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-1α, 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 reports 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, oesophageal and breast cancers. 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 on cancer incidence in US 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 \( \geq 40 \) kg/m\(^2\) have three times more mortality rate than lean women (BMI, \( \leq 20.5 \) kg/m\(^2\)), 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) cycling\(^9\) 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\(\kappa\)B via G protein coupled receptor (GPCR) pathway involving Bcl-10 and Malt-1\(^10\). It is well known that NF\(\kappa\)B is involved in the expression of anti-apoptotic proteins Bcl-2 and Bcl-xl in a variety of cells\(^11\), 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.

**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)\(^16,19\) 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 metastasis\(^22\). 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 study\(^23\), 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 considered\(^23\).

**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), di-carboxylate 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\(^18,27\). Besides genetic, environmental and epigenetic factors, metabolic signals also likely determine if a cell becomes cancerous. Thus, along with accel-

**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.
erated glycolysis, a hallmark of cancer cells, lipogenesis is markedly increased in breast cancer cells. 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 apoptosis. Many enzymes of lipid metabolism (Figure 2), which are up-regulated during adipogenesis including ATP-citrate lyase (ACL), fatty acid synthase (FAS), acetyl-CoA carboxylase-1 (ACC-1), dicarboxylate transporter (Slc25A10) and malic enzyme, are also increased in many types of cancer cells and abrogation of their activity leads to apoptosis. Similar results have been obtained with ACC-1. However, FL5.12 leukemia cells with ACL knockdown show impaired proliferatory response to cytokine IL3, which stimulates the conversion of glucose to lipid. ACL knockdown
Table I. The obesity and cancer link commonalities between oncogenesis and adipogenesis.

<table>
<thead>
<tr>
<th>Oncogenesis</th>
<th>Adipogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth Signals for Self-Sufficiency</td>
<td>Autocrine stimulation, e.g., PDGF, TGFβ, GF receptor overexpression,--EGFR, Her2/Neu; Altered RAS signaling etc.</td>
</tr>
<tr>
<td>Anti-Apoptosis Machinery</td>
<td>Bcl-2, Bcl-xl, Bcl-2, Bcl-w; Loss of function mutations in p53; IAPs. Bcl-2, Bcl-xl upregulation</td>
</tr>
<tr>
<td>Angiogenesis Capability</td>
<td>HIF overexpression, VEGF, FGF1/2, MMPs. HIF overexpression, VEGF, MMPs, FGF10.</td>
</tr>
<tr>
<td>Invasion, Metastasis &amp; Migration</td>
<td>Expression of MMPs; Loss of E-cadherin function; Expression of MMPs; Loss of N-cadherin function leads to increased adipogenesis.</td>
</tr>
<tr>
<td>Insensitivity to Anti-Growth Signals</td>
<td>Disruption of retinoblastoma protein/ E2F function. Reduced function of pRb during brown-adipogenesis.</td>
</tr>
<tr>
<td>Limitless Replicative Potential</td>
<td>Telomere maintenance</td>
</tr>
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</table>

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 HIF1α-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 tumors29,37. Dicarboxylate carrier (Slc25A10), which participates in the net export of mitochondrial citrate 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-1α (hypoxia inducible factor-1α) 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 debated30,39,40. 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 lipase (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 hydrolizing 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 adipocytes. 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 cells. 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, attenuated this interaction leading to elevated lipogenesis and altered b-oxidation, a characteristic of breast cancer cells.

**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. 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 suppressor. Activated AMPK phosphorylates and inhibits the activities of ACC, FAS and GPAT. 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. AMPK also brings about the activation of MCD to facilitate the decrease in the malonyl-CoA levels. In adipocytes AMPK activation can lead to enhanced lipolysis. 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 maintained. For example, in Peutz-Jeghers syndrome (PJS), a rare form of heritable cancer of gastrointestinal tract, LKB1 is mutated with the resultant loss of active AMPK. Activators of AMPK viz., metformin and AICAR inhibit the growth and survival of cancer cells. Recently, it has been hypothesized that 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-1α has been shown to be activated by mTOR in PTEN-null cancers. 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 cells. 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 PPARγ and disrupted adipocytes differentiation. LKB1, besides activating AMPK, is also implicated in the negative regulation of mTOR signaling by a mechanism dependent on AMPK.

**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 preadipocytes. Senescence-associated increase in the expression of p53 in human mesenchymal stem cells makes them to lose their capacity to differentiate into adipocytes. Interestingly, the ability of PPARγ ligands to induces apoptosis in cancer cells may be because these compounds induce the expression of p53 in these cells. Several recent reports have shown the involvement of p53 in the control of glycolysis. Liver cells from p53-knockout mice exhibit much
higher capacity for glycolysis and significantly elevated lactate production\(^{16}\). 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 enzymes\(^{77}\). Knockdown of LDH-A leads to increased mitochondrial oxidative phosphorylation and decreased ability to proliferate under hypoxic conditions associated with curtailed tumorigenicity\(^{77}\). 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 factors\(^{81}\). 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 diabetes\(^{48}\). AMPK, a well-known cellular energy sensor, has been shown to activate p53 by phosphorylation at ser-15\(^{79}\). 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 availability\(^{79}\). 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 to SIRT-1, which deacetylates and inactivates p53 tumor suppressor protein, and protects breast cancer cells from apoptosis\(^{80}\). 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-\(\alpha\)3 has been shown to stimulate the growth of mammary tumors in \emph{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\(^+\) content\(^{82}\). 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 types\(^{82}\). 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\(\gamma\) 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 lifespan\(^{84}\). Elevated SIRT-1 is noticed in various cancer cells\(^{85}\).

**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\(\alpha\) and malonyl-CoA levels. HIF-1\(\alpha\), which is induced by the hypoxic conditions that prevail in the core region cancer cells of many solid tumors\(^{86}\) and also in the internal adipocytes during adipogenesis\(^{19,87}\) leads to the expression of vascular endothelial growth factor (VEGF), which promotes angiogenesis\(^{89}\). Conditions that lead to an elevation of cellular malonyl-CoA levels, for example, elevated glucose concentration\(^{88-90}\) and lowering the activity of FAS either by C75 or siRNA\(^{91}\) 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 succinate\(^{82}\) and fumarate\(^{90}\) at millimolar concentrations, can inhibit this enzyme and lead to the accumulation of HIF in the cells thereby explaining the association of fumarase or succinate dehydrogenase deficiency with cancer. Lu et al\(^{89}\) 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 concentration\(^{7}\), 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-1α. Thus, decreased synthesis of malonyl-CoA can lead to lowered levels of HIF1α and the associated downstream 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) pathway, which can lead to a rise in HIF in the cells. Hypoxic conditions are also known to cause an elevation of TG and phosphatidic acid, the intermediates of TG/FFA cycle, 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, 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 metastasis. Also, under hypoxic conditions, induced either chemically or by high glucose, adipocytes express high levels of MMPs. 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 oncoproteins, 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 al. 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 al. 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 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. This compound was originally thought to specifically inhibit FAS and activate CPT-1. However, recent SAR studies revealed that C75 inhibits CPT-1. 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. It may be desirable to have inhibitors that target ACC-2 for treating obesity and promote weight-loss. 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 ACC, has been described as a potential drug for obesity. The HSP90 inhibitor, radicicol, which also inhibits ACL, has been suggested as a therapeutic against cancer. 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. 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 people. Orlistat also inhibits intra-cellular lipases and TG/FFA cycling and also FAS. This compound is also recognized for its anti-cancer efficacy. An inhibitor of DGAT and a probable ligand for farnesoid X receptor, xanthohumol was found to have anti-tumor properties in various systems and is also able to reduce white adipose
mass and lower plasma glucose levels in KK-A(y) mice. 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.

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