al. 1998) in the pathogenesis of breast cancer.

Skin Cancer

In a manner similar to the ability of KLF4 to bypass oncogenic RAS-mediated senescence (Rowland et al. 2005), KLF4 is found to cooperate with adenovirus E1A oncoprotein to transform epithelial cells (Foster et al. 1999). In oral squamous epithelium KLF4 is detected in the upper, differentiated cell layers (Foster et al. 1999). In contrast, the KLF4 level is increased in dysplastic epithelium and is diffusely expressed throughout the entire epithelium, indicating that KLF4 is misexpressed in the basal compartment early during tumor progression (Foster et al. 1999). In a mouse model, conditional expression of KLF4 in the basal keratinocytes in the skin leads to squamous epithelial dysplasia (Foster et al. 2005; Huang et al. 2005). A similar pattern of maturation-independent expression of KLF4 has been observed in human squamous cell carcinoma (Huang et al. 2005). As such, nuclear KLF4 expression has been correlated with progression and metastasis of human squamous cell carcinoma (Chen et al. 2008).

In contrast to the potential oncogenic role of KLF4 in skin cancer, KLF6 continues to behave as a tumor suppressor in human head and neck squamous cell carcinoma (Chen et al. 2008). Here, allelic loss of KLF6 is frequent and strongly correlated with tumor recurrence and decreased patient survival (Chen et al. 2008).

Pancreatic Cancer

The role of KLFs in pancreatic cancer has recently been reviewed (Buttar et al. 2006; Cook and Urrutia 2000). Among the best studied KLF members involved in the pathogenesis of pancreatic cancer is KLF11, also called transforming growth factor-β (TGF-β)-inducible early response gene 2 (TIEG2). KLF11, the expression of which is enriched in the pancreas, is an inhibitor of cell proliferation including pancreatic cells both in vivo and in vitro (Cook et al. 1998; Fernandez-Zapico et al. 2003).

Conversely, KLF11 expression is reduced in several human tumors including pancreatic cancer (Fernandez-Zapico et al. 2003). The mechanism by which KLF11 exerts its effect is to serve as a critical component of the TGF-β growth-inhibitory signaling in normal epithelial cells, an effect that is inactivated by oncogenic extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) in pancreatic cancer cells (Ellenrieder et al. 2004).

Conclusion

Substantial progress has been made since the first mammalian prototype Krüppel-like factor, KLF1, was identified some 15 years ago. The combined current family of 17 KLF members is shown to exhibit important functions in diverse physiological processes, including proliferation, differentiation, development, angiogenesis, and embryonic stem cell renewal. Many of the KLFs are also featured prominently in pathobiological processes including inflammation and carcinogenesis. This chapter reviewed the current knowledge on the role of KLFs in certain human cancers. They function either as tumor suppressors or oncoproteins. Some have functions that are dependent on the context. Further investigation on the role of KLFs in cancer will provide additional novel insight into the mechanism of tumorigenesis and may provide potential therapeutic approaches to the treatment of cancer.

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