

Link between obesity and cancer: role of triglyceride/free fatty acid cycling

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Abstract. – Obesity has long been suspected to be a risk factor for cancer. The relationship between body fat deposition and the pathogenesis of cancer has been the subject of many studies, however, no clear consensus has emerged linking these two biological processes. Recent epidemiological studies showed a strong association between cancer-related deaths and increased body-mass index. In fact, obesity has been identified as a cause for oesophageal, colon, uterine, kidney and post-menopausal breast cancers and also as a significant risk factor for the cancers of prostate, pancreas and non-Hodgkin lymphoma. Approximately 16-20% of cancer deaths in women and 14% of cancer deaths in men were found to be due to obesity. It is also recognized that there is a positive relationship between type-2 diabetes associated hyperinsulinemia and cancer incidence. Though the recent annual report in US finds that the incidence and mortality rates for many cancers have dropped in 2003 since 1975, this decline is mostly due to a substantial decrease in tobacco use among men. However, during the same period the rise in the prevalence of obesity might have contributed to the increased risk and incidence of prostate, liver, kidney, oesophageal and breast cancers.

Whether the elevated cancer risk in obesity arises from similar modulation of parallel signaling/metabolic pathways during adipogenesis and oncogenesis has not been hitherto addressed. In this Review we would like to bring out the similarities between adipogenesis and oncogenesis and how this relationship at molecular level may be relevant for the development of effective therapeutics for obesity, diabetes and cancer. While adipogenesis is the process of formation of mature adipocytes or fat cells under normal physiological conditions, oncogenesis is a pathological process, which results in the uncontrolled growth of cells leading to cancer. Though, both these processes at surface seem to be totally different, we believe that there are important common denominators for these processes that need to be recognized. We will discuss the role of two such underlying factors – (1) malonyl-CoA, an important regulator of fatty acid metabolism and (2) triglyceride/free fatty

acid (TG/FFA) cycling which is central to the generation of multiple signals for controlling various metabolic, physiological and signaling pathways in the cell.

Key Words:

Obesity, Cancer, Triglyceride/free fatty acid cycling, Adipogenesis, Oncogenesis, Hypoxia inducible factor-1 α , p53.

Introduction

Obesity has long been suspected to be a risk factor for cancer. The relationship between body fat deposition and the pathogenesis of cancer has been the subject of many studies, however, no clear consensus has emerged linking these two biological processes. Recent epidemiological reports¹ showed a strong association between cancer-related deaths and increased body-mass index (BMI). In fact, obesity has been identified as a cause for oesophageal, colon, uterine, kidney and post-menopausal breast cancers and also as a significant risk factor for the cancers of prostate, pancreas and non-Hodgkin lymphoma^{2,3}. Approximately 16-20% of cancer deaths in women and 14% of cancer deaths in men were found to be due to obesity¹. It is also recognized that there is a positive relationship between type-2 diabetes associated hyperinsulinemia and cancer incidence⁴. Though the recent annual report on cancer incidence in US⁵ finds that the incidence and mortality rates for many cancers (except cancers of prostate, liver, kidney and oesophagus and leukemias) have dropped in 2003 since 1975; this decline is mostly due to a substantial decrease in tobacco use among men. However, during the same period the rise in the prevalence of obesity might have contributed to the increased risk and incidence of certain types of cancers including

prostate, liver, kidney, oesophageal and breast. Whether the elevated cancer risk in obesity arises from similar modulation of parallel signaling/metabolic pathways during adipogenesis and oncogenesis has not been hitherto addressed. Women with a BMI of ≥ 40 kg/m² have three times more mortality rate than lean women (BMI, ≤ 20.5 kg/m²), making obesity as a poor prognosis of breast cancer^{2,6}. In this review we would like to bring out the relationship at molecular level between adipogenesis and oncogenesis and how this may be relevant for the development of effective therapeutics for obesity, diabetes and cancer. A close analysis and fresh look at these two processes reveals several parallels. Though, both these processes at surface seem to be totally different and not related, there are certain important common denominators for these processes that need to be recognized. We suggest that (1) malonyl-CoA, an important regulator of fatty acid metabolism (Figure 1)^{7,8} and (2) triglyceride/free fatty acid (TG/FFA) cycling⁹ which is central to the generation of multiple signals which in turn control various metabolic, physiological and signaling pathways in the cell (Figure 1), are these underlying factors. Recent evidence indicates that lysophosphatidic acid, a byproduct of TG/FFA cycling, can activate NF κ B via G protein coupled receptor (GPCR) pathway involving Bcl-10 and Malt-1¹⁰. It is well known that NF κ B is involved in the expression of anti-apoptotic proteins Bcl-2 and Bcl-xl in a variety of cells¹¹, thereby linking the TG/FFA cycling operation to cell survival. The link between obesity and cancer remains an enigma and raises the question: *do pre-cancerous cells employ lipid metabolism-derived signals, which play an important role in several signaling pathways and adipogenesis, to drive the oncogenic process?* We believe that altered lipid metabolism is central to the obesity-mediated risk for cancer.

Methods

We performed literature search in Pubmed, Google Scholar, Embase and other publicly available databases for relevant studies on obesity, cancer, ageing and diabetes mellitus, published during the last two decades. We used type 2 diabetes, breast cancer, prostate cancer, leukemia, oncogenesis and obesity as search terms. Only English language publications were selected and reviewed.

Cancer cells, during their transformation, acquire certain important characteristics that help them survive and proliferate^{12,13}. Interestingly, some of these characteristics are also acquired by the adipocytes during differentiation (Table I). These include, (1) the ability to evade apoptosis by the up-regulation of Bcl-2 family proteins^{14,15}; (2) the ability to self-sustain by producing the necessary growth factors (e.g., visfatin, IGF, leptin, epidermal growth factor-like growth factor, hepatocyte growth factor, etc.)^{16,17}; (3) angiogenesis (during the differentiation and formation of adipose tissue)^{18,19} and (4) tissue invasion and migration (of preadipocytes^{20,21}) to other parts of the body (akin to metastasis). Recently, it was observed that adipocytes at the front of the invasive breast tumor cells express stromelysin-3, a matrix metalloproteinase that is involved in metastasis²². Though considerable evidence suggests that excess adiposity can mediate the aggressive progression of breast tumors, the link between obesity and cancer was questioned in a recent study²³, which demonstrated significantly increased susceptibility of transgenic mice devoid of white adipose tissue to mammary carcinogenesis. It was suggested that adipose tissue might in fact have a protective role against cancer; however, a caveat with this study is that the possibility that lipids and lipid-derived molecules, which likely accumulate in other soft tissues in these adipose deficient mice, may act as signaling molecules for tumorigenesis was not considered²³.

Enzymes of Lipid Metabolism – Role in Oncogenesis and Adipogenesis

Many enzymes of lipid metabolism are up-regulated during adipogenesis^{18,24,25}. These include ATP-citrate lyase (ACL), fatty acid synthase (FAS), acetyl-CoA carboxylase-1 (ACC-1), dicarboxylate transporter (Slc25A10) and malic enzyme (ME) (Figure 2). These enzymes are essential for the *de-novo* synthesis of fatty acids through the formation of malonyl-CoA. Since cancer cells are rapidly multiplying cells they are dependent on continuous formation of phospholipids and sterols for membranogenesis. Tumor cells unlike many normal human cells, developed the capability for *de-novo* synthesis of fatty acids to meet the requirement for cell multiplication and the elevated synthesis of all the needed enzymes in these cells achieves this goal^{26,27}. Besides genetic, environmental and epigenetic factors, metabolic signals also likely determine if a cell becomes cancerous. Thus, along with accel-

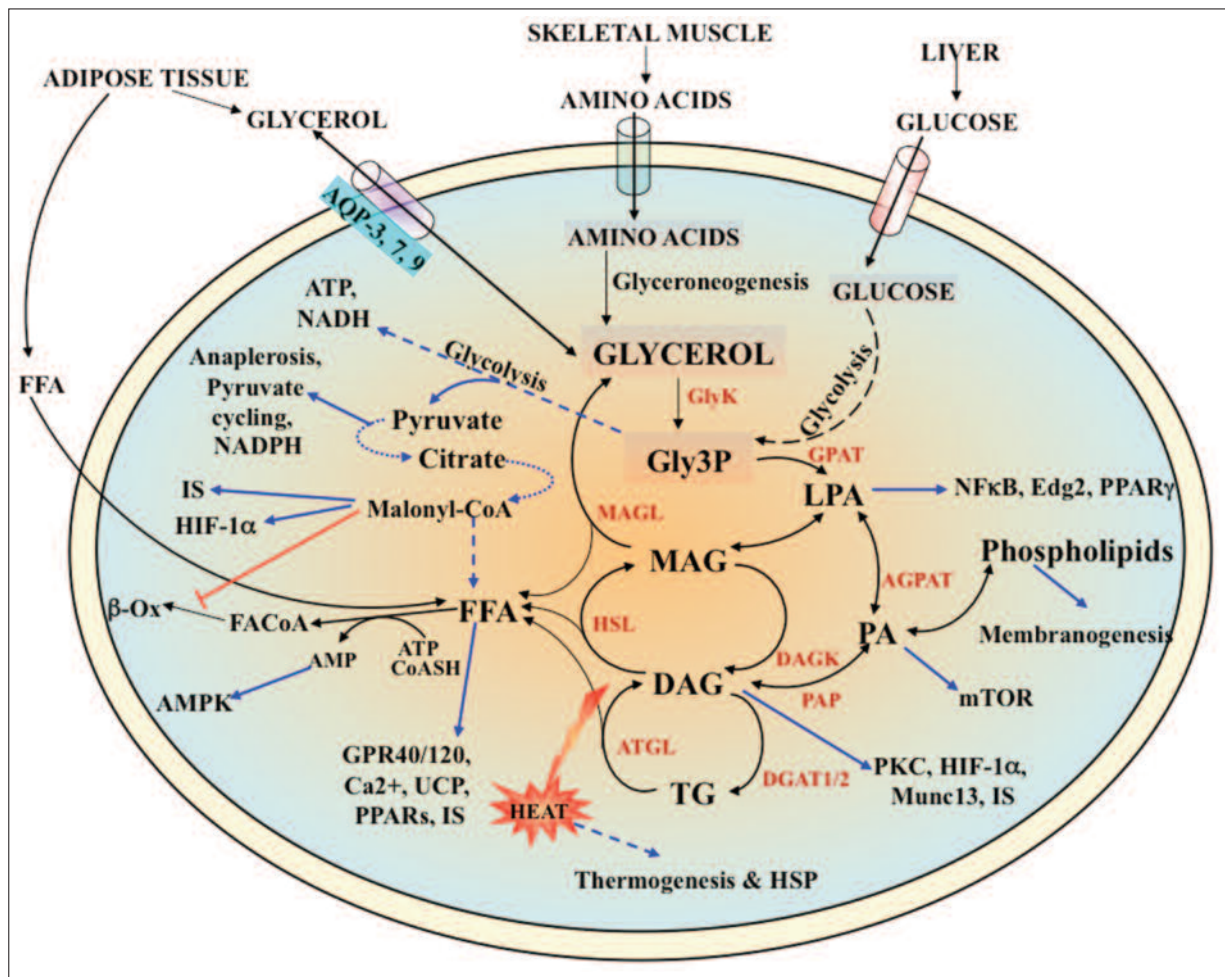


Figure 1. Generation of multiple signals for cell proliferation by triglyceride free fatty acid cycle. Triglyceride/Free fatty acid (TG/FFA) cycle consists of lipogenic and lipolytic segments. Lipogenesis starts with the formation of glycerol-3-phosphate (Gly3P) either from glycerol coming from glucose, aquaglyceroporin (AQP)-mediated transport, or glyceroneogenesis. Gly3P is acylated to lysophosphatidic acid (LPA), which is either further acylated to phosphatidic acid (PA) by acylglycerophosphate acyltransferase (AGPAT) or dephosphorylated to form monoacylglycerol (MAG). PA and MAG can be converted to 1,2-diacylglycerol (DAG) by acylation and dephosphorylation, respectively. DAG is acylated by DAG acyltransferases 1,2 (DGAT) to triglyceride (TG) in endoplasmic reticulum as the final step of lipogenic segment and TG thus formed is stored as lipid droplets. Lipolytic segment is composed of sequential hydrolysis of TG to DAG to 2-MAG on the surface of lipid droplet, by adipose TG lipase (ATGL) and hormone sensitive lipase (HSL), respectively. MAG is hydrolyzed by the ubiquitous MAG lipase (MAGL) to glycerol and FFA, both of which can re-enter the cycle. Gly3P can also be metabolized further via glycolysis yielding ATP, NADH and pyruvate. Pyruvate metabolism in mitochondria yields citrate, a significant amount of which enters cytosol where it contributes to FFA via malonyl-CoA. The different metabolites generated during TG/FFA cycling act as signaling molecules and influence the activity of various transcription factors, enzymes or receptors and may contribute to the regulation of cytosolic redox and energy charge ratios and cell survival, multiplication, motility and secretion.

erated glycolysis, a hallmark of cancer cells²⁸, lipogenesis is markedly increased in breast cancer cells²⁹⁻³⁵. Deletion of nuclear protein Spot14, which up-regulates the expression of lipogenic genes in breast cancer cells in response to fuels and hormonal status, induces apoptosis³⁶. Many enzymes of lipid metabolism (Figure 2), which are up-regulated during adipogenesis^{18,24,25} including ATP-citrate lyase (ACL), fatty acid syn-

thase (FAS), acetyl-CoA carboxylase-1 (ACC-1), dicarboxylate transporter (Slc25A10) and malic enzyme, are also increased in many types of cancer cells²⁹⁻³⁵ and abrogation of their activity leads to apoptosis. Similar results have been obtained with ACC-1³⁰. However, FL5.12 leukemia cells with ACL knockdown show impaired proliferative response to cytokine IL3, which stimulates the conversion of glucose to lipid. ACL knockdown

	Oncogenesis	Adipogenesis
Growth Signals for Self-Sufficiency	Autocrine stimulation, e.g., PDGF, TGF α etc.; GF receptor over-expression--EGFR, Her2/ <i>neu</i> ; Altered RAS signaling etc.	Autocrine stimulation, e.g. IL-6, leptin, visfatin, IGF, etc.; GF receptors-IGF-1R; Her2/ <i>neu</i> (?).
Anti-Apoptosis Machinery	Bcl-2, Bcl-xl, Mcl-1, Bcl-w; Loss of function mutations in p53; IAPs.	Bcl-2, Bcl-xl upregulation
Angiogenesis Capability	HIF overexpression, VEGF, FGF1/2, MMPs.	HIF overexpression, VEGF, MMPs, FGF10.
Invasion, Metastasis & Migration	Expression of MMPs; Loss of E-cadherin function;	Expression of MMPs; Loss of N-cadherin function leads to increased adipogenesis.
Insensitivity to Anti-Growth Signals	Disruption of retinoblastoma protein/ E2F function.	Reduced function of pRb during brown-adipogenesis.
Limitless Replicative Potential	Telomere maintenance	Terminally differentiated.

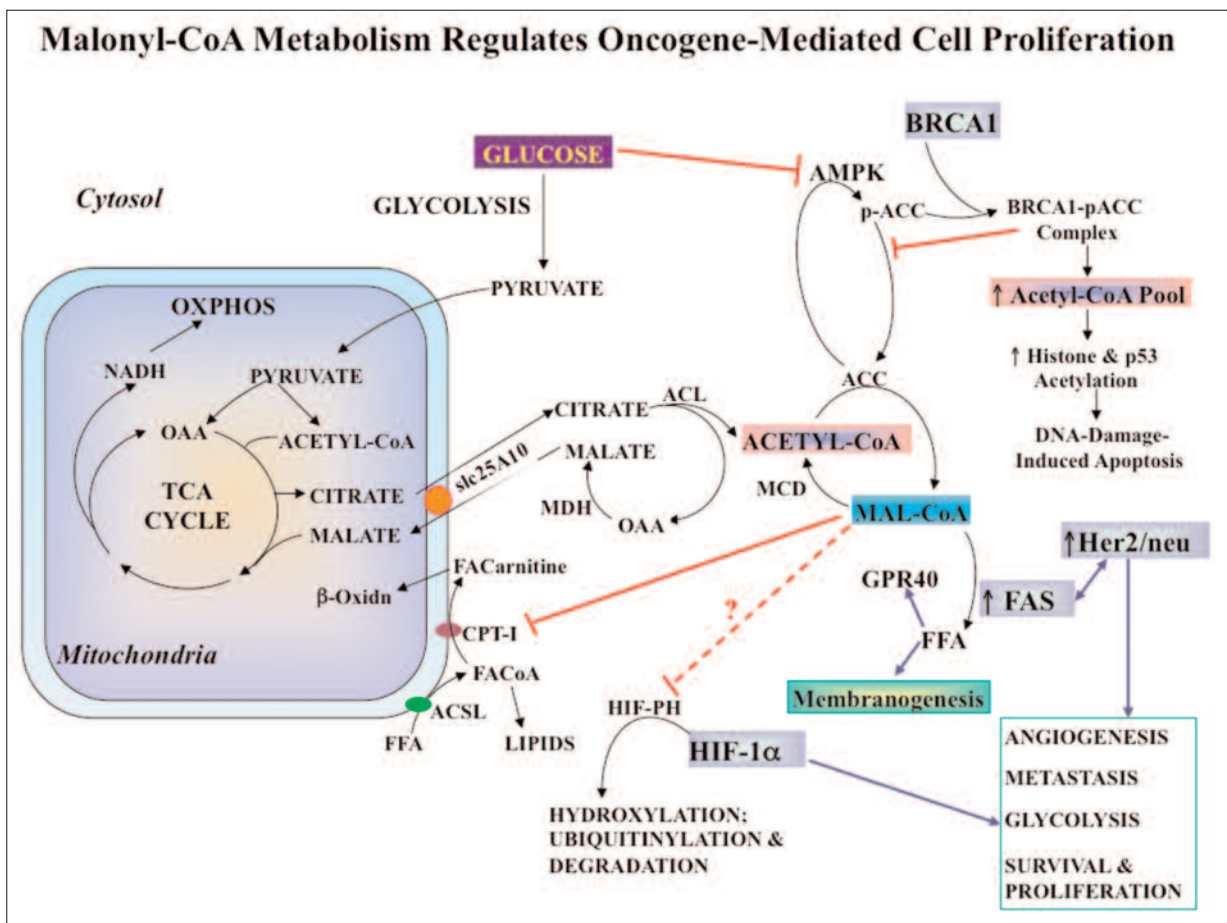


Figure 2. Malonyl-CoA metabolism regulates oncogene-mediated cell proliferation. The relationship between dicarboxylate carrier, synthesis of malonyl-CoA, the key intermediate in lipid metabolism and oncogene function is depicted here. The possibility that malonyl-CoA can influence the activity of HIF1 α -PH is hypothetical.

also significantly blunts the tumorigenesis by the FL5.12 cells *in vivo* indicating that this enzyme activity is necessary for the formation of tumors^{29,37}. Dicarboxylate carrier (Slc25A10), which participates in the net export of mitochondrial citrate in to cytosol, is important for *de novo* synthesis of fatty acids. Slc25A10 is also involved in the transport of succinate from mitochondria to cytosol, and because succinate can in turn promote HIF-1 α (hypoxia inducible factor-1 α) accumulation, it has been suggested that single nucleotide polymorphisms (SNP) in *slc25A10* gene could affect the penetrance and type of cancer³⁸.

Whether malonyl-CoA, which is formed by consecutive actions of Slc25A10, ACL and ACC in cytosol, directly or indirectly regulates the survival of the cancer cells has long been debated^{30,39,40}. Malonyl-CoA occupies a central position at the intersection of the glucose and fatty acid metabolic cross roads (Figure 2). After its formation, malonyl-CoA has only two metabolic fates, viz., to become a substrate for FAS and contribute to fatty acid synthesis or to get decarboxylated to acetyl-CoA by malonyl-CoA decarboxylase (MCD). Besides being a substrate for these enzymes, malonyl-CoA can also bind to CPT-I of mitochondrial outer membrane and inhibit its activity and, thereby, the β -oxidation of fatty acids⁴¹⁻⁴⁴. This regulatory role of malonyl-CoA is important for fuel partitioning by the diversion of fatty acids towards TG synthesis and may also be part of the central hypothalamic machinery involved in the food intake control⁴⁵.

The above mentioned lipogenic enzymes FAS, ACL, ACC-1, ME, stearoyl-CoA desaturase (SCD-1) and also the transcription factor SREBP-1c are co-ordinately induced in hepatocellular carcinoma⁴⁶ and in other cancers²⁶. The association between non-alcoholic steatohepatitis (NASH) and hepatocellular carcinoma is long recognized⁴⁷. Obesity, specifically, increased visceral adiposity can result in non-alcoholic fatty liver disease and NASH². Though it has been suggested that targeting any of these lipogenic enzymes may have beneficial anti-cancer effects, it must be realized that as these enzymes are essential for the metabolic activity of normal cells, such measures can be extremely toxic to the whole organism. Besides the lipogenic enzymes, lipolysis segment of TG/FFA cycle (Figure 1) also seems to be important in the cancer cells⁴⁸. Adipose triglyceride lipase (ATGL), which hydrolyzes triglycerides and hormone sensitive li-

pase (HSL), which preferentially breaks down diacylglycerols were found to be increased in patients with cancer cachexia, which leads to wastage of tissue and is considered an adverse prognostic factor⁴⁹. Interestingly, monoacylglycerol hydrolyzing enzymes, monoglyceride lipase (MGL) and alpha/beta hydrolase containing-6 are found to be increased in many cancers and it has been shown that inhibitors of MGL in fact induce apoptosis in cancer cells and prevent the growth of tumor xenografts in mice⁵⁰.

FAS, Her2/neu/erbB-2 and BRCA1 Signaling in Cancer

Recent studies showed that either inhibition or RNAi knockdown of FAS in cancer cells leads to the down regulation of Her2/neu/erbB-2 oncoprotein, which helps in the survival of breast cancer cells⁵¹. The molecular relationship between FAS and Her2/neu is not known. Her2/neu, when translocated to the surface of the plasma membrane transmits survival signals whereas, if translocated to the nucleus, it signals apoptosis. It is possible that *de novo* synthesized FFA by FAS are needed for the acylation and membrane anchoring of the Her2/neu protein. Thus, SREBP-1c, which up-regulates FAS, can help promote cell survival. In fact, it has been shown that overexpression of Her2/neu in MCF7 breast cancer cells up-regulates SREBP-1c—dependent FAS expression⁵². Her2/neu and FAS appear to regulate each other's expression and biological activity, which is reflected in cell survival and proliferation. It is interesting to note that oleic acid when added externally down regulates Her2/neu/erbB-2 oncoprotein⁵³. However, in many cancers SCD-1, which synthesizes oleate, is up regulated and abrogation of its activity leads to loss of cell proliferation⁵⁴. Thus, it is likely that *de novo* made oleate via FAS/SCD in the cell may be important for the Her2/neu/erbB-2 survival signaling pathway whereas, externally added oleate may antagonize this pathway. Another GPCR protein, GPR40, which is activated by fatty acids, has recently been shown by us⁵⁵ to play important role in the proliferation of breast cancer cells. Receptor crosstalk between GPR40 and Her2/neu is an intriguing possibility and needs to be explored. In adipocytes, FAS expression is regulated mostly by nutritional and hormonal signaling pathways. Adipocytes express significant levels of FAS and SCD-1 under the control of SREBP-1c. However, the expression of Her2/neu/erbB-2 oncoprotein was found to in-

crease several fold during the proliferation of preadipocytes followed by significant decline during differentiation to adipocytes⁵⁶. It is not clear if this protein would play a role in the survival of adipocytes and in the control of FAS activity. Lysophosphatidic acid, an intermediate in glycerolipid synthesis, has been shown to trans-activate Her2/*neu* in gastric cancer cells⁵⁷. Such activation may also be prominent in breast cancer cells inasmuch as many breast cancer cells are active in glycerolipid synthesis and upregulate Her2/*neu* oncoprotein.

Lipid metabolism also appears to be associated with the expression/activity of breast cancer-related oncogenes. Thus BRCA1 tumor suppressor protein is found to sequester the phosphorylated form of lipogenic enzyme, ACC-1, by binding via BRCT-domain and to control ACC activity and lipogenesis in normal breast epithelial cells (Figure 2). Mutations in the BRCT domain of BRCA1, seen in many breast cancers, attenuate this interaction leading to elevated lipogenesis^{30,39,40,58,59} and altered β -oxidation⁶⁰, a characteristic of breast cancer cells^{58,59}.

AMPK, mTOR and Malonyl-CoA

Thus, it appears that many enzymes involved in the metabolism of malonyl-CoA may play a crucial role both in adipogenesis and oncogenesis. The biosynthesis of malonyl-CoA is regulated by AMP-activated protein kinase (AMPK), which is a heterotrimeric enzyme containing three distinct subunits^{8,61}. This enzyme is activated by conformational-change induced phosphorylation at high AMP/ATP ratio (i.e., decreased energy state) in the cell. AMPK is also phosphorylated by an upstream kinase, LKB1, which is known as a tumor suppressor⁶¹. Activated AMPK phosphorylates and inhibits the activities of ACC, FAS and GPAT⁴⁰. Thus, activation of AMPK results in lowered cellular malonyl-CoA levels associated with decreased *de-novo* biosynthesis of fatty acids and TG and increased fatty acid oxidation^{7,61}. AMPK also brings about the activation of MCD to facilitate the decrease in the malonyl-CoA levels⁶². In adipocytes AMPK activation can lead to enhanced lipolysis⁶³. In cancer cells, it appears that AMPK activity is kept at relatively low levels so that elevated activities of the lipogenic enzymes, ACC, ACL and FAS are maintained⁴⁰. For example, in Peutz-Jeghers syndrome (PJS), a rare form of hereditary cancer of gastrointestinal tract, LKB1 is mutated with the resultant loss of active AMPK^{61,64}. Activators of AMPK viz., met-

formin and AICAR inhibit the growth and survival of cancer cells^{4,65}. Recently, it has been hypothesized that⁶⁶ premalignant tumors may gain a replicative advantage by keeping AMPK activity low, whereas malignant tumors are able to tolerate partial AMPK activation and shift to active glycolysis to relieve from substrate limitation stress on the cell. However, whether this anti-cancer effect of activated AMPK is related to its ability to block malonyl-CoA synthesis or to other known effects such as mTOR inactivation, etc., is not known. In fact, nutrients like glucose, amino acids and fatty acids appear to reciprocally regulate AMPK and mTOR activation so that under nutrient-rich conditions an active mTOR-pathway helps in the growth and proliferation of cells. Lowering of malonyl-CoA level is an essential component of the anti-obesity, pro-apoptotic and anti-cancer effects of AMPK. HIF-1 α has been shown to be activated by mTOR in PTEN-null cancers⁶⁷. The increased HIF-1 in melanoma cells has been shown to be dependent on mTOR and that inhibition of mTOR by rapamycin results in the apoptosis of melanoma cells⁶⁸. Surprisingly, mTOR pathway is found to play significant role during adipogenesis and its inhibition by rapamycin leads to the loss of the positive feed back between C/EBP and PPAR γ and disrupted adipocytes differentiation⁶⁹. LKB1, besides activating AMPK, is also implicated in the negative regulation of mTOR signaling by a mechanism dependent on AMPK⁷⁰.

Role of Tumor Suppressor p53 in Tumor Energy Metabolism and Adipogenesis

It is well known that tumor suppressor gene p53 is either mutated or deleted in most cancers and this contributes to the ability of the malignant cells to escape and evade apoptosis. It appears that besides its role in the regulation of cell death, cell cycle and as the sentinel of the chromosomal integrity, p53 also participates in the control of energy metabolism and adipogenesis. The expression of p53 was found to decline during adipogenesis from 3T3-L1 preadipocytes⁷¹. Senescence-associated increase in the expression of p53 in human mesenchymal stem cells makes them to lose their capacity to differentiate into adipocytes⁷². Interestingly, the ability of PPAR γ ligands to induce apoptosis in cancer cells may be because these compounds induce the expression of p53 in these cells^{73,74}. Several recent reports have shown the involvement of p53 in the control of glycolysis^{75,76}. Liver cells from p53-knockout mice exhibit much

higher capacity for glycolysis and significantly elevated lactate production⁷⁶. However, it is not known whether p53 controls the expression of lactate dehydrogenase (LDH) gene. This is an intriguing possibility since it has been observed that the glycolytic phenotype of cancers is highly likely due to LDH-A activity in these cells besides the upregulation of glycolytic enzymes⁷⁷. Knockdown of LDH-A leads to increased mitochondrial oxidative phosphorylation and decreased ability to proliferate under hypoxic conditions associated with curtailed tumorigenicity⁷⁷. Can LDH play a role in the adipogenic process? Hypoxic conditions, which are likely to prevail in the adipose mass, are shown to enhance the production of lactate by the adipocytes and this is associated with the elevated levels of angiogenic factors¹⁹. Also, the increased plasma lactate levels were proposed to contribute to the insulin resistance in obese individuals and thus can be a significant risk factor for type 2 diabetes⁷⁸. AMPK, a well known cellular energy sensor, has been shown to activate p53 by phosphorylation at ser-15⁷⁹. Under conditions of low glucose availability, cell proliferation is prevented by AMPK mediated activation of p53 followed by cell cycle arrest, which is reversed upon the restoration of glucose availability⁷⁹. In tumors that do express p53 and in adipose tissue, the cells that are far from circulation and nutrient supply may employ this low-glucose regulated AMPK/p53-dependent reversible cell cycle arrest to prevent cell death due to excessive proliferation. Also, accelerated GL/FFA cycle in breast cancer cells probably ensures a continuous supply of reoxidized NAD substrate to SIRT-1, which deacetylates and inactivates p53 tumor suppressor protein, and protects breast cancer cells from apoptosis⁸⁰. Acetylation-mediated activation of p53 is also likely regulated by the size of cytosolic acetyl-CoA pool, which is controlled by ACC-1 (Figure 2).

Adipocytes, besides possessing certain characteristics of cancer cells, can also stimulate the proliferation of many cancer cells. The strong link between obesity and various cancers including liver, prostate, pancreas, colon, breast, leukemia etc. makes increased adiposity as a high risk factor and poor prognostic marker in the treatment of cancer. Adipocyte-derived collagen- α 3 has been shown to stimulate the growth of mammary tumors *in vivo*⁸¹. The adipocytokines, leptin, IL6, IGF-1, adiponectin and visfatin secreted by the adipocytes act as signals for proliferation and survival. Recent studies have shown that visfatin, also known as Pre-B-Cell

colony Enhancing Factor (PBEF), enhances cell survival by elevating the activity of NAD⁺-dependent protein deacetylases (known as SIRT) and cellular NAD⁺ content⁸². There is evidence to show that visfatin/PBEF is in fact nicotinamide phosphoribosyltransferase, a cytosolic enzyme involved in NAD biosynthesis and is produced in other cell types⁸². SIRT class enzymes and NAD⁺ are important contributors for lifespan increase. SIRT-1 can attenuate adipogenesis by enhancing TG/FFA cycling through the repression of PPAR γ in mouse adipocytes^{83,84}. Starvation increases the activities of both SIRT-1 and SIRT-3 in adipocytes and in liver and it is speculated that this increase is instrumental in the extension of mammalian lifespan⁸⁴. Elevated SIRT-1 is noticed in various cancer cells⁸⁵.

TG/FFA Cycling, Malonyl-CoA and Hypoxia Inducible Factor (HIF)

Several indirect evidences indicate a positive relationship between the expression and activity of HIF-1 α and malonyl-CoA levels. HIF-1 α , which is induced by the hypoxic conditions that prevail in the core region cancer cells of many solid tumors⁸⁶ and also in the internal adipocytes during adipogenesis^{19,87} leads to the expression of vascular endothelial growth factor (VEGF), which promotes angiogenesis²⁶. Conditions that lead to an elevation of cellular malonyl-CoA levels, for example, elevated glucose concentration⁸⁸⁻⁹⁰ and lowering the activity of FAS either by C75 or siRNA⁹¹ lead to enhanced MAPK activity and a rise in HIF protein. HIF levels in the cells are controlled by the availability of oxygen and this regulation takes place both at its transcription and at degradation. HIF levels rise in proportion to the concentration of glucose supplied. HIF-prolylhydroxylase (HIF-PH) is an important enzyme in determining the fate of the HIF, as it hydroxylates HIF at specific proline residues and marks it for further VHL (von Hippel Landau) protein-dependent ubiquitinylation and proteolysis. HIF-PH uses 2-oxoglutarate as a cofactor and recent studies have shown that succinate⁹² and fumarate⁹³ at millimolar concentrations, can inhibit this enzyme and lead to the accumulation of HIF in the cells thereby explaining the association of fumarate or succinate dehydrogenase deficiency with cancer. Lu et al⁸⁹ provided evidence for pyruvate, derived from glucose metabolism, being important for the inhibition of HIF-PH.

It is possible that malonyl-CoA, which increases at high glucose concentration⁷, being

similar to fumarate and succinate, may also be able to inhibit HIF-PH (Figure 2). In this regard, it is important to note that radicicol, an inhibitor of HSP90 and also of ACL, an enzyme involved in malonyl-CoA synthesis, potently inhibits the growth of tumour cells both *in vivo* and *in vitro* and this is shown to be due to the enhanced degradation of HIF-1 α ⁹⁴. Thus, decreased synthesis of malonyl-CoA can lead to lowered levels of HIF1 α and the associated down-stream signaling. If malonyl-CoA does inhibit HIF-PH, it can also explain the role of elevated ACL, ACC and dicarboxylate carrier activities in cancer cells and in adipocytes in their survival by stimulating glycolysis and vascularization (Figure 2). Another possibility is the involvement of elevated malonyl-CoA levels in the high glucose activation of MAPK (ERK 1/2) pathway⁹⁵, which can lead to a rise in HIF in the cells⁹⁶. Hypoxic conditions are also known to cause an elevation of TG and phosphatidic acid, the intermediates of TG/FFA cycle⁹⁷, and this accumulation likely plays an important role in the expression of HIF.

It is interesting to note that HIF promotes metastasis in tumor cells^{98,99}, probably by regulating the expression of integrins and since HIF levels rise during adipogenesis, it may have a parallel role in the migration of adipocytes. Adipocytes at the front of the invasive breast tumor cells express stromelysin-3, a matrix metalloproteinase (MMP) that is involved in metastasis²². Also, under hypoxic conditions, induced either chemically or by high glucose, adipocytes express high levels of MMPs¹⁹. The expression of MMPs is a prerequisite for angiogenesis and cellular migration. Thus prolonged elevation of malonyl-CoA in cells may predispose them to become cancerous if the same cells also harbor mutations that cause either over-expression of oncogenes, which otherwise may trigger apoptosis (e.g., *c-myc*, *bcl-2* etc.) or inactivation of p53.

Thus, malonyl-CoA and TG/FFA cycling in combination likely exert potent survival pressure on cells through interconnected metabolic and signaling pathways. These metabolic signals are probably strong enough to commit the cells to proliferate even if they suffered a mutational insult thereby leading to oncogenesis.

Therapeutic Approaches for Obesity and Cancer

As mentioned above, the onset of obesity and pathogenesis of cancer may share same metabolic and biological pathways. This indicates that

there can be targets for therapeutic development that are common to both these processes. In an interesting study Choi et al¹⁰⁰ described a series of compounds, identified on the basis of their anti-adipogenesis activity, to have potential anti-cancer effects as well in cell culture experiments. In a recent review, Swinnen et al¹⁰¹ suggested that since there is an increased lipogenesis in cancer due to the disturbances in signaling pathways, the lipogenic enzymes involved can be good targets for anti-cancer drug development. It has already been suggested^{45,102} that FAS inhibitor, C75, can be useful as a therapeutic against obesity and type-2 diabetes and also certain types of cancer. However, C75 suffers from lack of specificity and several side effects^{103,104}. This compound was originally thought to specifically inhibit FAS and activate CPT-1. However, recent SAR studies revealed that C75 inhibits CPT-1¹⁰⁵. Similarly, inhibitors of ACC are being developed by several pharmaceutical and biotechnology companies as therapeutics against obesity/metabolic syndrome and recent findings indicate that it can be an important target for anti-cancer drug development. So far, no specific inhibitors that target either ACC-1 or ACC-2 are described^{106,107}. It may be desirable to have inhibitors that target ACC-2 for treating obesity and promote weight-loss¹⁰⁸. However, because of the essential nature of this enzyme's function (particularly ACC-1) in the cell, a global inhibition of this enzyme can have potentially unwanted side effects. Hydroxycitrate, an inhibitor of ACL, has been described as a potential drug for obesity¹⁰⁹. The HSP90 inhibitor, radicicol, which also inhibits ACL, has been suggested as a therapeutic against cancer¹¹⁰. Although the importance of ACL in lipogenesis has been known since long, this enzyme has not been intensively studied as a potential target for anti-obesity drug development. Its significance as a probable target for anti-cancer drug discovery is only currently being realized^{29,37}. Another lipid metabolism inhibitor orlistat, which inhibits lipases in the digestive tract and prevents fat absorption, has been recently approved by FDA for inducing weight loss in clinically obese people¹¹¹. Orlistat also inhibits intra-cellular lipases and TG/FFA cycling and also FAS¹¹². This compound is also recognized for its anti-cancer efficacy¹¹³.

An inhibitor of DGAT and a probable ligand for farnesoid X receptor, xanthohumol was found to have anti-tumor properties in various systems¹¹⁴ and is also able to reduce white adipose

mass and lower plasma glucose levels in KK-A(y) mice¹¹⁵. Compounds that can specifically inhibit TG/FFA cycling can have beneficiary effects by reducing the capacity of adipose tissue to store TG and also by antagonizing the various pathways by which TG/FFA cycling produces different signaling molecules needed for cellular growth and proliferation. Thus inhibition of TG/FFA cycling in cancer cells can induce apoptosis in these cells. However, the efficacy and specificity of this approach to combat cancer remains to be seen.

Conclusions

Multiple lines of epidemiological, clinical and biochemical evidences strongly implicate obesity and diabetes as risk factors for various types of cancer. We have summarized evidences showing the parallels between adipogenesis and oncogenesis pathways. Though it still remains enigmatic how the existing normal cellular machinery for adipogenesis can be exploited by the pathological oncogenic process, the lessons we learned from studies on cancer pathology and the development of obesity demonstrate that there is a potential for both the processes to be targeted by common pharmacological intervention.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

- 1) CALLE EE, RODRIGUEZ C, WALKER-THURMOND K, THUN MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. Adults. *N Engl J Med* 2003; 348: 1625-1638.
- 2) CALLE EE, KAKS R. Overweight, obesity and cancer: Epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* 2004; 4: 579-591.
- 3) COLDITZ GA, SELLERS TA, TRAPIDO E. Epidemiology--identifying the causes and preventability of cancer? *Nat Rev Cancer* 2006; 6: 75-83.
- 4) BOWKER SL, MAJUMDAR SR, VEUGELERS P, JOHNSON JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. *Diabetes Care* 2006; 29: 254-258.
- 5) HOWE HL, WU X, RIES LA, COKKINIDES V, AHMED F, JEMAL A, MILLER B, WILLIAMS M, WARD E, WINGO PA, RAMIREZ A, EDWARDS BK. Annual report to the nation on the status of cancer, 1975-2003, featuring cancer among U.S. Hispanic/Latino populations. *Cancer* 2006; 107: 1711-1742.
- 6) CARMICHAEL AR. Obesity as a risk factor for development and poor prognosis of breast cancer. *BJOG* 2006; 113: 1160-1166.
- 7) PRENTKI M, JOLY E, EL-ASSAAD W, RODUIT R. Malonyl-CoA signaling, lipid partitioning, and glucolipotoxicity: Role in beta-cell adaptation and failure in the etiology of diabetes. *Diabetes* 2002; 51(Suppl 3): S405-413.
- 8) RUDERMAN N, PRENTKI M. Amp kinase and malonyl-CoA: Targets for therapy of the metabolic syndrome. *Nat Rev Drug Discov* 2004; 3: 340-351.
- 9) RESHEF L, OLSWANG Y, CASSUTO H, BLUM B, CRONIGER CM, KALHAN SC, TILGHMAN SM, HANSON RW. Glycerooneogenesis and the triglyceride/fatty acid cycle. *J Biol Chem* 2003; 278: 30413-30416.
- 10) KLEMM S, ZIMMERMANN S, PESCHEL C, MAK TW, RULAND J. Bcl10 and malt1 control lysophosphatidic acid-induced nf-kappa activation and cytokine production. *Proc Natl Acad Sci U S A* 2007; 104: 134-138.
- 11) BUREAU F, VANDERPLASSCHEN A, JASPAR F, MINNER F, PASTORET PP, MERVILLE MP, BOURS V, LEKEUX P. Constitutive nuclear factor-kappa activity preserves homeostasis of quiescent mature lymphocytes and granulocytes by controlling the expression of distinct bcl-2 family proteins. *Blood* 2002; 99: 3683-3691.
- 12) HANAHAN D, WEINBERG RA. The hallmarks of cancer. *Cell* 2000; 100: 57-70.
- 13) KLAUSNER RD. The fabric of cancer cell biology--weaving together the strands. *Cancer Cell* 2002; 1: 3-10.
- 14) MAGUN R, BOONE DL, TSANG BK, SORISKY A. The effect of adipocyte differentiation on the capacity of 3T3-L1 cells to undergo apoptosis in response to growth factor deprivation. *Int J Obes Relat Metab Disord* 1998; 22: 567-571.
- 15) ZHANG HH, KUMAR S, BARNETT AH, EGGO MC. Dexamethasone inhibits tumor necrosis factor-alpha-induced apoptosis and interleukin-1 beta release in human subcutaneous adipocytes and preadipocytes. *J Clin Endocrinol Metab* 2001; 86: 2817-2825.
- 16) MATSUZAWA Y. The metabolic syndrome and adipocytokines. *FEBS Lett* 2006; 580: 2917-2921.
- 17) SAIKI A, WATANABE F, MURANO T, MIYASHITA Y, SHIRAI K. Hepatocyte growth factor secreted by cultured adipocytes promotes tube formation of vascular endothelial cells in vitro. *Int J Obes (Lond)* 2006; 30: 1676-1684.

- 18) LAFONTAN M. Fat cells: Afferent and efferent messages define new approaches to treat obesity. *Annu Rev Pharmacol Toxicol* 2005; 45: 119-146.
- 19) LOLMEDE K, DURAND DE SAINT FRONT V, GALITZKY J, LAFONTAN M, BOULOUMIE A. Effects of hypoxia on the expression of proangiogenic factors in differentiated 3t3-f442a adipocytes. *Int J Obes Relat Metab Disord* 2003; 27: 1187-1195.
- 20) LIN YT, TANG CH, CHUANG WJ, WANG SM, HUANG TF, FU WM. Inhibition of adipogenesis by rgd-dependent disintegrin. *Biochem Pharmacol* 2005; 70: 1469-1478.
- 21) OMATSU-KANBE M, INOUE K, FUJII Y, YAMAMOTO T, ISONO T, FUJITA N, MATSUURA H. Effect of atp on preadipocyte migration and adipocyte differentiation by activating p2y receptors in 3t3-l1 cells. *Biochem J* 2006; 393: 171-180.
- 22) ANDARAWEWA KL, MOTRESCU ER, CHENARD MP, GANSMULLER A, STOLL I, TOMASETTO C, RIO MC. Stromelysin-3 is a potent negative regulator of adipogenesis participating to cancer cell-adipocyte interaction/crosstalk at the tumor invasive front. *Cancer Res* 2005; 65: 10862-10871.
- 23) NUNEZ NP, OH WJ, ROZENBERG J, PERELLA C, ANVER M, BARRETT JC, PERKINS SN, BERRIGAN D, MOITRA J, VARTICOVSKI L, HURSTING SD, VINSON C. Accelerated tumor formation in a fatless mouse with type 2 diabetes and inflammation. *Cancer Res* 2006; 66: 5469-5476.
- 24) MIZUARAI S, MIKI S, ARAKI H, TAKAHASHI K, KOTANI H. Identification of dicarboxylate carrier Slc25a10 as malate transporter in de novo fatty acid synthesis. *J Biol Chem* 2005; 280: 32434-32441.
- 25) ROSEN ED. The molecular control of adipogenesis, with special reference to lymphatic pathology. *Ann N Y Acad Sci* 2002; 979: 143-158; discussion 188-196.
- 26) SANTOS CR, SCHULZE A. Lipid metabolism in cancer. *FEBS J* 2012; 279: 2610-2623.
- 27) CURRIE E, SCHULZE A, ZECHNER R, WALTHER TC, FARESE RV, Jr. Cellular fatty acid metabolism and cancer. *Cell Metab* 2013; 18: 153-161.
- 28) GATENBY RA, GILLIES RJ. Why do cancers have high aerobic glycolysis? *Nat Rev Cancer* 2004; 4: 891-899.
- 29) HATZIVASSILIOU G, ZHAO F, BAUER DE, ANDREADIS C, SHAW AN, DHANAK D, HINGORANI SR, TUVESON DA, THOMPSON CB. Atp citrate lyase inhibition can suppress tumor cell growth. *Cancer Cell* 2005; 8: 311-321.
- 30) BRUSSELMANS K, DE SCHRUIVER E, VERHOEVEN G, SWINEN JV. Rna interference-mediated silencing of the acetyl-CoA-carboxylase- α gene induces growth inhibition and apoptosis of prostate cancer cells. *Cancer Res* 2005; 65: 6719-6725.
- 31) HALPERIN ML, TAYLOR WM, CHEEMA-DHADLI S, MORRIS JP, FRITZ IB. Effects of fasting on the control of fatty-acid synthesis in hepatoma 7777 and host liver. Role of long-chain fatty acyl-CoA, the mitochondrial citrate transporter and pyruvate dehydrogenase activity. *Eur J Biochem* 1975; 50: 517-522.
- 32) RAO KN, ELM MS, KELLY RH, CHANDAR N, BRADY EP, RAO B, SHINOZUKA H, EAGON PK. Hepatic hyperplasia and cancer in rats: Metabolic alterations associated with cell growth. *Gastroenterology* 1997; 113: 238-248.
- 33) KUHAJDA FP, JENNER K, WOOD FD, HENNIGAR RA, JACOBS LB, DICK JD, PASTERNAK GR. Fatty acid synthesis: A potential selective target for antineoplastic therapy. *Proc Natl Acad Sci U S A* 1994; 91: 6379-6383.
- 34) ALLI PM, PINN ML, JAFFEE EM, MCFADDEN JM, KUHAJDA FP. Fatty acid synthase inhibitors are chemopreventive for mammary cancer in neu-n transgenic mice. *Oncogene* 2005; 24: 39-46.
- 35) MENENDEZ JA, COLOMER R, LUPU R. Why does tumor-associated fatty acid synthase (oncogenic antigen-519) ignore dietary fatty acids? *Med Hypotheses* 2005; 64: 342-349.
- 36) KINLAW WB, QUINN JL, WELLS WA, ROSER-JONES C, MONCUR JT. Spot 14: A marker of aggressive breast cancer and a potential therapeutic target. *Endocrinology* 2006; 147: 4048-4055.
- 37) BAUER DE, HATZIVASSILIOU G, ZHAO F, ANDREADIS C, THOMPSON CB. Atp citrate lyase is an important component of cell growth and transformation. *Oncogene* 2005; 24: 6314-6322.
- 38) GOTTLIEB E, TOMLINSON IP. Mitochondrial tumour suppressors: A genetic and biochemical update. *Nat Rev Cancer* 2005; 5: 857-866.
- 39) KUHAJDA FP. Fatty-acid synthase and human cancer: New perspectives on its role in tumor biology. *Nutrition* 2000; 16: 202-208.
- 40) LUO Z, SAHA AK, XIANG X, RUDERMAN NB. Ampk, the metabolic syndrome and cancer. *Trends Pharmacol Sci* 2005; 26: 69-76.
- 41) MCGARRY JD, MANNAERTS GP, FOSTER DW. A possible role for malonyl-CoA in the regulation of hepatic fatty acid oxidation and ketogenesis. *J Clin Invest* 1977; 60: 265-270.
- 42) MURTHY MS, PANDE SV. Some differences in the properties of carnitine palmitoyltransferase activities of the mitochondrial outer and inner membranes. *Biochem J* 1987; 248: 727-733.
- 43) MURTHY MS, PANDE SV. Malonyl-CoA binding site and the overt carnitine palmitoyltransferase activity reside on the opposite sides of the outer mitochondrial membrane. *Proc Natl Acad Sci U S A* 1987; 84: 378-382.
- 44) MURTHY MS, PANDE SV. Characterization of a solubilized malonyl-CoA-sensitive carnitine palmitoyltransferase from the mitochondrial outer membrane as a protein distinct from the malonyl-CoA-insensitive carnitine palmitoyltransferase of the inner membrane. *Biochem J* 1990; 268: 599-604.
- 45) LOFTUS TM, JAWORSKY DE, FREHYWOT GL, TOWNSEND CA, RONNETT GV, LANE MD, KUHAJDA FP. Reduced food intake and body weight in mice treated with fatty acid synthase inhibitors. *Science* 2000; 288: 2379-2381.

- 46) YAHAGI N, SHIMANO H, HASEGAWA K, OHASHI K, MATSUZAKA T, NAJIMA Y, SEKIYA M, TOMITA S, OKAZAKI H, TAMURA Y, IZUKA Y, OHASHI K, NAGAI R, ISHIBASHI S, KADOWAKI T, MAKUUCHI M, OHNISHI S, OSUGA J, YAMADA N. Co-ordinate activation of lipogenic enzymes in hepatocellular carcinoma. *Eur J Cancer* 2005; 41: 1316-1322.
- 47) SMEDILE A, BUGIANESI E. Steatosis and hepatocellular carcinoma risk. *Eur Rev Med Pharmacol Sci* 2005; 9: 291-293.
- 48) ARNER P, LANGIN D. Lipolysis in lipid turnover, cancer cachexia, and obesity-induced insulin resistance. *Trends Endocrinol Metab* 2014; 25: 255-262.
- 49) DAS SK, EDER S, SCHAUER S, DIWOKY C, TEMMEL H, GUERTL B, GORKIEWICZ G, TAMILARASAN KP, KUMARI P, TRAUNER M, ZIMMERMANN R, VESELY P, HAEMMERLE G, ZECHNER R, HOEFLE G. Adipose triglyceride lipase contributes to cancer-associated cachexia. *Science* 2011; 333: 233-238.
- 50) NOMURA DK, LONG JZ, NIESSEN S, HOOVER HS, NG SW, CRAVATT BF. Monoacylglycerol lipase regulates a fatty acid network that promotes cancer pathogenesis. *Cell* 2010; 140: 49-61.
- 51) MENENDEZ JA, VELLON L, MEHMI I, OZA BP, ROPERO S, COLOMER R, LUPU R. Inhibition of fatty acid synthase (fas) suppresses her2/neu (erbb-2) oncogene overexpression in cancer cells. *Proc Natl Acad Sci U S A* 2004; 101: 10715-10720.
- 52) MENENDEZ JA, DECKER JP, LUPU R. In support of fatty acid synthase (fas) as a metabolic oncogene: Extracellular acidosis acts in an epigenetic fashion activating fas gene expression in cancer cells. *J Cell Biochem* 2005; 94: 1-4.
- 53) MENENDEZ JA, VELLON L, COLOMER R, LUPU R. Oleic acid, the main monounsaturated fatty acid of olive oil, suppresses her-2/neu (erbb-2) expression and synergistically enhances the growth inhibitory effects of trastuzumab (herceptin) in breast cancer cells with her-2/neu oncogene amplification. *Ann Oncol* 2005; 16: 359-371.
- 54) NTAMBI JM, MIYAZAKI M, DOBRZYNSKI A. Regulation of stearoyl-CoA desaturase expression. *Lipids* 2004; 39: 1061-1065.
- 55) HARDY S, ST-ONGE GG, JOLY E, LANGELIER Y, PRENTKI M. Oleate promotes the proliferation of breast cancer cells via the g protein-coupled receptor gpr40. *J Biol Chem* 2005; 280: 13285-13291.
- 56) PAGANO E, CALVO JC. Erbb2 and egfr are down-modulated during the differentiation of 3t3-l1 preadipocytes. *J Cell Biochem* 2003; 90: 561-572.
- 57) SHIDA D, KITAYAMA J, YAMAGUCHI H, YAMASHITA H, MORI K, WATANABE T, NAGAWA H. Lysophospholipids transactivate her2/neu (erbb-2) in human gastric cancer cells. *Biochem Biophys Res Commun* 2005; 327: 907-914.
- 58) MOREAU K, DIZIN E, RAY H, LUQUAIN C, LEFAI E, FOUFFELLE F, BILLAUD M, LENOIR GM, VENEZIA ND. Brca1 affects lipid synthesis through its interaction with acetyl-CoA carboxylase. *J Biol Chem* 2006; 281: 3172-3181.
- 59) CHAJES V, CAMBOT M, MOREAU K, LENOIR GM, JOULIN V. Acetyl-CoA carboxylase alpha is essential to breast cancer cell survival. *Cancer Res* 2006; 66: 5287-5294.
- 60) GOLD B, KIRCHHOFF T, STEFANOV S, LAUTENBERGER J, VIALE A, GARBER J, FRIEDMAN E, NAROD S, OLSHEN AB, GREGERSEN P, KOSARIN K, OLSH A, BERGERON J, ELLIS NA, KLEIN RJ, CLARK AG, NORTON L, DEAN M, BOYD J, OFFIT K. Genome-wide association study provides evidence for a breast cancer risk locus at 6q22.33. *Proc Natl Acad Sci U S A* 2008; 105: 4340-4345.
- 61) KAHN BB, ALQUIER T, CARLING D, HARDIE DG. Amp-activated protein kinase: Ancient energy gauge provides clues to modern understanding of metabolism. *Cell Metab* 2005; 1: 15-25.
- 62) SAHA AK, SCHWARSIN AJ, RODUIT R, MASSE F, KAUSHIK V, TORNHEIM K, PRENTKI M, RUDERMAN NB. Activation of malonyl-CoA decarboxylase in rat skeletal muscle by contraction and the amp-activated protein kinase activator 5'-aminoimidazole-4-carboxamide-1-beta-d-ribofuranoside [in process citation]. *J Biol Chem* 2000; 275: 24279-24283.
- 63) YIN W, MU J, BIRNBAUM MJ. Role of amp-activated protein kinase in cyclic amp-dependent lipolysis in 3t3-l1 adipocytes. *J Biol Chem* 2003; 278: 43074-43080.
- 64) JENNE DE, REIMANN H, NEZU J, FRIEDEL W, LOFF S, JESCHKE R, MULLER O, BACK W, ZIMMER M. Peutz-jeghers syndrome is caused by mutations in a novel serine threonine kinase. *Nat Genet* 1998; 18: 38-43.
- 65) RATTAN R, GIRI S, SINGH AK, SINGH I. 5-aminoimidazole-4-carboxamide-1-beta-d-ribofuranoside inhibits cancer cell proliferation in vitro and in vivo via amp-activated protein kinase. *J Biol Chem* 2005; 280: 39582-39593.
- 66) ASHRAFIAN H. Cancer's sweet tooth: The janus effect of glucose metabolism in tumorigenesis. *Lancet* 2006; 367: 618-621.
- 67) MAJUMDER PK, FEBBO PG, BIKOFF R, BERGER R, XUE Q, McMAHON LM, MANOLA J, BRUGAROLAS J, McDONNELL TJ, GOLUB TR, LODA M, LANE HA, SELLERS WR. Mtor inhibition reverses akt-dependent prostate intraepithelial neoplasia through regulation of apoptotic and HIF-1-dependent pathways. *Nat Med* 2004; 10: 594-601.
- 68) MICHAYLIRA CZ, NAKAGAWA H. Hypoxic microenvironment as a cradle for melanoma development and progression. *Cancer Biol Ther* 2006; 5: 476-479.
- 69) KIM JE, CHEN J. Regulation of peroxisome proliferator-activated receptor-gamma activity by mammalian target of rapamycin and amino acids in adipogenesis. *Diabetes* 2004; 53: 2748-2756.
- 70) SHAW RJ, BARDEESY N, MANNING BD, LOPEZ L, KOSMATA M, DePINHO RA, CANTLEY LC. The lkb1 tumor suppressor negatively regulates mtor signaling. *Cancer Cell* 2004; 6: 91-99.
- 71) BERBERICH SJ, LITTERAL V, MAYO LD, TABESH D, MORRIS D. Mdm-2 gene amplification in 3t3-l1 preadipocytes. *Differentiation* 1999; 64: 205-212.

- 72) PARK JS, KIM HY, KIM HW, CHAE GN, OH HT, PARK JY, SHIM H, SEO M, SHIN EY, KIM EG, PARK SC, KWAK SJ. Increased caveolin-1, a cause for the declined adipogenic potential of senescent human mesenchymal stem cells. *Mech Ageing Dev* 2005; 126: 551-559.
- 73) LOVEKAMP-SWAN T, CHAFFIN CL. The peroxisome proliferator-activated receptor gamma ligand troglitazone induces apoptosis and p53 in rat granulosa cells. *Mol Cell Endocrinol* 2005; 233: 15-24.
- 74) DANIELA B, SAVERIA A, STEFANIA C, SABRINA G, MARIA B, EMILIA M, HONGYAN Q, CATIA M, MARIAELENA G, MARCELLO M, SEBASTIANO A. Peroxisome proliferator-activated receptor (ppar) gamma activates p53 gene promoter binding to the nfkb sequence in human MCF7 breast cancer cells. *Mol Endocrinol* 2006; 20: 3083-3092.
- 75) GREEN DR, CHIPUK JE. P53 and metabolism: Inside the tigar. *Cell* 2006; 126: 30-32.
- 76) MATOBA S, KANG JG, PATINO WD, WRAGG A, BOEHM M, GAVRILOVA O, HURLEY PJ, BUNZ F, HWANG PM. P53 regulates mitochondrial respiration. *Science* 2006; 312: 1650-1653.
- 77) FANTIN VR, ST-PIERRE J, LEDER P. Attenuation of Idh-a expression uncovers a link between glycolysis, mitochondrial physiology, and tumor maintenance. *Cancer Cell* 2006; 9: 425-434.
- 78) SANDQVIST MM, ERIKSSON JW, JANSSON PA. Increased lactate release per fat cell in normoglycemic first-degree relatives of individuals with type 2 diabetes. *Diabetes* 2001; 50: 2344-2348.
- 79) JONES RG, PLAS DR, KUBEK S, BUZZAI M, MU J, XU Y, BIRNBAUM MJ, THOMPSON CB. Amp-activated protein kinase induces a p53-dependent metabolic checkpoint. *Mol Cell* 2005; 18: 283-293.
- 80) ZHAO W, KRUSE JP, TANG Y, JUNG SY, QIN J, GU W. Negative regulation of the deacetylase sirt1 by dbc1. *Nature* 2008; 451: 587-590.
- 81) IYENGAR P, ESPINA V, WILLIAMS TW, LIN Y, BERRY D, JELICKS LA, LEE H, TEMPLE K, GRAVES R, POLLARD J, CHOPRA N, RUSSELL RG, SASISEKHARAN R, TROCK BJ, LIPPMAN M, CALVERT VS, PETRICIOIN EF, 3RD, LIOTTA L, DADACHOVA E, PESTELL RG, LISANTI MP, BONALDO P, SCHERER PE. Adipocyte-derived collagen vi affects early mammary tumor progression in vivo, demonstrating a critical interaction in the tumor/stroma microenvironment. *J Clin Invest* 2005; 115: 1163-1176.
- 82) STEPHENS JM, VIDAL-PUIG AJ. An update on visfatin/pre-b cell colony-enhancing factor, an ubiquitously expressed, illusive cytokine that is regulated in obesity. *Curr Opin Lipidol* 2006; 17: 128-131.
- 83) PICARD F, KURTEV M, CHUNG N, TOPARK-NGARM A, SENAWONG T, MACHADO DE OLIVEIRA R, LEID M, MCBURNEY MW, GUARENTE L. Sirt1 promotes fat mobilization in white adipocytes by repressing ppar-gamma. *Nature* 2004; 429: 771-776.
- 84) CURTIS R, GEESAMAN BJ, DiSTEFANO PS. Ageing and metabolism: Drug discovery opportunities. *Nat Rev Drug Discov* 2005; 4: 569-580.
- 85) LIM CS. Sirt1: Cellular senescence, cancer and organismal aging? *Med Hypotheses* 2006; 67: 989-990.
- 86) ESTEBAN MA, MAXWELL PH. Hif, a missing link between metabolism and cancer. *Nat Med* 2005; 11: 1047-1048.
- 87) WADA T, SHIMBA S, TEZUKA M. Transcriptional regulation of the hypoxia inducible factor-2alpha (HIF-2alpha) gene during adipose differentiation in 3t3-l1 cells. *Biol Pharm Bull* 2006; 29: 49-54.
- 88) KWON SJ, LEE YJ. Effect of low glutamine/glucose on hypoxia-induced elevation of hypoxia-inducible factor-1alpha in human pancreatic cancer mia-paca-2 and human prostatic cancer du-145 cells. *Clin Cancer Res* 2005; 11: 4694-4700.
- 89) LU H, DALGARD CL, MOHYELDIN A, MCFATE T, TAIT AS, VERMA A. Reversible inactivation of HIF-1 prolyl hydroxylases allows cell metabolism to control basal HIF-1. *J Biol Chem* 2005; 280: 41928-41939.
- 90) VORDERMARK D, KRAFT P, KATZER A, BOLLING T, WILLNER J, FLENTJE M. Glucose requirement for hypoxic accumulation of hypoxia-inducible factor-1alpha (HIF-1alpha). *Cancer Lett* 2005; 230: 122-133.
- 91) MENENDEZ JA, VELLON L, OZA BP, LUPU R. Does endogenous fatty acid metabolism allow cancer cells to sense hypoxia and mediate hypoxic vasodilatation? Characterization of a novel molecular connection between fatty acid synthase (fas) and hypoxia-inducible factor-1alpha (HIF-1alpha)-related expression of vascular endothelial growth factor (VEGF) in cancer cells overexpressing her-2/neu oncogene. *J Cell Biochem* 2005; 94: 857-863.
- 92) LEE S, NAKAMURA E, YANG H, WEI W, LINGGI MS, SAJAN MP, FARESE RV, FREEMAN RS, CARTER BD, KAELEN WG, JR., SCHLISIO S. Neuronal apoptosis linked to egl3 prolyl hydroxylase and familial pheochromocytoma genes: developmental culling and cancer. *Cancer Cell* 2005; 8: 155-167.
- 93) ISAACS JS, JUNG YJ, MOLE DR, LEE S, TORRES-CABALA C, CHUNG YL, MERINO M, TREPEL J, ZBAR B, TORO J, RATCLIFFE PJ, LINEHAN WM, NECKERS L. HIF overexpression correlates with biallelic loss of fumarate hydratase in renal cancer: Novel role of fumarate in regulation of HIF stability. *Cancer Cell* 2005; 8: 143-153.
- 94) KUREBAYASHI J, OTSUKI T, KUROSUMI M, SOGA S, AKINAGA S, SONOO H. A radicicol derivative, kf58333, inhibits expression of hypoxia-inducible factor-1alpha and vascular endothelial growth factor, angiogenesis and growth of human breast cancer xenografts. *Jpn J Cancer Res* 2001; 92: 1342-1351.
- 95) GIBSON TB, LAWRENCE MC, GIBSON CJ, VANDERBILT CA, MCGLYNN K, ARNETTE D, CHEN W, COLLINS J, NAZIRUDDIN B, LEVY MF, EHRLICH BE, COBB MH. Inhibition of glucose-stimulated activation of extracellular signal-regulated protein kinases 1 and 2 by epinephrine in pancreatic {beta}-cells. *Diabetes* 2006; 55: 1066-1073.
- 96) BERRA E, MILANINI J, RICHARD DE, LE GALL M, VINALS F, GOTHIE E, ROUX D, PAGES G, POUYSEGUER J. Signaling angiogenesis via p42/p44 map kinase and hypoxia. *Biochem Pharmacol* 2000; 60: 1171-1178.

- 97) TEMES E, MARTIN-PUIG S, ARAGONES J, JONES DR, OL-MOS G, MERIDA I, LANDAZURI MO. Role of diacylglycerol induced by hypoxia in the regulation of HIF-1 α activity. *Biochem Biophys Res Commun* 2004; 315: 44-50.
- 98) CHANG Q, QIN R, HUANG T, GAO J, FENG Y. Effect of antisense hypoxia-inducible factor 1 α on progression, metastasis, and chemosensitivity of pancreatic cancer. *Pancreas* 2006; 32: 297-305.
- 99) SCHOPPMANN SF, FENZL A, SCHINDL M, BACHLEITNER-HOFMANN T, NAGY K, GNANT M, HORVAT R, JAKESZ R, BIRNER P. Hypoxia inducible factor-1 α correlates with VEGF-C expression and lymphangiogenesis in breast cancer. *Breast Cancer Res Treat* 2006; 99: 135-141.
- 100) CHOI Y, KAWAZOE Y, MURAKAMI K, MISAWA H, UESUGI M. Identification of bioactive molecules by adipogenesis profiling of organic compounds. *J Biol Chem* 2003; 278: 7320-7324.
- 101) SWINNEN JV, BRUSSELMANS K, VERHOEVEN G. Increased lipogenesis in cancer cells: New players, novel targets. *Curr Opin Clin Nutr Metab Care* 2006; 9: 358-365.
- 102) HU Z, CHA SH, CHOHNAN S, LANE MD. Hypothalamic malonyl-CoA as a mediator of feeding behavior. *Proc Natl Acad Sci U S A* 2003; 100: 12624-12629.
- 103) TAKAHASHI KA, SMART JL, LIU H, CONE RD. The anorexigenic fatty acid synthase inhibitor, c75, is a nonspecific neuronal activator. *Endocrinology* 2004; 145: 184-193.
- 104) LANDREE LE, HANLON AL, STRONG DW, RUMBAUGH G, MILLER IM, THUPARI JN, CONNOLLY EC, HUGANIR RL, RICHARDSON C, WITTERS LA, KUHAJDA FP, RONNETT GV. C75, a fatty acid synthase inhibitor, modulates amp-activated protein kinase to alter neuronal energy metabolism. *J Biol Chem* 2004; 279: 3817-3827.
- 105) BENTEBIBEL A, SEBASTIAN D, HERRERO L, LOPEZ-VINAS E, SERRA D, ASINS G, GOMEZ-PUERTAS P, HEGARDT FG. Novel effect of c75 on carnitine palmitoyltransferase i activity and palmitate oxidation. *Biochemistry* 2006; 45: 4339-4350.
- 106) TONG L. Acetyl-coenzyme a carboxylase: Crucial metabolic enzyme and attractive target for drug discovery. *Cell Mol Life Sci* 2005; 62: 1784-1803.
- 107) HARWOOD HJ, JR. Treating the metabolic syndrome: Acetyl-CoA carboxylase inhibition. *Expert Opin Ther Targets* 2005; 9: 267-281.
- 108) ABU-ELHEIGA L, MATZUK MM, ABO-HASHEMA KA, WAKIL SJ. Continuous fatty acid oxidation and reduced fat storage in mice lacking acetyl-CoA carboxylase 2. *Science* 2001; 291: 2613-2616.
- 109) PREUSS HG, GARIS RI, BRAMBLE JD, BAGCHI D, BAGCHI M, RAO CV, SATYANARAYANA S. Efficacy of a novel calcium/potassium salt of (-)-hydroxycitric acid in weight control. *Int J Clin Pharmacol Res* 2005; 25: 133-144.
- 110) HARASHIMA K, AKIMOTO T, NONAKA T, TSUZUKI K, MITSUHASHI N, NAKANO T. Heat shock protein 90 (hsp90) chaperone complex inhibitor, radicicol, potentiated radiation-induced cell killing in a hormone-sensitive prostate cancer cell line through degradation of the androgen receptor. *Int J Radiat Biol* 2005; 81: 63-76.
- 111) KAPLAN LM. Pharmacological therapies for obesity. *Gastroenterol Clin North Am* 2005; 34: 91-104.
- 112) KNOWLES LM, AXELROD F, BROWNE CD, SMITH JW. A fatty acid synthase blockade induces tumor cell-cycle arrest by down-regulating skp2. *J Biol Chem* 2004; 279: 30540-30545.
- 113) MENENDEZ JA, VELLON L, LUPU R. Orlistat: From antiobesity drug to anticancer agent in her-2/neu (erbB-2)-overexpressing gastrointestinal tumors? *Exp Biol Med (Maywood)* 2005; 230: 151-154.
- 114) GOTO K, ASAI T, HARA S, NAMATAME I, TOMODA H, IKEMOTO M, OKU N. Enhanced antitumor activity of xanthohumol, a diacylglycerol acyltransferase inhibitor, under hypoxia. *Cancer Lett* 2005; 219: 215-222.
- 115) NOZAWA H. Xanthohumol, the chalcone from beer hops (*humulus lupulus* L.), is the ligand for farnesoid x receptor and ameliorates lipid and glucose metabolism in kk-a(y) mice. *Biochem Biophys Res Commun* 2005; 336: 754-761.