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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].