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Review

Human cancer: Is it linked to dysfunctional lipid metabolism?

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ABSTRACT

Background: Lipid metabolism dysfunction leading to excess fat deposits (obesity) may cause tumor (cancer) development. Both obesity and cancer are the epicenter of important medical issues. Lipid metabolism and cell death/proliferation are controlled by biochemical and molecular pathways involving many proteins, and organelles; alteration in these pathways leads to fat accumulation or tumor growth. Mammalian Krüppel-like factors, KLFs play key roles in both lipid metabolism and tumor development.
Scope of review: Substantial epidemiological and clinical studies have established strong association of obesity with a number of human cancers. However, we need more experimental verification to determine the exact role of this metabolic alteration in the context of tumor development. A clear understanding of molecules, pathways and the mechanisms involved in lipid metabolism and cell death/proliferation will have important implications in pathogenesis, and prevention of these diseases.
Major conclusion: The regulatory role of KLFs, in both cell death/proliferation and lipid metabolism suggests a common regulation of both processes. This provides an excellent model for delivering a precise understanding of the mechanisms linking altered expression of KLFs to obesity and tumor development.
General significance: Currently, mouse and rats are the models of choice for investigating disease mechanisms and pharmacological therapies but a genetic model is needed for a thorough examination of KLF function in vivo during the development of an organism. The worm *Caenorhabditis elegans* is an ideal model to study the connectivity between lipid metabolism and cell death/proliferation.

1. Introduction

The surplus lipids in obesity represent one of the biggest public health problems facing the world today. It is predicted that by 2025 about 700 million people will be either over-weight or obese worldwide. The concern relating to obesity is that it raises the risk for many chronic and potentially life-threatening illness, including diabetes, and cardiovascular disease. In spite of serious attempts to control diet and perform physical activities, these strategies alone are not effective in preventing obesity and maintaining weight loss. Obesity may account for 25–30% of major cancers, such as colon, breast, gallbladder, ovaries, pancreas, kidney, and cancer of the esophagus [161]. In the United Sates about 3.2% of all new cancers are linked to obesity [127], and about 14% of cancer deaths in men and 20% of cancer deaths in women have been reported in over-weight individuals. Increased body weight was associated with increased death rates for all cancers combined and for cancers at multiple specific sites [21]. In Calle et al.'s [21] extensive study, increased body weight was associated with 57,000 deaths from cancers among 900,000 men and women who were free of cancer at base line. As discussed below, numerous observations in mice, rodent and cell culture models as well as obese individuals have shown that chronic lipid accumulation is associated with tumor development. However, we need more experimental verification to determine the exact role of this metabolic alteration in the context of cancer.

In mammals, excess fat in the form of triglycerides is stored in adipose tissue and, when needed, is able to fuel the function of other organs within the body. Lipid metabolism is complex involving a large number of enzymes catalyzed metabolic reactions with regulation at different levels. It also involves several organs, including the brain, adipose tissue, muscles, liver, and gut. These organs are part of complex homeostatic system and communicate through hormones, neurons and metabolites. Just a small shift in the regulation of lipid metabolism can lead to a large change in energy homeostasis; it can result in excess fat accumulation and it may also affect many important cellular processes, including cell growth, proliferation, and differentiation. It is not unforeseen that many of these changes in cellular development have been detected in cancer. Increased cancer cell proliferation is directly linked to the rapid synthesis of lipids for the generation of biological membranes. The disparity between energy intake and its expenditure may lead to

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fat buildup in mammalian adipose tissue and the physiological, biochemical and molecular alterations that result from the excess fat buildup can cause cancer pathology. Both external and internal sources of lipids provide the energetic, structural, and oncogenic signaling requirements of cancer cells.

Normally, fat builds up in muscle, liver and adipose tissues; defects in their ability to metabolize fatty acids, result in insulin resistance. Insulin resistance and increased production of insulin-like growth factors upsurge the risk of tumor development. Muscle, liver and adipose tissues are also the major tissues for maintaining blood glucose levels. In insulin resistance state, glucose uptake by muscle and fat cells is deregulated and glycogen synthesis and storage are reduced in liver cells. That results in uncontrolled glucose production and its release into the blood. Insulin resistance also causes reduced insulin action on lipids and results in decreased uptake of circulating lipids and increased hydrolysis of stored triglycerides. As a result free fatty acid level is increased in the blood plasma. Increased fatty acids and their metabolites cause phosphorylation of insulin receptor substrate 1 (IRS-1) at serine, which blocks IRS-1 tyrosine phosphorylation and activation of phosphatidylinositol-3′ kinase (PI3K) activity. That results in reduced translocation of the glucose transporter GLUT4 to muscle membrane and liver cells [146,147]. The defects in mitochondrial fatty acid oxidation may increase fatty acid content in muscle and liver, which, in turn, negatively affects glucose transport and defective glycogen synthesis in muscle, and continued yield of glucose from the liver, which leads to insulin resistance.

Cells obtain much of their usable energy from oxidative phosphorylation, and most cancer cells depend on substrate level phosphorylation to meet energy demands. The metabolic switch from oxidative phosphorylation to aerobic glycolysis provides intermediates for cell growth and division and is regulated by both oncogenes and tumor suppressor genes [128]. Among these genes the tumor protein p53 encoded by the *TP53* gene plays a vital role in regulating several aspects of cellular metabolism [165]. Thus p53 is crucial in multicellular organisms; it regulates the cell cycle and functions as a tumor suppressor, p53 gene mediates metabolic changes in cells through the regulation of energy metabolism and oxidative stress to its range of activities. The continuation of un-regulated proliferation, differentiation and survival of cells leads to cancer. This is a multistep route comprising gene mutation and selection for cells with ability of proliferation, survival, invasion, and metastasis. These cells become malignant through a series of these gradual changes. Cancer cells are able to adjust their metabolism by *de novo* FA synthesis that yields lipids [106]. Then lipids regulate some important oncogenic pathways such as PI3K/AKT, Ras, or Wnt pathways [62]. But perhaps the most important signaling pathway that directly links high fat build up to cancer is the PI3K/Akt/mTOR cascade, which has been identified as target of many of the obesity-associated factors regulating cell proliferation and survival [33]. Accordingly, several factors take part in the activation of three important pathways, which include phosphoinositide 3-kinase (PI3K/Akt), mitogen-activated protein kinase (MAPK) and signal transducer and activator of transcription 3 (STAT3) pathways. Increased fat accumulation leads to mammalian target of rapamycin (mTOR), activation which contributes to the PI3K/Akt pathway inhibition and further activation of STAT3 pathway [33].

There are other key factors including hormones, transcription factors and proteins that are essential in both lipid metabolism and cellular development. Members of the mammalian Krüppel-like factors, KLFs are key transcription factors that regulate both lipid metabolism and tumor development. The KLF family members, regulate numerous critical cellular processes, including differentiation, cell proliferation, growth-related signal transduction, and angiogenesis. The studies conducted in our lab suggest that *Caenorhabditis elegans* KLFs are also important regulators of lipid metabolism and apoptosis; mutation in KLFs leads to excess fat accumulation and tumor development [72–74,186–189]. Thus blocking one gene activity leads to dramatically deleterious outcomes including fat accumulation and defective apoptosis. This provides a model where we can study both processes in one single organism. The critical challenge is determining the connectivity between fat accumulation and tumor development. Mammalian KLFs, including KLF4, KLF5, and KLF6, the highly characterized KLFs in regard to cell death/proliferation are also involved in lipid metabolism. These KLFs provide a basis to explore the connectivity between obesity and cancer. The present review is organized around KLF, lipid metabolism, and tumor development. We have discussed the functional interaction of KLFs with important signaling pathways that are important and necessary in lipid metabolism, and cell death/proliferation.

2. Fat buildup and its implication on cancer

Cellular energy metabolism dysfunction is an important feature of almost all cancers regardless of cellular or tissue origin. Apart from controversies [33], several early cross-sectional studies clearly establish strong association of fat accumulation with the incidence and mortality of a number of human cancers, such as those of the colon, pancreas, kidney, prostate cancer in men and breast cancer and endometrial cancer in women. Currently, experimental verification in many cases is missing, but there are substantial epidemiological and clinical studies involving a large population that have linked obese or over-weight individuals with increased risk of breast cancer [44], colon cancer [23], cancer of kidney [40], prostate cancer [12] cancer of the gallbladder, and pancreas [11,102]. It is widely believed that fat build up in the body increases the risk of tumor development because of its effect on secretion and action of insulin and insulin-like growth factors (IGFs) (Fig. 1). Insulin signals cells to grow; it can also increase the levels of some growth factors, such as IGFs. Because cancer cells have the ability to grow uncontrollably and resist programmed cell death, the growth factors are critical to the initial development of cancers, as well as to their progression. High insulin and IGFs can directly promote tumor cell proliferation via insulin/IGF signaling pathway and thus are important risk factor for various cancers in over-weight individuals [12,83,91,161] and are known to be a powerful signaling system in the body that prohibits cells from committing suicide. Defect in this signaling system may allow insulin and IGFs to increase which may foster the development of colon, premenopausal breast, and aggressive prostate cancers [12,83,91,161]. Insulin resistance causes cells to become less sensitive to insulin effects in transporting glucose into cells but unlikely to reduce the growth promoting properties of insulin. Glucose uptake across the plasma membrane is one of the rate-limiting steps in glucose metabolism of cancer cells. Glucose is transported into the cell via facilitative glucose transporters (GLUT) present in all cell types and thus their regulation, expression and activity play a key role in the supply of glucose and other sugars to the metabolically active cells. Several GLUT isoforms have been identified [172]; they all share a common transmembrane topology, highly conserved (97%), transmembrane domain. Many tumors show a high rate of glucose uptake and thus majority of cancers and isolated cancer cell lines over-express the GLUT family members which are present in the respective tissue of origin under non-cancerous. For example, dysregulation of GLUT 1, 3, 4, 5, 9 and 12 expressions has been reported in renal cell carcinoma, prostate carcinoma cell lines, lung tumor, liver metastasis, gastric tumor, and colorectal cancer conditions [18,67,97,108,109,131,152,180]. GLUT1 and 4 play an important role at several stages in cancer progression. During glucose transport, if glucose enters the muscle cell through GLUT4 and phosphorylated by hexokinase II, then it is directed to glycogen synthesis and glycolysis. On the other hand, if glucose enters via GLUT1 and phosphorylated by hexokinase I, the glucose 6-phosphate thus formed is accessible for all metabolic pathways, including the hexosamine pathway. Hexosamines show a negative feedback effect on GLUT4, hence, reduced GLUT4 activity reduces insulin-mediated glucose uptake. If glucose enters via GLUT1 and the activation of the hexosamine pathway is in ample, it can reduce the insulin-mediated glucose transport through GLUT4 leading to insulin resistance [53].

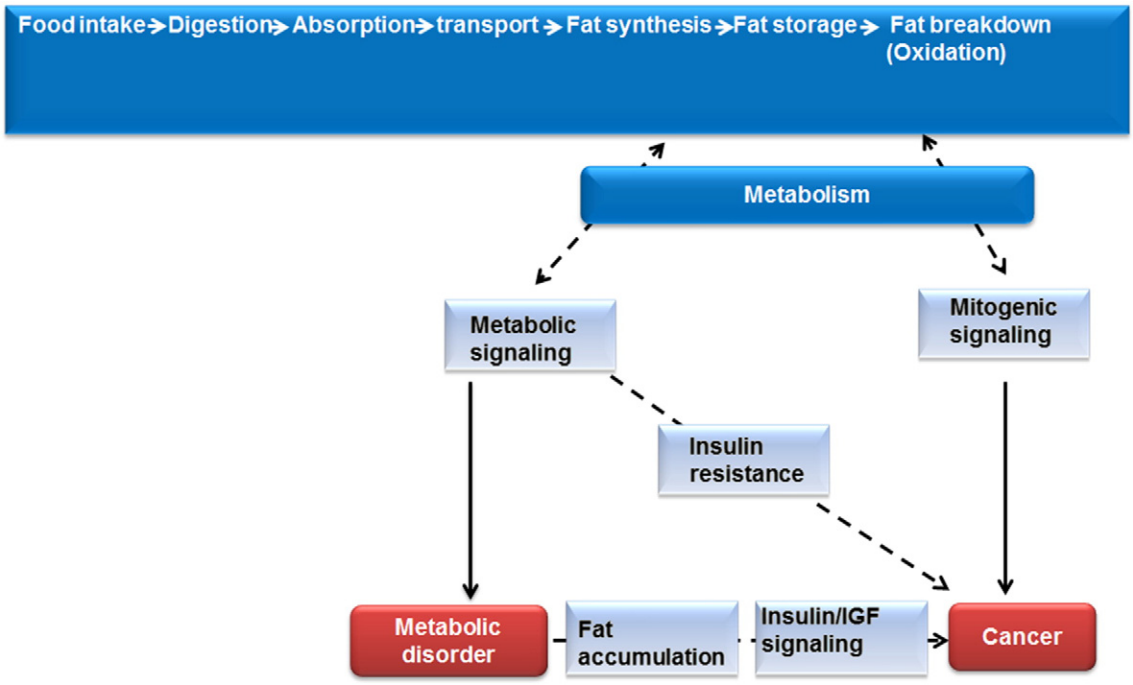

Fig. 1. The relationship between lipid metabolism, metabolic disorder, and cancer. Metabolic disorder can lead to fat accumulation, which can cause obesity. Obesity can affect insulin/IGF pathway. High insulin and IGFs can directly promote tumor cell proliferation via insulin/IGF signaling pathway. The blue box indicates the stages of lipid metabolism, the gray box indicates the various signaling involved in the pathways. Disruption in these pathways can lead to metabolic disorder and cancer (indicated by red box).

Malignant cells are known to have increased metabolism, high glucose requirements, and elevated glucose uptake. Identifying the mechanisms of lipid action on insulin secretion, glucose uptake and insulin resistance could provide important information about fat accumulation and tumor growth. Insulin resistance is an area in which KLFs have crucial functions suggesting that a broad transcriptional program, regulated by KLFs within cells might trigger cancer progression. Recent key studies on the biological role of KLF in both lipid metabolism and cell death/proliferation reflect the growing interest in this family of protein in identifying a common route connecting obesity with tumor growth.

3. Lipid metabolism: Transcriptional control of KLF regulation

Investigations into pre-adipocyte and fibroblast cultured cell lines have produced an abundance of data concerning the transcriptional cascade governing adipogenesis. A complex network of transcription factors including activators, co-activators, and repressors coordinates the expression of hundreds of proteins that take part in the development of mature fat cells. There are three classes of transcription factors, PPARγ (peroxisome proliferator-activated receptors), C/EBPα, (CCAAT/enhancer-binding proteins) and the basic-helix-loop-helix protein ADD1/SREBP (sterol regulatory element binding proteins) that play a key role in mammalian adipogenesis [132]. Upon exposure to hormonal stimuli, 3T3-L1 fibroblasts develop into fat-loaded adipocytes in about 7 days. This transformation is accompanied by the expression of a number of adipocyte-specific factors as well as cell-cycle regulators that together facilitate the expression of PPARγ and C/EBPα [43]. The designated cells undergo a terminal differentiation that is apparent by both the production of lipid droplets and the emergence of many metabolic factors unique to a developed fat cell. During the entire differentiation process there are several essential molecular interactions that occur among members of C/EBP, the PPAR and ADD1/SREBP1c [132]. C/EBPβ and C/EBPδ induce PPARγ, which in turn initiates the adipogenic program that is required to promote fat cell differentiation [8,133]. C/EBPα induces PPARγ, and continues to maintain PPARγ levels while conferring insulin sensitivity to adipocytes [173]. ADD1/SREBP1c promotes adipogenesis by several mechanisms including direct stimulation of PPARγ, expression, and production of the endogenous ligand that activates PPARγ [92,93]. There are other transcription factors, such as KLFs, that act as molecular switches in determining the fate of progenitors. The KLF proteins belong to a family of Sp1-like zinc-finger proteins, with 17 members identified to date [13,15,85,137,162]. KLF2, 3, 4, 5, 6, 7, 11, and 15 function as positive or negative regulators of adipocyte differentiation (Fig. 2).

3.1. KLF2 and 3

KLF2 and 3 inhibit adipocyte differentiation. Both KLF2 and 3 are expressed intensely in undifferentiated pre-adipocytes, but their expressions are reduced in mature adipocytes [7,151,174]. Constitutive expression of KLF2 inhibits PPARγ expression but has no effect on upstream regulators C/EBPβ and C/EBPδ. KLF2 also inhibits expression of both C/EBPα and ADD1/SREBP1c, two factors that play integral roles in adipocyte differentiation. Wu et al. [174] generated tetracycline-responsive lines of 3T3-L1 which expressed physiological levels of KLF2 and found that KLF2 prevented pre-adipocyte differentiation by partially restoring pre-adipocyte factor-1 (Pref-1). Embryonic cells derived from KLF2$^{-/-}$ knockout mice differentiated into adipocytes, suggesting that the presence of KLF2 is only important during later development, inhibiting pre-adipocyte maturation into adipocytes.

The overexpression of KLF3 in 3T3-L1 cell line blocks adipocyte differentiation because of its direct association with the *C/ebpα* promoter, and a reduced KLF3 level inhibits differentiation and inhibits C/EBPα expression [151]. KLF3 inhibits transcription by recruiting to its N terminal repression domain the corepressor C-terminal binding protein (CtBP) [160]. Mouse embryonic fibroblasts (MEFs) deficient of *Klf3* (*Klf3* −/−) are more predisposed to differentiate into adipocytes, suggesting that KLF3 inhibits adipogenesis *in vivo*. In a recent discovery Crossley group [9] noted that KLF3-null mice are lean and are protected from diet-induced obesity and glucose intolerance. Further observations indicated reduced plasma levels of leptin, and increased adiponectin. KLF3 binds the Fam132a promoter in both *in vitro* and *in vivo* leading to repression of promoter activity. Authors suggested that boosting levels of adipolin

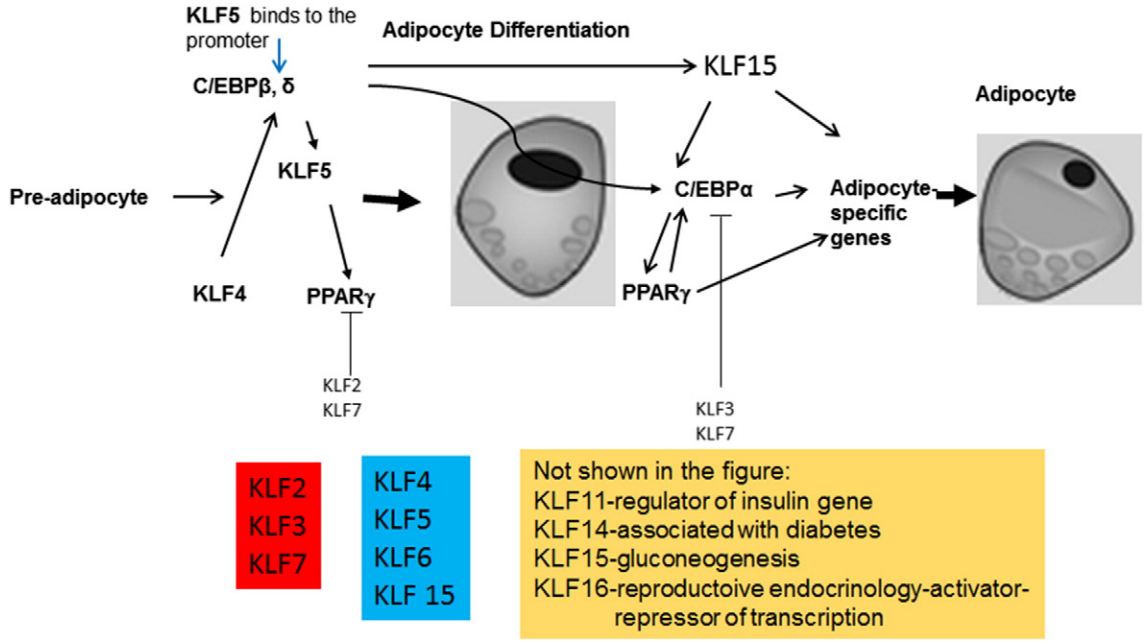

Fig. 2. The roles of mammalian KLFS in the regulation of various stages of adipogenesis. In the process of adipogenesis, Pre-adipocytes advance through an early stage of differentiation in which they become dedicated to their fate, followed by a later stage of differentiation into mature adipocytes. Several members of KLFs take part in the transcriptional control of adipocyte differentiation. KLFs act as positive and negative regulator of adipogenesis. KLFs that promote adipogenesis (boxed in blue) and those that inhibit this process are boxed in red. Some KLF members regulate insulin genes and diabetes (boxed in yellow).

via targeting of KLF3 offers a novel therapeutic strategy for the treatment of insulin resistance [9].

3.2. KLF4 and 5

KLF4 promotes adipogenesis and is an essential early regulator of this process. KLF4 is highly expressed in differentiated, post-mitotic cells of the skin and the gastrointestinal tract; it is also involved in differentiation–proliferation switch and functions as a regulator of the cell cycle [63,155]. KLF4 knockout mice die essentially after 12 h of birth probably resulting from defects in skin development and a failure to form a normal basement membrane [142]. The fat layer of the skin of these mice is disrupted, resulting in a malfunctioning of the skin barrier accompanied by a rapid loss of body fluids suggesting that this protein possesses a significant regulatory role in the development of adipose tissue [36]. KLF4 is expressed in 3T3-L1 cells within 30 min of exposure to a standard adipogenic cocktail; elimination of KLF4 activity in these cells inhibits adipogenesis and reduces C/EBPβ levels [36], suggesting that KLF4 is an upstream regulator of C/EBPβ. KLF4 binds C/EBPβ promoter and, in concert with Krox2 [14,36], transactivates its expression. Knockdown of C/EBPβ increases levels of KLF4 and Krox20, indicating that C/EBPβ normally controls KLF4 and Krox20 expression via a negative feedback loop.

Krüppel-like factor 5 also promotes adipogenesis and expresses early in adipocyte differentiation, and its promoter binds to C/EBPβ/δ factor [123]. KLF5 then acts in concert with C/EBPβ and C/EBPδ, to facilitate the expression of PPARγ. By such interactions, these factors mediate the early and late stages of adipogenesis as has been observed in neonatal heterozygous KLF5 +/− knockout mice [123]. KLF5 regulates proliferation of fibroblasts, smooth muscle cells, white adipose tissue and intestinal epithelial cells, and its SUMoylation seems to act as a molecular switch in response to PPARδ, altering adipogenic signals that can activate or repress the genes involved in lipid synthesis [37]. KLF5 interacts with SREBP-1 and acts as a critical regulator, of FASN (fatty acid synthase). KLF5 binds to SREBP-1 and increases the SREBP-1-mediated FASN promoter activity [38]. Overexpression of KLF5 spontaneously induces adipocyte differentiation, whereas expression of a dominant negative form of KLF5 inhibits adipogenesis [123]. *Klf5* +/− mice have defects in development of white adipose tissue and MEFs obtained from Klf5 +/− mice have attenuated adipocyte differentiation [123]. *Klf5* +/− mice are resistant to high fat diet induced obesity, and glucose intolerance, despite their consumption of more food than wild-type mice [124]. Instead *Klf5* +/− mice have increased energy expenditure, in part from increased expression of genes that encode lipid oxidation in the soleus muscle such as carnitine-palmitoyl transferase-1b (Cpt1b) and uncoupling proteins Ucp2 and Ucp3.

3.3. KLF6

Krüppel-like factor 6, a tumor suppressor gene, promotes adipogenesis by the transcriptional suppression of proto-oncogene delta-like 1 (*Dlk1*), a gene which encodes a transmembrane protein that inhibits adipocyte differentiation through its interaction with HDAC3 [98]. HDAC3 deacetylase represses PPARγ function as result of its interaction with hypophosphorylated retinoblastoma (*pRb*) [57]. Although *pRb* interacts with a considerable number of growth-promoting transcription factors [194], *pRb* phosphorylation is involved in pre-adipocyte differentiation [41]. KLF6 can, independent of *Rb,* moderate adipocyte differentiation through the transcriptional activation of adipocyte inducers such as PPARγ, C/EBPα/β, and steroyl-CoA desaturase-1 (SCD1).

3.4. KLF7

KLF7 is a negative regulator of adipogenesis. Kanazawa and colleagues analyzed 12 *klf* genes for single nucleotide polymorphisms (SNPs) and identified an SNP in KLF7 that was expressively linked to type 2 diabetes in Japanese subjects [86]. Kanazawa et al. [86] observed decreased expression of KLF7 during 3T3-L1 adipocyte differentiation, whereas overexpression of KLF7 inhibited adipogenesis [86], and also reduced expression of adipogenic genes such as C/EBPα and PPARγ [89]. In the insulin secreting cell line (HIT-T15 cells), an overexpression of KLF7 dramatically suppressed the glucose-induced secretion of insulin and reduced the expression of PPARγ and C/EBPα, thereby blocking adipogenesis [89]. Hence KLF7 may contribute to the pathogenesis of diabetes by impairing insulin biosynthesis and secretion in pancreatic β cells and reducing insulin sensitivity in peripheral tissues.

3.5. KLF11

KLF8, 9, and 10 have no definite roles in adipogenesis. KLF11 is a TGF-β-inducible member of the Sp1/KLF family and plays a key role in exocrine tissue growth. Neve et al. [120] noted that KLF11 is a glucose-induced up-regulator of the insulin gene in pancreatic β-cells [58,120]. However, KLF11 may also function in adipogenesis and metabolic control [24]. The gene variants of KLF11 that impair its transcriptional activity are associated with Type 2 diabetes (T2D). Further analysis of the KLF11 gene-related sequences revealed 19 frequent SNPs. Among those, four SNPs (SNP1, 9, 16, 17) clearly showed significant association with diabetes and the link between KLF11 SNPs and T2D is likely to result from one or more KLF11 variants. KLF11 regulates expression of pancreatic-duodenal homeobox-1, which is required for pancreatic organogenesis and activity of insulin secreting β cells in adults [59]. Genetic analysis of *KLF11* among North European populations identified several rare variants that impaired its transcriptional activity and are associated with early onset of type 2 diabetes [120]. KLF11 also regulates cholesterol-mediated gene expression. Following exposure of vascular endothelial cells to cholesterol, KLF11 represses the gene that encodes caveolin-1, which is involved in cholesterol homeostasis [24]. Upon depletion of cholesterol, KLF11 is displaced from a Sp1-site that flanks a sterol-response element in the *caveolin-1* promoter, allowing the binding the binding of SREBP and Sp1 and activation of the *caveolin-1* promoter [24]. Yin et al. [176] screened for (PPAR) co-regulators using a genome-wide high-throughput co-activation system and identified KLF11 as a co-regulator of PPAR, which interacts with (PPAR) to regulate its function in mouse cerebral vascular endothelial cell cultures. KLF11 is also a direct transcriptional target of (PPAR).

3.6. KLF14

In an exciting discovery, Small et al. [148] have shown that the maternally expressed KLF14 which is associated with type 2 diabetes (T2D) and the cis-acting expression quantitative trait locus (eQTL) of high-density lipoprotein cholesterol act as a master trans-regulator of adipose gene expression. Expression levels of genes regulated by this *trans*-eQTL are highly correlated with concurrently measured metabolic traits, and a subset of the *trans*-regulated genes harbor variants directly associated with metabolic phenotypes. These data are consistent with a model whereby *KLF14* acts as a major regulator of events in fat tissue, with these alterations in the levels of *KLF14* leading, through as yet unspecified mechanisms, to peripheral insulin resistance and T2D. Authors suggest that this *trans*-eQTL network provides a mechanistic understanding of the effect of the *KLF14* locus on metabolic disease risk and offers a potential model for other complex traits [148].

3.7. KLF15

Krüppel-like factor 15 positively controls adipogenesis through its regulation of PPARγ expression. KLF15 is up-regulated at the time of pre-adipocytes differentiation into adipocytes but blocking its expression reduces the PPARγ expression and prevents adipogenesis [114]. Transcription factors C/EBPβ and C/EBPδ activate KLF15 and while acting together, KLF15 and C/EBPα enhance PPARγ expression following a reduction in C/EBPβ and C/EBPδ transcript levels in NIH 3T3 cells [114]. The same PPARγ further increases C/EBPα levels, suggesting that a positive feedback mechanism is present between the two factors [173]. KLF15 regulates expression of glucose transporter GLUT4 in both adipose and muscle tissues [69]. KLF15 is involved in gluconeogenesis. *Klf15* −/− knockout mice is defective in amino acid catabolism because of the reduced expression of enzymes needed for amino acid degradation; reductions of these enzymes limit the availability of substrates for gluconeogenesis [70].

3.8. KLF16

KLF16 has a regulatory role in reproductive endocrinology; it controls the expression of key endometrial genes involved in metabolism and endocrine function in uterine cells, and functions as either activator or repressor of transcription [49]. KLF16 functions by coupling to two antagonistic chromatin-mediated pathways, the Sin3a-HDAC and HAT systems and complexes with the Sin3a-HDAC system by binding to the PAH2 domain, primarily by hydrophobic interactions in a manner that differ from the MAD1-SID but highly resemble the HBP1-SID and interact with all three Sin3 isoforms (Sin3a, Sin3bL, and Sin3bS). The structural domains of KLF16 are highly related to KLF9, 10, 11, 13, and 14 and suggest that the mechanisms used for KLF16 are likely applicable to understanding these KLF family members.

KLFs have different roles during fat cell differentiation and development depending on the sites of expression and their post-translational modification. The functions of KLFs are in some cases overlapping and in others widely divergent. Members of KLFs are modified by co-regulatory proteins through acetylation, phosphorylation, ubiquitination, and sumoylation to improve their transcriptional activity. Following are the selected examples of those KLFs that function in lipid metabolism and or tumor development (Table 1 and Fig. 3).

4. Post-translational modification of KLFs

4.1. Acetylation

The acetylation is regulated by signaling pathways that affect the association of histone acetyl transferases (HATs) and histone deacetylases (HDACs) with KLF proteins. For instance, KLF4 functions in smooth muscle cell differentiation. Treatment of vascular smooth muscle cells (SMCs) with all-*trans* retinoic acid (ATRA) induces HDAC2 phosphorylation mediated by JNK signaling. This causes HDAC2 to dissociate from KLF4, which results in an increase in KLF4 acetylation [110]. While activation of TGFbeta recruits p300 to the KLF5-Smad complex to acetylate KLF5, then the acetylated KLF5 binds to the Smad and modifies the binding of other factors to p15 promoter to induce its transcription [68]. These changes influence KLF5 recruited cofactors to the promoter of the gene encoding the cell cycle inhibitor p15 (*CDKN2B*) [68]. However, the KLF5 interaction with HDAC1 blocks binding of KLF5 to p300, reducing KLF5 binding and activation of transcriptional targets [104]. KLF6 and 13 are also acetylated, resulting in enhanced transcriptional activity [98,149].

4.2. Phosphorylation

There are significant bodies of literature that provide evidence for the post-translation modification of KLFs in the form of phosphorylation. KLF5 specifically binds to several effector proteins including, c-Jun [75], CBP [184], retinoic acid receptor-α [186,189], and the ubiquitin ligase, F-box [100]. Phosphorylation of KLF13 in T cell by the serine/threonine kinase PRP4 increases nuclear localization of KLF13 and transcriptional activation of chemokine C-C motif ligand 5 (*CCL5*) [79]. On the other hand, phosphorylation of KLF11 by extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) disrupts the interaction of KLF11 with Sin3A to block repression of *Smad*7 [55]. Expression of an Erk-insensitive KLF11 mutant restores both mSin3a binding and Smad7 repression and results in enhanced TGF-beta signaling in pancreatic cancer cells [55].

4.3. Ubiquitination

KLF4 and 6 are regulated by degradation through ubiquitination. Degradation of KLF4 removes its cell cycle inhibitory effects, and allows the cells to re-enter the cell cycle. KLF6 is ubiquitinated and undergoes proteasomal degradation in cultured cells following exposure to DNA

Table 1
Role of mammalian KLFs in adipogenesis and cancer.

Transcription factor	Tissue function	Cancers with KLFs alteration
KLF 2	Negative regulator, inhibitor of adipogenesis	Breast, colon, intestine, prostate
KLF3	Negative regulator, inhibitor of adipogenesis	Not found
KLF4	Promotes adipogenesis; down regulate C/EBPβ	Tumor suppressor in colon, oncogene in breast. bladder, brain, esophagus, head, neck, liver, lung, melanoma, pancreas, prostate, skin, stomach
KLF5	Involved in the induction of PPARγ, promotes adipogenesis	Breast, colon, intestine, esophagus, gastro-intestinal stromal tumor, lung, pancreas, prostate, stomach
KLF6	Promotes adipogenesis via PPARγ	Tumor suppressor in prostate cancer, silenced or mutated in other cancers. Brain, breast, colon, intestine, liver, lung, ovary, pancreas
KLF7	Negative regulator of adipogenesis, inhibits adipocyte differentiation. Single nucleotide polymorphisms (SNPs) associated with type 2 diabetes	Not found
KLF8	No definite role in adipogenesis	Breast, kidney, liver, ovary, prostate, stomach
KLF9	No definite role in adipogenesis	Brain, colon, intestine, uterus
KLF10	No definite role in adipogenesis	Breast, kidney, pancreas,
KLF11	Glucose-induced regulator of the insulin gene variants associated with early-onset type 2 diabetes	Tumor suppressor in pancreatic cancer, breast colon, intestine, kidney, lung, ovary, stomach
KLF12	No definite role in adipogenesis	Breast, stomach, gastric cancer cell
KLF13	No definite role in adipogenesis	Head and neck, oral cancer cell
KLF14	Associated with type 2 diabetes, master trans-regulator of adipose gene expression. In metabolism and endocrine function in uterine cells	Not found
KLF15	Positive regulator of adipogenesis, through its regulation of PPARγ expression, regulates glucose transporter GLUT4 in both adipose and muscle tissues	Not found
KLF16	Controls the expression of key endometrial genes involved in metabolism, activator or repressor of transcription	Not found

damaging agents [6]. Whereas high levels of DNA damage can degrade KLF6, the lower levels of DNA damage can enhance KLF6 levels, resulting in cell cycle arrest. This indicates that degradation of KLF6 is an important event in regulating cell fate decisions between cell cycle arrest and cell death. Cancer cells overexpressing a KLF6 splice variant KLF6-SV1, binds to the pro-apoptotic protein NOXA, resulting in ubiquitination and degradation of both proteins, promoting cancer cell survival [50]. KLF2 and 5 bind the ubiquitin ligase WWP-1, while ubiquitination of these KLFs promotes their rapid degradation by the proteasomal complex [31,34,35,185]. Overexpression of WWP-1 in certain prostate and breast cancer cell lines increases degradation that leads to a loss of KLF5 activity [31,34,35]. Similarly, KLF5 is ubiquitinated by E3 ubiquitin ligase and tumor suppressor, Fbw7/hCDC4, in a CDC4 phosphodegron (CPD)-dependent manner [100]. KLF10 is a target of the E3 ligase Itch, which mediates both mono- and poly-ubiquitination in response to TGF-β signaling in naïve T cells [164].

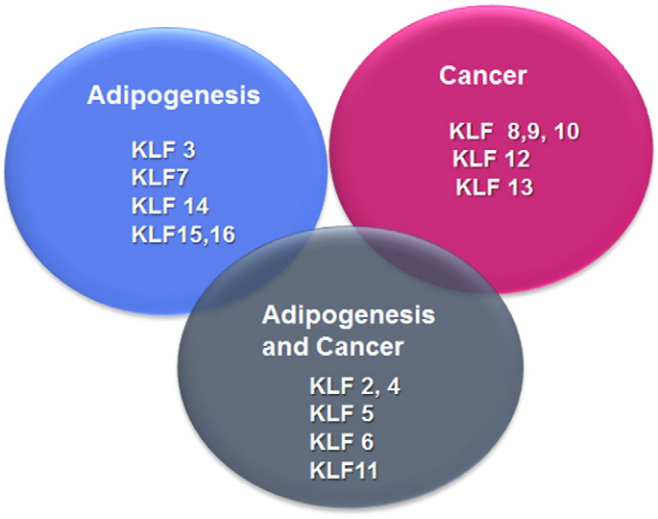

Fig. 3. The function of mammalian KLFs in lipid metabolism and tumor biology. Some KLFs function as a positive or negative regulator of adipogeneis (indicated in blue circle). Some other members of KLFs function as an activator or suppressor of tumor (indicated in red circle). KLF2, 4, 5, 6 and 11 play critical roles in both adipogenesis and tumor biology (indicated black circle).

4.4. Sumoylation

Members of KLFs are modified by the small ubiquitin-like modifier (SUMO) peptide affecting their transcriptional activity. For instance, KLF3 interacts with the E2 SUMO-conjugating enzyme Ubc9 and is co-valently modified by SUMO-1 *in vitro* and *in vivo* [126]. Another family member, KLF8 promotes cell cycle progression via positive regulation of the cyclin D1 promoter. KLF8 can be sumoylated via interaction with a number of SUMO E3 ligase family members such as, protein inhibitor of activated STAT1 (PIAS1), PIASy and PIASxα [170,171]. While overexpression of SUMO-1 can suppress the cell-cycle promoting effects of KLF8, the mutation of the primary sumoylation site in KLF8 enhances its effects on cell cycle progression. The family members KLF4 and 5 interact with the SUMO E3 ligase, PIAS1 which promotes KLF4 sumoylation and subsequent degradation, making it unable to repress α-smooth muscle actin (*α-SMA*) in SMCs [90]. However, sumoylation of KLF5 increases its nuclear localization and promotes its activation of the cell cycle genes *cyclin D1* and *Cdc2* [51,52]. KLF5 regulates lipid metabolism through PPAR-δ signaling; KLF5 is sumoylated and functions with transcriptional repressor complexes regulating *CPt1b, Ucp2* and *Ucp3* genes involved in lipid oxidation. PPARδ interacts with an agonist that leads its de-sumolytion and binding to transcriptional activation complexes that drive expression of lipid metabolic genes [124].

The members of KLF family play a significant role in various cancer relevant processes. KLF expression has been shown to mediate tumor initiation, progression or suppression through their interaction with a number of oncogenic signaling pathways. Thus, depending on the cellular environment KLFs can act as tumor suppressor or tumor promoter.

5. KLFs: Regulatory roles in cancer cell apoptosis

In nature new cells are continuously produced, and many other cells are programmed to die and removed. Resistance to programmed cell death or apoptosis is a characteristic of cancer. Autophagy, necrosis and apoptosis are known cell death pathways. Cross-talk among the different types of cell death pathways happens at manifold levels. Autophagy, a non-apoptotic programmed cell death is a self-degradative process in which cells digest parts of their own cytoplasm, clear intracellular mass as well as damaged organelles. Similar to autophagy,

necrosis is also a non-specific cell death and is essentially occurred by rupture of the plasma membrane which results in inflammatory response and damage of the surrounding cells. Apoptosis is a naturally occurring process associated with cell death, engulfment and removal of cell corpses. Evidently, apoptosis is controlled by a series of regulated events involving many factors that have imperative roles in apoptotic flows [56,71,87,101,157]. The mutations in some genes disrupt the normal process of apoptosis, which leads to tumor initiation–progression, while other genetic alterations stimulate programmed cell death and thus prevent tumor formation. The Bcl-2 family, the p53 family, death receptors and inhibitor of apoptosis proteins (IAPs) play important roles in cell death pathways [87,101]. Cell proliferation and cell death pathways are frequently interrelated hence many of the pathways where KLFs are important and necessary in cancer cell proliferation, for examples, p53, E2F, MYC and the MAPKs are also significant for cell death. KLFs regulate quite a few apoptotic and survival factors that include the BCL-2 family members, BIRC5 and Jun N-terminal kinase (JNK). Several members of mammalian KLFS perform critical role in the pathobiology of many human cancer. KLF activity is changed in human cancers; some KLFs can be a tumor suppressor or an oncogene depending on tissue, tumor type or cancer stage. Uncontrolled cell proliferation is critical for the initial of cancer development, and several KLFs have been reported to be involved in the dysregulation of proliferation. Cell cycle regulators such as the cyclins, cyclin-dependent kinases (CDKs), and CDK inhibitors are common transcriptional targets for KLFs including for KLF4, 5 and 6 which are well characterized KLFs in human cancers. In the following paragraphs we discussed the interacting role of representative KLF family members with important pathways involved in tumor biology.

5.1. KLF4

KLF4 is an important regulator of normal cell proliferation, inhibits proliferation or tumor growth in pancreatic, gastric, colorectal, bladder, cervical and lung carcinomas and suppression of its activity leads to various types of cancer [105]. This protein is expressed in terminally differentiated epithelial cells at the villus borders of the mucosa, known to induce growth arrest, inhibits cell proliferation by blocking G1/S progression of the cell cycle and to mediate p53 dependent G1/S cell cycle arrest in response to DNA damage [28,179]. KLF4 performs critical function in cell-cycle-checkpoint in response to DNA damage, via its induction of p21Cip1/Waf1 expression contributing to its tumor suppressor activity, for example, in GI tract. Upon KLF4 induction, the expression of cell cycle inhibitor p21/Cip1 is increased [183], while cell cycle promoter cyclin D1 is decreased [143,144]. KLF4 uses various mechanisms depending on the target genes to either activate or repress transcription. It acts as a tumor suppressor, but when its ability to induce cell cycle arrest is blocked [134,135], then it can contribute to tumor progression by inhibiting apoptosis. Ectopic expression of KLF4 in γ-irradiated RKO colon cancer cells reduces the number of apoptotic cells, forcing these cells to growth arrest [66]. Over-expression of KLF4 in the human colon cancer cell line RKO reduces colony formation, cell migration and invasion [47]. Interestingly, increased KLF4 expression inhibits trans-activation of the Bax promoter by p53 [66] and modulates apoptosis through regulation of p53 expression. In MDA-MB-134 breast cancer cells, KLF4 binds to p53 promoter and suppresses its transcription [134]. In addition, reduced expression of KLF4 in breast cancer cells has been shown to restore p53 expression, leading to p53-dependent apoptosis [134]. The question is that how KLF4 determines the p53 response to DNA damage. Recently, Zhou et al. [192] observed a KLF4 activation response by p53 following mild DNA damage, but also noted a strong repression response from increased production of mRNA on severe DNA damage driving cells to apoptosis. Obstructing KLF4 repression results in the silencing of p53-mediated apoptosis. Furthermore, removing the effect of KLF4 induction changes the p53 response from cell cycle arrest to cell death [192]. KLF4 regulates differentiation and maintenance of cell cycle checkpoint and loss of its expression known to induce tumor formation, which may lead to colorectal, stomach, esophageal and bladder cancers [39,45,46,84,88,122,143,144,158,166,169,169–171,185,190]. KLF4 is known as a tumor suppressor, but there are many other reports those based on genetic screens that suggest that KLF4 may also act as a putative oncogene [60,134,153]. For instance, increased level of KLF4 has been observed in ~70% of mammary carcinomas [61]. KLF4 has also been reported as a potential biomarker in head and neck cancer [113].

5.2. KLF5

KLF5 is normally expressed in both esophageal epithelial cells, and proliferating epithelial cells at the base of the intestinal crypts while promoting cell growth. Remarkably, the presence of bacterial pathogens in colon may cause KLF5 activation which is likely to be involved in the pro-proliferative and pro-inflammatory responses to infection. KLF5 functions in cell proliferation and mediate various features of cardiovascular remodeling, differentiation and development [65,115,154] and is also involved in tumor progression in breast and prostate cancers [27,29,30,32]. KLF5 reduced cell viability and inhibited cell proliferation in esophageal and breast cancer cell lines [29,175]. The loss of KLF5 activity has been reported in many cancers [27,30–32,34,35,136] and suggests its putative tumor suppressor role. For instance, KLF5 is absent in human esophageal squamous cell carcinoma (ESCC), however, upon induction ESCC cells show increased apoptosis, decreased viability, and increased activity of the proapoptotic factor BAX [156], as well as increased JNK signaling which is an important upstream mediator of proapoptotic pathways including BAX. KLF5 activates JNK signaling mediated by transactivation of *ASK1* and *MKK4*, two key upstream regulators of the JNK pathway, and inhibition of JNK blocks apoptosis. In a recent publication, Zhao et al. [191] identified KLF5 as an important modulator of apoptosis secondary to DNA damage in a p53-independent manner. The apoptotic phenotype consequent to DNA damage is associated with down-regulation of Pim1. KLF5 binds to putative Sp1-binding consensus sequences present in the Pim1 promoter, the binding increases soon after DNA damage. During apoptosis, KLF5 plays pro-proliferative role in the intestinal epithelium, and consequently mediate some oncogenic events in this tissue. Hence its increased expression is linked to shorter disease-free survival and overall survival of breast cancer patient while its low expression has been correlated with better survival [159]. It is true that in most cases KLF5 promotes proliferation but it may also, activate growth-suppressive or pro-apoptotic factors that can inhibit its growth promoting activity. In this context, TGF-beta a potentially downstream target of KLF5 may function as mediator of this tumor suppressor effect [145]. TGF-beta has long been known as a negative regulator of epithelial cell growth, and it shows its tumor suppressor activity early in tumorigenesis [4]. Perhaps KLF5 mediates pro-apoptotic events through Bax and p21Cip1/Waf1 induction [175]; its pro-proliferative function in intestinal epithelial cells depends on the activation of important cell-cycle promoting genes. Yang et al.[175] have proposed that the growth-promoting properties of KLF5 may help mediate transforming events, such as those activated by oncogenic H-Ras.

5.3. KLF6

KLF6 is known to regulate key cellular functions ranging from differentiation to proliferation and apoptosis [64,96,139]. Owing to the biological importance of KLF6 in cell proliferation and apoptosis, there have been many excellent studies to define the role of KLF6 in tumor biology. It has been proposed that KLF6 is a tumor suppressor because of its reduced expression or the existence of frequent somatic inactivating mutations within the *klf6* gene in prostate carcinoma, colorectal tumors, glioblastoma, hepatocellular carcinoma and lung-derived tumors [20,22,27,30,32,81,111,117,140,178]. However, a significant number of

other studies concluded that genetic alterations in *klf6* were not seen frequently in distinct types of human cancers, moreover, the *klf6* gene expression was enhanced and not reduced in some tumors [2,16,20,94,95,99,112]. As yet, there is no definite answer as to what is the mechanism of KLF6 regulation of growth arrest and tumor biology. While KLF6 is mutated or deleted in human prostate tumors [117], the ectopic expression of KLF6 in prostate cancer cells induces apoptosis [78,81]. KLF6 induces apoptosis in prostate cancer cells by ATF3 (activating transcription factor 3) expression and binds directly to and activates the *atf3* promoter. ATF3 induced apoptosis when ectopically expressed in cells, whereas knockdown of ATF3 by siRNA blocked KLF6-induced apoptosis. KLF6 mutants derived from clinical prostate cancers failed to activate the *atf3* promoter and were unable to induce apoptosis [78]. Downregulation of KLF6-SV1 isoform induces spontaneous apoptosis in ovarian, lung, and prostate cancer cell lines [50,118,140] suggesting that KLF6-SV1 might be a therapeutic target for cancer. KLF6 suppresses tumor growth via induction of apoptosis in NSCLC (non small cell lung cancer) which may suggest that KLF6 is a tumor suppressor for NSCLC [81]. A study by Benzeno et al. [10] has shown that KLF6 directly interacts with cyclin D1 to suppress cyclin-dependent kinase 4 and causes cell cycle arrest [10].

5.4. KLF8

KLF8 functions in tumorigenesis through its ability to induce both cell cycle progression via activation of cyclin D1 [181] and in promoting epithelial to mesenchymal transition, oncogenic transformation and invasion [167,168]. The post-translational regulation of KLF8 takes place by the interaction between histone acetyltransferase (HAT) co-activator mediated acetylation and C-terminal binding protein (CtBP) promoted sumoylation. KLF8 functions both as a repressor [168,170,171] or activator [170,171,181] by recruiting the CtBP co-repressor via the 86PVDLS90 repressor motif or the p300 and PCAF-HAT co-activators via the Q118 and Q248 residues to target gene promoters. KLF8 is involved in DNA repair in breast cancer cells [103] and that KLF8 expression is required for protecting human breast cancer cells from doxorubicin-induced DNA damage and cell death. In response to the DNA damage, KLF8 is phosphorylated by the DNA-dependent protein kinase catalytic subunit and, subsequently, SUMOylated by SUMO E3 ligases protein inhibitors of activated STAT (PIASs), which depends upon the interaction of KLF8 with DNA-dependent protein kinase catalytic subunit, PIASs, and PARP-1 as well as their enzymatic activities. Also, SUMOylation does not affect KLF8 nuclear localization but does regulate its function as a transcriptional repressor [107].

5.5. KLF9

Endometrial cancer is the most commonly diagnosed female genital tract malignancy. KLF9 is expressed in uterine stroma and glandular epithelium, where it affects cellular proliferation, differentiation, and apoptosis. It has been suggested that KLF9 loss-of-expression accompanying endometrial carcinogenesis may predispose endometrial epithelial cells to mechanisms of escape from estrogen-mediated growth regulation, leading to progression of established neoplasms [138]. KLF9 is a negative regulator of ligand-dependent ERα signaling in endometrial carcinoma cells [163].

5.6. KLF10

Members of the TGFβ family of peptides are known to exert antiproliferative effects and induce apoptosis in many epithelial cell types [150]. Overexpression of KLF10 in the TGFβ-sensitive epithelial cell line PANC1 and hepatoma cell lines has been found to induce apoptosis [129]. This KLF10-induced apoptosis appears to be similar to the P53 induced mitochondrial apoptosis pathway, which occurs in pancreatic epithelial [129], other epithelial cells [26], and lymphoma cells [141]. In subsequent publication Jin et al. [82] showed that KLF10 induce apoptosis in leukemic or melanoma cells through the mitochondrial pathway by up-regulating Bax and Bim, and down-regulating Bcl-2 and Bcl-XL release of cytochrome *c* from the mitochondria, and activation of caspase 3. The induction of apoptosis by KLF10 in many cancer cells, such as breast, prostate and several other cancer lines suggests its role as tumor suppressor in many cancers including breast cancer (reviewed by [150]. Reinholz et al. [130] measured the mRNA levels of KLF10 and its target genes, Smad7, Smad2, and BARD1 in 14 normal human breast, 5 noninvasive, 57 invasive and 5 metastatic human breast tumor tissues [130]. KLF10 and Smad7 mRNA levels were lower in all noninvasive tumors compared with normal breast tissues but Smad7 mRNA levels increased in more advanced stages of cancer. KLF10, BARD1, and Smad2 mRNA levels were lower in invasive cancers compared with normal breast tissues. KLF10 is also involved in human prostate cancer [54,125,177], pancreatic cancer [5,43,195], colorectal cancer [27,30,32], and brain cancers [193].

5.7. KLF11

KLF11 functions as a tumor suppressor. KLF11 represses TGF-beta-induced transcription from the Smad7 promoter by recruiting mSin3a via GC-rich sites. This function is inhibited in pancreatic cancer cells with oncogenic Ras mutations, in which Erk/mitogen-activated protein kinase phosphorylates KLF11, leading to disruption of KLF11–mSin3a interaction [55] suggesting the importance of this mechanism for oncogenesis. Buck et al. [19] demonstrated that KLF11 is an essential partner of Smad3 in the transcriptional silencing of the growth-stimulatory *c-myc* proto-oncogene in normal epithelial cells, a key step in TGFβ-induced cell growth inhibition [19]. Aberrant activation of ERK–MAPK interferes with KLF11–Smad3 complex formation, preventing the binding of both KLF11–Smad3 to the TIE promoter element, that results in impaired *c-myc* repression and loss of growth inhibition by TGFβ in pancreatic cancer cells [19].

5.8. KLF12 and 13

KLF12 is known as a repressor of transcription factor AP-2α [80]. While knockdown of KLF12 in HGC27 gastric cancer cells results in growth arrest in this cell lines [116], the overexpression of this protein in NIH3T3 and AZ-521 cells increases their invasive potential suggesting that KLF12 plays an important role in the progression of gastric cancer. The role of KLF13 is more complex. Zhou and colleagues recently developed *klf13* (*klf13 −/−*) knockout mice [182]. These mice showed enlarged thymuses and spleens because of low thymocyte cell death. This may be the result of the inhibitory effect of KLF13 on anti-apoptotic factor BCLXL expression [182]. The translational regulation of KLF13 expression occurs through the 5′-untranslated region of its mRNA a cell type-specific manner [121], overexpression of the translation initiation factor eIF4E and Mnk1 increases KLF13 levels. These processes are regulated by ERK1/2 and p38 MAPKs which allow T cells to quickly adjust levels of chemokine gene RANTES (regulated on activation normal T cell expressed and secreted) expression in response to changes in the cellular environment. KLF13 recruits several transcription co-activators and the serine/threonine protein kinase PRP4 (for its phosphorylation) to activate RANTES [3,79] and knockdown of KLF13, which is typically overexpressed in oral cancer cells, decreases cell growth (possibly through *CCND1*, which is a direct transcriptional target for KLF13 [119].

The studies in cancer epidemiology have identified dysfunctional lipid metabolism associated excess fat deposits and cancer development. There is a tight balance of relative expression/activity of KLFs influencing their physiological and pathological effects in both lipid metabolism and tumor development and progression. We have learned a great deal about the roles of KLFs in both metabolism and cancer using animal models, such as mouse and rat, however, a genetic model, such as *C. elegans* is

needed for a thorough examination of KLF function in vivo during the development of an organism. Findings in worm addresses processes known to be dysregulated in various steps of cancer development including cell cycle progression, terminal differentiation, growth factor signaling, tumorigenesis, invasion, and metastasis. Comprehensive genetic studies of programmed cell death in *C. elegans* have identified many key players that take part in this important physiological process [1,48,76,77]. The cell death protease caspases that are highly conserved, cysteine-dependent aspartate-specific proteases have been identified in *C. elegans*. Genome-wide exploration of genes required for fat metabolism and program cell death in this organism significantly broadens experimental access to the complex molecular processes and regulation of these processes. This relatively simple organism can provide important clues about the changes occurred during lipid metabolism that can disrupt the pathways through which cancer development is mediated.

6. *C. elegans* model to study KLF regulation of lipid metabolism and cell death-proliferation

The *C. elegans* genome predicts three KLFs, which include the gene *klf1* [17,72], *klf2* and *klf3* [73,74,186–189]. All three *C. elegans* KLFs share the highest identity with several members of mammalian KLFs, including KLF2, 3, 4, 5, 6 and 8 in terms of their C-terminal C_2H_2 zinc fingers, despite little homology in their N-terminal regions. Our recent studies have shown that *C. elegans* KLF3 has an important regulatory role in FA biosynthesis, lipid secretion, mitochondrial proliferation, insulin signaling, and beta-oxidation [17,73,74,186–189]. These are significant findings because it provides a basis for further studies in cellular, mouse or rat models aimed at understanding the effect of alterations in lipid metabolism in human. We have also identified the critical regulatory function of *klf1* in both lipid metabolism, and cell death pathway [72]. Suppression of *klf1* activity not only results in fat accumulation but also causes more cell death. We do not know if cell death is the consequences of excess fat accumulation in the *klf1* worm. Although there is requirement for more experimental verification, our current model provides an excellent opportunity and a basis for further studies aiming to understand obesity and its connection to cancer in human.

Recently, *C. elegans* KLF1 has been identified as an essential and specific regulator of DR-induced longevity and a substrate for ubiquitylation by WWP-1 [25]. Knockdown of *klf-1* suppresses the extended lifespan of both DR animals and wwp-1-overexpressing animals, indicating that KLF1 functions within the same pathway as WWP-1. In addition, overexpression of *klf1* in the intestine is sufficient to extend the lifespan of WT animals on an ad libitum diet, and requires wwp-1 or pha-4/FoxA. WWP-1 directly interacts with KLF1 and mediates multiple monoubiquitylation of KLF1.

7. Summary

Fat buildup that in most part results from lipid metabolism dysfunction can also cause various cancers. Both lipid metabolism and cell death/proliferation are controlled by biochemical and molecular pathways involving many proteins, various cells, tissues and organelles, alteration in these pathways leads to fat accumulation or tumor growth. The development of molecular profiling methodologies has created opportunities for understanding the relationship of obesity to cancer at a mechanistic level. The potential role of lipids in facilitating the spread of cancerous cells to secondary sites, is not fully understood. Is there something special in the relationship between cellular lipids and tumor formation? In other word, is there a system of lipid instructions that conditions the killing activity of pro-apoptotic proteins? The experimental innovations that have been made in *C. elegans* make it possible to count individual cells in whole animals and offer a promising avenue to understand protein function in multi-cellular environments. Moreover, the recent development in quantitative time-laps microscopy and fluorescent reporter genes, together allow us to track the dynamic behavior of specific protein over time in individual living cells. If factors that contribute to obesity and changes in cancer incidence can be known, our understanding of carcinogenesis would be significantly enhanced. In this regard, the modulation of energy balance, multiple signaling pathways, and inflammatory processes are some of the mechanisms linking obesity to cancer. This information could have important implications for understanding cancer etiology, pathogenesis, and prevention.

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