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Adipose tissue dysfunction and its effects on tumor metabolism

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Abstract

Growing by an alarming rate in the Western world, obesity has become a condition associated with a multitude of diseases such as diabetes, metabolic syndrome and various cancers. Generally viewed as an abnormal accumulation of hypertrophied adipocytes, obesity is also a poor prognostic factor for recurrence and chemoresistance in cancer patients. With more than two-thirds of the adult population in the United States considered clinically overweight or obese, it is critical that the relationship between obesity and cancer is further emphasized and elucidated. Adipocytes are highly metabolically active cells, which, through release of adipokines and cytokines and activation of endocrine and paracrine pathways, affect processes in neighboring and distant cells, altering their normal homeostasis. This work will examine specifically how adipocyte-derived factors regulate the cellular metabolism of malignant cells within the tumor niche. Briefly, tumor cells undergo metabolic pressure towards a more glycolytic and hypoxic state through a variety of metabolic regulators and signaling pathways, i.e., phosphoinositol-3 kinase (PI3K), hypoxia-inducible factor-1 alpha (HIF-1α), and c-MYC signaling. Enhanced glycolysis and high lactate production are hallmarks of tumor progression largely because of a process known as the Warburg effect. Herein, we review the latest literature pertaining to the body of work on the interactions between adipose and tumor cells, and underlining the changes in cancer cell metabolism that have been targeted by the currently available treatments.

Keywords

adipose tissue; cancer; glycolysis; metabolic pathologies; obesity; tumor metabolism

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Introduction: fifty shades of fat

Adipose tissue is a versatile organ, crucial for maintaining homeostasis by storing and dispersing energy, producing and releasing adipokines and cytokines, with the ability to influence other cells of the body in autocrine, paracrine and endocrine fashion [1]. This highly metabolically active tissue is distributed throughout the body in discrete depots, and its development, expansion and energy balance are regulated by an integrated network of genetic, environmental, epigenetic and pharmacological factors [1, 2]. When unbalanced, or when caloric intake exceeds energy expenditure, adipose tissue becomes problematic and can detrimentally affect physiological processes.

Different types of adipose tissue: brown vs. white fat

Long-thought to have homogenous characteristics throughout the entire body, adipose tissue actually exhibits depot-specific differences in metabolic profiles, and these variations appear to correlate with susceptibility to obesity and specific metabolic disorders [1]. In addition to its localization-based classification, adipose tissue is also commonly categorized based on its coloration, and is divided into brown, white and beige tissues with distinct functional, metabolic and endocrine differences [1].

The main role of brown adipose tissue (BAT) is to provide non-shivering thermogenesis by the means of energy expenditure. Mitochondria and cytochrome content are abundant in BAT, a characteristic that attributes, in part, to the color and name of BAT [3]. Brown adipocytes are multilocular, meaning they contain multiple fat droplets. Uniquely, they express an uncoupling protein-1 (UCP1), the function of which is to uncouple respiratory chain proteins in the abundant cellular mitochondria. The uncoupling of respiratory chain proteins results in the metabolic substrates being oxidized purely for the purpose of heat energy dissipation [3]. The progenitors of BAT can be traced through the expression of myogenic factor 5 (Myf5), which is also expressed in skeletal myocytes [4]. In humans, BAT develops during the fetal stage and is the most abundant throughout the body at infancy and throughout the first decade of life. It eventually declines in its abundance and retires predominately to areas surrounding vital organs such as suprarenal and para-aortic [3, 5] and the supraclavicular area [6]. Cold temperature [6–8] and β-adrenergic stimulation [9, 10] can trigger the expression of UCP1, induction of substrate oxidation and activation of BAT. Increased expression of UCP1 in rodents caused by over-feeding sprouted a theory of the relevance of BAT in evading obesity. The fact that activity of BAT declines in overweight individuals [7, 11] supports the evidence of inverse correlation between propensity to obesity and abundance of BAT [12, 13].

In contrast to BAT, the white adipose tissue (WAT) development begins in utero and continues to evolve throughout life [14, 15]. WAT serves as primary energy storage and based on its location in the body, it is often referred to as subcutaneous or visceral (intra-abdominal) fat that includes mesenteric, epididymal and perirenal depots. In humans, subcutaneous fat develops prior to visceral [16] and can be distinctively different in its pathophysiological processes [17]. Importantly, the morphology of white adipocytes differs from brown as they are unilocular cells containing less mitochondria and do not express UCP1 [18].

"Browning" is a phenomenon described when adipocytes located in the typical WAT sites switch from anabolic to catabolic mechanism, producing "beige" adipocytes [19]. They do so by developing multilocular morphology with increased numbers of mitochondria and expression of UCP1. This occurrence has been well-described in rodents and is triggered by cold exposure and β_3-adrenergic stimulation [20–22]. Although closely resembling the brown fat morphology, BAT residing in the WAT depots does not express the same lineage marker, Myf5, as a "classical BAT" [23]. There has been a growing interest in understanding the capacity of brown and beige adipocytes to counteract obesity, diabetes and other metabolic diseases [19]. Strategies are being developed to selectively enhance respiratory uncoupling in adipose tissue to induce weight loss and reverse obesity-driven pathological processes.

Bone marrow fat and its roles in physiological processes and disease

Bone marrow fat, known as yellow adipose tissue (YAT), represents a depot dispersed throughout the bone marrow with primary localization to trabecular cavities [24, 25], and often viewed as having mixed characteristics of both WAT and BAT [25–27]. No longer considered just a "space-filler", YAT is recognized as a highly active organ, functions of which extend far beyond the storage of triglycerides and lipid metabolism, and they include systemic energy regulation and management of insulin sensitivity [28, 29]. Importantly, the systemic changes related to adipose tissue homeostasis critically affect glucose and energy balance [30] and reciprocally influence bone health. If the stability in signaling pathways that integrate bone remodeling and energy metabolism gets perturbed by metabolic events related to age and obesity, the physiological processes in the bone, like osteogenesis and hematopoiesis, are critically affected [25, 28]. The latter results in susceptibility to pro-inflammatory events and dysregulated bone remodeling [24].

It is well-established, that during the normal aging process, healthy, hematopoietically active red marrow of the bone is progressively replaced by the fatty yellow marrow [24–26]. There is also increasing evidence that obesity and associated metabolic pathologies can have detrimental effects on bone health that go beyond age-driven changes in skeletal homeostasis [24, 31, 32]. Until recently, obesity was thought to have a protective effect on bone metabolism due to the positive impact of body weight on bone formation [31, 33]. Current evidence suggests that percent body fat, waist circumference, and waist-to-hip ratio correlate with the risk of osteoporotic fractures, especially in men, who have larger amounts of marrow fat than age-matched women [34–36]. These epidemiological data are mirrored by the results of animal studies, where marrow adiposity has been shown to result in decreases in trabecular bone volume and overall reduced bone mineral density (BMD) [31, 37, 38]. Despite these findings, the relationship between adiposity and bone turnover remains controversial and additional, controlled studies are needed to truly understand the effects of obesity on bone health in humans.

There is growing clinical and epidemiological evidence that metabolic syndrome (MetS), a cluster of metabolic abnormalities that include abdominal obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, high blood pressure, and glucose intolerance [39–41] is a strong contributor to marrow adiposity. This condition is highly prevalent in the

United States as demonstrated by its presence in approximately 25–30% of adults over the age of 18 years [42, 43], and is a strong risk factor for cardiovascular disease, diabetes and stroke [44, 45]. A study of metabolic syndrome in normal-weight individuals with only regional accumulation of fat (visceral/abdominal and inter-muscular) was associated with fasting hyperinsulinemia, a risk factor for type 2 diabetes mellitus (T2DM) [46, 47]. Importantly, general obesity was shown to correlate with accumulation of marrow fat in both control and diabetic individuals [48]; however, only in diabetic patients was marrow adiposity correlated with visceral adipose tissue (VAT) [48]. This finding pinpoints the potential importance of visceral fat depot in bone health, and its implications for development of diabetes. This also underlines the importance of distinguishing VAT from other adipose tissues in studies investigating the impact of obesity and metabolic disorders on skeletal health, because using the central obesity measures continues to lead to inconsistent results [49].

One specific metabolic consequence of excess adiposity is diabetes, a condition highly linked with marrow adiposity [48, 50] and profound effects on bone health [51, 52]. Numerous reports suggest that the following are potential biological links between obesity and diabetes: changes in insulin levels, altered calcium metabolism, reduced renal function, vitamin D de-regulation, higher concentrations of inflammatory molecules and collagen glycation products, polypeptides, such as osteocalcin and osteopontin, and certain adipokines [27–29, 53, 54]. Increases in circulating levels of bone resorption markers such as tartrate resistant acid phosphatase (TRAP 5b) and cathepsin K (CTSK) have been reported in diabetic patients [55] and animal experimental models of diabetes [56, 57]. Serum levels of osteocalcin, an osteoblast-specific polypeptide, were reported to be inversely correlated with adiposity and measures of insulin resistance [58, 59]. In contrast, a positive association with insulin sensitivity and HDL cholesterol was demonstrated for osteoprotegerin, a known inhibitor of bone resorption, further evidence of clear association between the metabolic features and bone degradation [60]. It is noteworthy, similar to other fat depots, that adipogenesis in the bone marrow is under the regulation of PPARγ [28]. This has led to serious concerns in terms of treatment with anti-diabetic thiazolidinedione drugs, which were shown to induce bone marrow adiposity [61], likely even further exacerbating the environment already altered by diabetes itself. It is also important to keep in mind that marrow adiposity associated with diabetes appears to be characterized by low unsaturation and high saturation levels of fats [48, 62]. This suggests that perhaps apart from an overall increase in adiposity, the composition of marrow fat might be a more important factor in bone health, and potentially other physiological processes, a phenomenon that warrants further investigations.

Adipocyte artillery

Contrary to the previous view of adipocytes being metabolically inert, growing evidence from the last decades of research has revealed that they are in fact metabolically active cells highly involved in the uptake, production, and secretion of many different factors with systemic implications [63]. Through the production of lipids and secretion of hormones, cytokines or adipokines, adipocytes have the ability to influence neighboring cells within

their microenvironment and throughout the body as a whole, working as a functional paracrine and endocrine tissue [1, 2, 63].

Hormones

The two most commonly studied hormones secreted by white adipocytes are adiponectin and leptin. Adiponectin is a protein hormone responsible for regulating multiple metabolic processes [64]. This hormone is secreted primarily by adipocytes and is released into the bloodstream where it binds to adiponectin receptor 1 (AdipoR1), adiponectin receptor 2 (AdipoR2), and has the potential to bind a membrane receptor, T-cadherin [65, 66]. Adiponectin-receptor binding results in activation of AMP-activated protein kinase (AMPK) and subsequent signaling through peroxisome proliferator-activated receptor (PPAR)-α transcription factor [67–69]. Adiponectin levels have been associated with many different metabolic diseases. Interestingly, adiponectin is shown to be down-regulated in patients with obesity and/or diabetes and is upregulated upon treatment with insulin-sensitizers [70, 71]. It was recently discovered that bone marrow adipose tissue (MAT), in response to caloric restriction and chemotherapy, secretes adiponectin at a much larger scale as compared to the levels secreted by WAT, suggesting that MAT-derived adiponectin is circulated throughout the body, exhibiting endocrine and metabolic effects on cells [72]. Circulating adiponectin is shown to be decreased in patients with T2DM, cardiovascular disease, liver disease, and hypertension [73–75]. In addition, adiponectin binding to AdipoR1 and AdipoR2 has been shown to have anti-diabetic effects, which further underlines positive effects of this hormone on metabolic homeostasis [76].

Leptin, also known as the “satiety hormone”, is the other most commonly studied factor produced and secreted by white adipocytes [77, 78]. Canonical leptin signaling occurs through the leptin receptor which, upon the binding of its ligand, dimerizes and induces phosphorylation and activation of Janus tyrosine kinase-2 (JAK2) [79]. This leads to STAT3 phosphorylation and downstream transcription of leptin target genes. Mutations in the gene encoding leptin or its receptors in the hypothalamus result in disturbed leptin signaling and consequently promote hyperphagic obesity, diabetes mellitus, and neuroendocrine dysfunctions [80]. Interestingly, although leptin is secreted by adipocytes to inhibit hunger, this adipokine is produced and secreted at high rates in obese individuals [81]. Enhanced leptin signaling has been implicated in many different cancers [82]. Leptin binding to its receptor on mammary cancer cells has been shown to play a role in maintaining cancer stem cell phenotype and promoting stem cell-like properties of triple negative breast cancers [83].

Inflammatory cytokines

Obesity is characterized as a state of chronic inflammation. It has been speculated that expansion of adipose tissue occurring in obesity results in oxygen deprivation of adipocytes which are most distant from the capillary network [84]. This hypoxia triggers the activation of hypoxia-inducible factor 1-alpha (HIF-1α), which in turn, signals for the macrophage infiltration and induction of inflammation [85]. There is growing evidence that multiple pro- and anti-inflammatory cytokines in obese adipose tissue form a functional circuitry that regulates local and systemic glucose tolerance and insulin sensitivity [86]. These cytokines

are secreted by adipocytes, macrophages and other cell types residing in the inflamed tissue [86, 87].

TNF-α was one of the first identified WAT-derived pro-inflammatory cytokines, thought to be primarily secreted by myeloid cells via activation of MAPK and NFκB signaling pathways and stimulating the release of other inflammatory cytokines, such as IL-1β and IL-6 [88]. It has since been determined that adipocytes themselves are a significant source of TNF-α, whose induction in fat cells occurs in response to free fatty acids (FFA), and activation of JNK signaling pathway [89]. TNF-α, in turn, via activation of ERK signaling pathway stimulates lipolysis, a process resulting in a positive feedback mechanism that further contributes to the chronic state of obesity-induced inflammation [90]. The abundant secretion of this TNF-α has been directly linked to obesity-associated insulin resistance [89, 91] and tumorigenesis [92].

IL-6 is a pleiotropic cytokine, that is released in response to hypoxic stimulation of white adipocytes [93] and its secretion is associated with insulin resistance [94], immune responses and host defense mechanisms [88], as well as tumorigenesis and metastatic potential [95]. Approximately 30% of circulating IL-6 levels are thought to originate from WAT, categorizing it as an adipokine [88]. Circulating levels of IL-6 appear to correlate with increased body mass, waist circumference and FFA concentrations; however, its functions in obesity and insulin resistance in regards to tissue and metabolic rate remain controversial [88].

IL-1β is another important regulator of inflammatory responses whose levels are elevated in obesity and associated metabolic disorders [86]. A blockade of IL-1β activity in animal models and human subjects with neutralizing antibodies to this cytokine or its receptor improve insulin sensitivity and help to treat T2DM [86, 96, 97]. However, IL-1β-deficient animals have reported glucose intolerance, while IL-1RA-null mice are resistant to diet-induced obesity, findings revealing the need for further investigations of pro-inflammatory axes in obesity and metabolic disorders.

Lipolysis

Key components released by all types of adipocytes that can influence metabolic processes in neighboring cells are glycerol and FFA. In times of excess energy, fatty acids are stored as triglycerides, forming lipid droplets that are housed in the specialized domains within the endoplasmic reticulum [98, 99]. Fat cells are constantly both synthesizing triglycerides, and breaking them down to glycerol and fatty acids during a catabolic process known as lipolysis [100]. This process is driven by activation of the rate-limiting enzyme, adipose triglyceride lipase (ATGL), phosphorylation and activation of hormone-sensitive lipase (HSL), and monoacylglycerol hydrolysis by monoglyceride lipase (MGL). Lipolysis and its rates are regulated by hormonal and biochemical signaling. The process of lipid breakdown is stimulated through the binding of catecholamines, epinephrine and norepinephrine, to β-adrenergic receptors 1 and 2 and the α-adrenergic receptor [101]. A key process for lipolysis and lipase regulation occurs through activation or suppression of protein kinase A (PKA) [102, 103]. PKA has the ability to both activate HSL and also facilitate the trafficking of proteins involved in lipolysis [104]. ATGL, conversely, is not a direct target of PKA and has

high affinity for triacylglycerides and no activity against either diacylglycerides or monoacylglycerides [105]. HSL-null mice exhibit severely impaired glycerol release and large accumulation of DAG in several tissues, confirming that this lipase is a rate-limiting enzyme in DAG hydrolysis [106]. In contrast to HSL, ATGL deficiency leads to severe lipid-associated phenotype with high lipid accumulation, poor lipid mobilization, reduced biochemically-induced lipolysis, and myopathy [107–112], indicating its essential function in lipolysis. Absence of ATGL reduces fatty acid release from adipose tissue by 75% and a mutation in the *ATGL* gene in humans causes lipid storage dysfunction called neutral lipid storage disease with myopathy (NLSDM) [111, 113]. Because lipolysis is such a fundamental and crucial process for energy homeostasis and metabolism, dysfunction in this process has been suggested as a hallmark to the onset or maintenance of obesity [114].

Obesity-cancer link: the concerning problem

Currently, obesity is a global epidemic characterized by excess adipocyte size and numbers. Recent reports indicate that more than two-thirds of Americans are overweight or obese and this number has been increasing for decades [115, 116]. Obesity is a serious health concern and a major risk for the development and onset of a multitude of different cancers [117–119]. Studies have demonstrated that the fraction of patients that have cancer caused by excess weight has reached about 20% of all cancers [119]. The Million Women Study reported that around 50% of cancers in postmenopausal women are linked to obesity [120]. For the high-risk obese patients in general, the most common malignancies appear to be esophageal adenocarcinoma, colorectal, postmenopausal breast, prostate, and renal cancers [121, 122]. Malignant melanoma, thyroid cancers, leukemias, non-Hodgkin's lymphomas, and multiple myelomas have been associated with obesity but to a lesser extent [123, 124].

Role of circulating adipokines in tumorigenesis and tumor progression

As experimental and epidemiological evidence linking obesity with cancer risk or recurrence increases, the mechanisms behind this association are still largely unknown. It is becoming increasingly accepted that dysregulation of adipocyte function and obesity-driven chronic inflammation are the main culprits in adiposity-induced tumorigenesis [117, 125]. This is particularly evident in cancers that grow in adipocyte-rich environments like breast carcinomas, or cancers that have propensity to metastasize to fat-rich sites, such as ovarian or gastric malignancies [126]. In addition to acting as local paracrine signaling molecules, adipokines also exert systemic effects and allow for communication with distant sites. The increased levels of adipose tissue-derived factors, such as TNF-α, IL-6, IL-8, macrophage chemoattractant protein (MCP-1), and leptin and their role in tumor progression have been well-documented [82, 126].

Levels of circulating leptin are enhanced in obese individuals, and elevated leptin is a poor prognostic factor for breast cancer patients, underlining the role of this adipokine in tumor progression [127]. Leptin expression is higher in patients that have prostate cancer compared to benign prostate hyperplasia and higher in patients with advanced, metastatic disease compared to patients with localized, early stage prostate cancer, implicating leptin expression as a biomarker for prostate cancer staging and prognosis [128, 129]. Notably, a

polymorphism associated with an overexpression of the mutated leptin in some patients has been suggested as a risk factor for prostate cancer [130]. Furthermore, increased levels of leptin receptor were reported in breast cancer tissue as compared to normal tissue and suggested to correlate with immune response, angiogenesis, reproduction, growth factor signaling and lipid metabolism pathways [131–134]. In gastric cancer, leptin has been shown to increase tumor invasiveness by activating Rho/ROCK signaling pathways [135] while inhibitory effects of this adipokine on mitochondrial respiration have been linked with colon cancer progression [136].

In contrast to leptin, adiponectin, an adipokine with insulin-sensitizing effects, has been suggested to have anti-tumor effects [126, 137]. Low levels of adiponectin, as observed in obese individuals, have been correlated with an increased risk of prostate cancer [138]. Treatment with recombinant adiponectin has resulted in anti-tumor effects in some cancer types such as fibrosarcoma, myelomonocytic leukemia, and breast carcinoma [139–142]. Similarly, inhibitory effects of adiponectin on survival and proliferation of prostate cancer cells was reported, with anti-tumor effects linked to the high molecular form (HMW) of this adipokine, which is known to be responsible for its biological activity [143, 144]. These results were shown both in androgen-dependent LNCaP-FGC cells and androgen-independent DU145 cells, indicating a global effect on prostate cancer cells regardless of androgen receptor status.

Bone marrow adipocytes and skeletal metastases

Although numerous studies have identified obesity as a risk factor for various cancers [124, 145–147], it is only recently that accumulation of bone marrow fat has emerged as a risk factor for the development and progression of skeletal metastases, particularly from prostate cancer [24, 148]. Specifically, we and others have shown that marrow adipocytes mediate translocation of the lipids to the metastatic cancer cells [149, 150]. These adipocyte-supplied lipids serve as an energy source for cancer cells, and consequently induce tumor cell proliferation, motility and invasion [148, 151]. Moreover, fatty acid binding protein 4 (FABP4), a lipid transporter expressed predominantly in adipocytes, macrophages, and endothelial cells [152], and originally identified as a key mediator of adipocyte-tumor interactions in ovarian cancer [126, 153], is highly upregulated in metastatic prostate cancer cells interacting with adipocytes [148]. We have shown that through its interplay with PPARγ and IL-1β, FABP4 is involved in driving the aggressiveness of prostate tumors in bone [148]. Our studies have also demonstrated that additional pro-inflammatory factors such as cyclooxygenase-2 (COX-2) and MCP-1 are highly induced in metastatic tumor cells under conditions of high marrow adiposity [24]. This underlines the interaction between the lipid-driven and the inflammatory pathways in bone and offers new avenues for investigation of mechanisms behind development and progression of skeletal metastases.

Feeding the enemy

Warburg Effect

The role of adipocytes in regulating tumor metabolism is largely understudied and not well-understood. The growth-, proliferation-, and survival-promoting effects of fat cells on the

tumor cells have been clearly demonstrated in breast, prostate, gastric, colon and ovarian cancers [126]; however, little is known about the contribution of altered tumor metabolism to these effects. A recent publication by Nieman et al. showed that ovarian cancer cells utilize white adipocytes to gain energy for rapid division by inducing fat cell-driven lipolysis and increasing availability of lipids for uptake by the tumor cells [153]. Subsequent to lipid uptake, there is an overexpression of fatty acid transporter, FABP4, and significant elevation of β-oxidation, which can be blocked by the treatment with inhibitor of carnitine-palmitoyltransferase 1 (CPT-1), etomoxir [153]. Notably, β-oxidation has also been shown to be a main source of energy in prostate cancer cells [154], further suggesting that metabolic reprogramming may be playing an important role in tumorigenesis.

For most of the normal cells in the human body, glucose is an essential energy source. In the presence of oxygen glucose is broken down to pyruvate, which enters the mitochondria and is further oxidized to carbon dioxide with the release of energy in the form of ATP [155]. In the absence of oxygen, normal cells will produce high rates of lactate and undergo a metabolic shift to a more glycolytic phenotype. It has been well-documented that unlike normal cells, tumor cells show high rates of glycolysis and lactate production, regardless of the presence or absence of oxygen [156]. This metabolic switch to aerobic glycolysis, also known as the Warburg effect, provides energy and essential carbon sources for lipogenesis and nutrient production for the rapidly dividing cancer cells [157, 158]. This enhanced glycolytic phenotype was originally postulated to be a direct effect of mitochondrial dysfunction within cancer cells [157]. Under normal physiological conditions ATP is generated through oxidative phosphorylation in the mitochondria in which acetyl-CoA is oxidized to CO_2, releasing energy in the form ATP [159]. It has been shown that oncogenic transformation leads to an increase in glycolytic genes, while tumor suppressor proteins induce expression of oxidative phosphorylation (OxPhos) genes, showing the implications of glycolysis in carcinogenesis [160, 161].

Many of the enzymes responsible for glucose metabolism in both normal and cancer cells have significant functions that are non-glycolytic and tumor promoting [162]. Specifically, it was revealed that hexokinase II (HKII) has an anti-apoptotic effect on the mitochondria by binding to the mitochondrial membrane, antagonizing interaction with pro-apoptotic factors Bad and Bax [163–165]. Along the same lines, pyruvate kinase M2 (PKM2) was shown to have non-glycolytic functions in facilitating tumor survival [166, 167]. PKM2 appears to be activated through epidermal growth factor receptor (EGFR) signaling and obese patients have higher levels of serum heparin-binding epidermal-like growth factor, which is able to activate EGFR [168, 169]. Other functions of PKM2 include the phosphorylation of histone H3 and releasing histone deacytelase 3, which leads to induction of many cell cycle genes including *Cyclin D* and metabolic regulator *c-MYC* [170]. PKM2 is also known to act as a transcriptional regulator through its interactions with Oct4, a transcription factor that drives the expression of many genes in tumorigenesis and nuclear signaling [171, 172].

Glycolysis is much less energy-efficient compared to the OxPhos pathway as it generates two net ATP molecules, vs. 36 molecules of ATP produced by the OxPhos pathway. Consequently, cancer cells must undergo very high rates of glycolysis in order to generate a large amount of ATP quickly. Interestingly, cells utilizing aerobic glycolysis have high ratios

of ATP/ADP and NADH/NAD^+ even when proliferating at high rates [173]. The aerobic glycolytic phenotype is important for tumor progression through the following postulates: 1) high rates of lactate production and secretion can break down and degrade the surrounding extracellular matrix and aid tumor expansion and metastasis; 2) enhanced glycolysis supplies an abundance of ATP to the cancer cells; and 3) associated mitochondrial dysregulation inhibits or reduces apoptosis [174–176]. It has also been shown that aerobic glycolysis creates byproducts that increase the ability of the cells to produce precursors for biosynthesis of multiple different macromolecules essential for rapid division such as lipids, nucleic acids, and proteins [177]. Also, the generated lactate can create a toxic environment for immune cells, contributing to decreased immunosurveillance and thus the ability of the tumor to hide from an immune response within its microenvironment and prevent detection [178]. Excess lactate production has also been implicated in the stimulation of endothelial cells surrounding the tumor to allow vascularization of the tumor and to provide nutrients through the circulation [179, 180].

It is known that the transcription factor c-MYC acts as a master regulator of cellular metabolism by actively transcribing genes associated with glycolysis. Specifically, it has been shown that c-MYC upregulates lactate dehydrogenase alpha (LDH-α), an enzyme crucial for the conversion of pyruvate to lactate during the Warburg effect [181, 182]. The c-MYC transcription factor is also known to regulate key proteins involved in both nucleic acid synthesis and fatty acid synthesis, processes utilized by tumor cells to meet the demands of rapid cellular division, which underlines its role as a crucial regulator of cellular metabolism [183, 184]. Furthermore, overexpression of c-MYC has been correlated with upregulation of pyruvate kinase M2, the splice variant most commonly seen in tumor cells during aerobic glycolysis [185–187]. The M2 isoform of pyruvate kinase is overexpressed in cancer cells through c-MYC-regulated overexpression of heterogeneous nuclear ribonucleoprotein 1 and 2 (hnRNPA1 and hnRNPA2). These ribonucleoproteins preferentially splice the M2 isoform over the M1 isoform, which is critical for aerobic glycolysis [185, 188]. There is a proposed positive feedback in which PKM2 is upregulated by c-MYC and, in turn, PKM2 is involved in the upregulation of c-MYC [189]. Notably, c-MYC has been shown to be overexpressed in an estimated 50% of all human cancers [190, 191].

Along with an enhanced glycolytic phenotype, tumorigenesis is often associated with mitochondrial dysfunction [192]. Mitochondria become dysfunctional when the mitochondrial DNA (mtDNA) is reduced or mutated and obese individuals have been shown to have a reduction in mitochondrial DNA in white adipocytes [193]. Dysregulation in mitochondrial activity has also been shown to play a role in the inhibition of tumor suppressor protein p53 in epithelial cells, leading to aberrant proliferation checkpoints and tumorigenesis [194]. There is also emerging evidence demonstrating that obesity-induced adipokines promote mitochondrial defects and promote glycolytic phenotype in normal tissue, thereby driving tumorigenesis [195].

HIF-1α signaling pathways in cancer

Anaerobic respiration, a hallmark of tumorigenesis, drives a hypoxic phenotype in cancer cells even in the presence of oxygen [196]. Hypoxic signaling occurs when transcription factor HIF-1α becomes stabilized and translocates to the nucleus where it binds to and activates hypoxic response elements (HRE) [197]. In normoxia, prolyl hydroxylase domain (PHD) proteins hydrolyze HIF-1α, which is then ubiquitinated by Von Hippel-Lindau (VHL) and targeted to the proteasome. However, under hypoxic conditions, PHD is inhibited and HIF-1α is stabilized and translocated to the nucleus where it dimerizes with HIF-1β to activate hypoxia-responsive genes [198]. In addition to the hypoxic effect seen in low oxygenated tissue, there is also an oxygen-independent HIF-1α signaling in which HIF-1α becomes stabilized and activates target genes in the presence or absence of oxygen [199].

The role of HIF-mediated signaling pathway in tumorigenesis and clinical response to treatments is well-established [200]. Many tumors have areas of low oxygenation or intratumoral hypoxia. Patients with poorly oxygenated primary tumors have a higher risk of both metastases and mortality owing to a more aggressive cancer phenotype [201]. Elevated HIF-1α expression has been correlated to increased mortality risk in a plethora of different cancers including solid tumors of the bladder, brain, breast, colon, esophageal, head and neck, oropharynx, liver, lung, pancreas, skin, stomach, and uterus as well as acute lymphocytic and myeloid leukemias [202].

HIF-1α acts as a transcriptional activator and regulates the expression of many different glycolytic enzymes involved in metabolic reprogramming. Specifically, *LDH-A*, the enzyme responsible for the high conversion of pyruvate to lactate in cancer cells, is trans-activated only through HIF-1α transcriptional regulation [203]. Along with HIF-1α, the HIF-2α isoform signals in a similar way, but trans-activates different target genes. A study in renal cell carcinoma cells showed that HIF-1α and HIF-2α signaling converge at genes involved in glucose transport [i.e., *glucose transporter 1* (*Glut1*)], lipid metabolism [i.e., *adipose differentiation-related protein* (*ADRP*)], pH homeostasis [i.e., *carbonic anhydrase IX* (*CAIX*)], interleukin responses, (i.e., *IL-6*), and angiogenesis [i.e., *vascular endothelial growth factor* (*VEGF*)] [204]. Interestingly, however, there were many significant differences in gene regulation between HIF-1α and HIF-2α. This study also revealed that HIF-1α but not HIF-2α is highly involved in a glycolytic response, functioning as a trans-activating factor for the following enzymes involved in glycolysis: *hexokinase1* (*HK1*), *hexokinase2* (*HK2*), *phosphofructokinase* (*PFK*), *aldolase A* (*ALDA*), *phosphoglycerate kinase 1* (*PGK1*), and *LDH-A* [204]. There has also been a proposed feed-forward mechanism in which the Warburg Effect-associated enzyme PKM2 can act as a coactivator for HIF-1α target gene transcription [205]. It was recently demonstrated that Jumonji c domain-containing dioxygenase (JMJD5), is upregulated through HIF-1α signaling and that JMJD5 interacts with PKM2, enhancing its translocation to the nucleus and is recruited to the *LDH-A* promoter [206, 207]. The inhibition of JMJD5 causes a decrease in glucose metabolism and lactate secretion associated with Warburg effect [206, 207].

HIFs do not only regulate glycolytic genes to promote a more glycolytic phenotype, but they are also involved in mitochondrial effects and decreased OxPhos activity. Among HIF target genes are microRNAs, particularly miR-210, which has been reported to be overexpressed in

hypoxia in a number of cancer cells [208]. MicroRNAs bind to sequences in messenger RNA and either inhibit their translation or, in some cases, initiate their degradation [209]. MiR-210 targets the *iron-sulfur cluster assembly enzyme* (*ISCU*) gene, which is required for the activity of complex I in the mitochondrial electron transport chain during oxidative metabolism, the constituents of cytochrome c oxidase assembly protein (COX10), NADH-dehydrogenase 1a subcomplex 4 (NDUFA4), and subunit D of succinate dehydrogenase complex (SDHD) [210–214]. Accordingly, miR-210 has been labeled as a biomarker of tumor hypoxia, and its high levels have been implicated in poor patient prognosis for several cancers [215]. Because many of the targets of miR-210 affect mitochondrial activity, it is evident that this molecule plays a central role in cellular metabolism and homeostasis. Notably, it was also reported that there is a positive feedback loop between miR-210 and HIF-1α in human lung cancer cell lines, where miR-210 stabilizes HIF-1α [213]. This leads to increased transcription of HIF-1α target genes and establishment of hypoxic tumor microenvironment. In addition, lung cancer cells that overexpress miR-210 have been shown to have decreased mitochondrial activity and increased glycolytic phenotype, and exhibit elevated resistance to radiotherapy [213]. This decrease in β-oxidation in parallel with increased HIF activity is important for tumor cell survival because it prevents malignant cells from developing high levels of reactive oxygen species (ROS) and allows them to survive under hypoxic stress.

Another important effect of hypoxia on tumor cells is the initiation of angiogenesis, a process of formation of new blood vessels from pre-existing vasculature. Tumor growth and metastatic progression depend heavily on angiogenesis for the continuing supply of nutrients [216]. Accordingly, studies have shown that tumors with functional angiogenesis grow much larger than those without proper vascularization and blood supply, and that reduced blood supply often results in necrosis or apoptosis [217, 218]. The most well-known pro-angiogenic factor regulated by HIF-1α is *vascular endothelial growth factor* (*VEGF*) [219]. It has been shown that *VEGF* transcript and protein levels are upregulated in response to hypoxia and that targeting HIF-1α with small-interfering RNA (siRNA) significantly reduces *VEGF* gene and protein expression in epithelial cells [220]. Interestingly, we have previously demonstrated that treatment of tumor cells with media conditioned by bone marrow adipocytes in vitro, as well as in vivo establishment of skeletal tumors under conditions of high marrow adiposity result in significant upregulation of oxidative stress markers and VEGF, suggesting potential activation of HIF-1α [148]. Particularly important to the obesity-cancer link might be the evidence that obese patients have higher levels of HIF-1α activity in white adipocytes due to rapid proliferation and expansion of the fat cells and an increase in VEGF expression [221–225]. VEGF alone has been implicated in tumorigenesis through the stimulation of proliferative signaling pathways through the vascular endothelial growth factor receptor (VEGFR) and through cancer stem cell maintenance [226, 227]. Further studies are required to elucidate the role of adipose tissue hypoxia and VEGF secretion in obesity on tumor initiation and maintenance.

ER stress and tumor metabolism

It is well-established that high levels of endoplasmic reticulum (ER) activity occur in cancer cells because high rates of cellular division generate a need for a surplus of protein synthesis

and proper folding [228]. Elevated levels of fatty acids caused by conditions such as obesity can also contribute to ER stress and mitochondrial damage in neighboring cells, including cancer cells [229]. Consequently, misfolded proteins accumulate in the ER lumen triggering a series of intracellular signaling pathways called the unfolded protein response (UPR). UPR can either trigger apoptosis or, oppositely, stimulate the cells to overcome stress, contributing to tumorigenesis and survival.

ER stress has been viewed as one of the mechanisms of cell survival and tumor progression [230–232]. Hypoxia was demonstrated to activate UPR via PERK/eIF2α signaling in tumor cells as a mechanism to promote metastases [233]. ER stress allows malignant cells to thrive in hostile hypoxic microenvironments where nutrients are limited and pH is generally lower than physiological range [234–236]. In fact, there is emerging data that links hypoxia, ER stress response, and metabolic adaptation by the tumor cells. Specifically, a recent study by Chen et al. reported that ER stress in triple negative breast cancer cells leads to the activation of X-box binding protein-1 (XBP1) and that XBP1 complexes with HIF-1α to enhance a hypoxic phenotype [237]. They further demonstrated that XBP1/HIF-1α complex can bind to and regulate *pyruvate dehydrogenase kinase*-1 (PDK1), a gene associated with the Warburg Effect. It was also shown that activating transcription factor 4 (ATF4), an ER stress response protein, has the ability to bind to HREs and HIF-1α target genes such as *VEGF*, potentiating HIF-1α activity under stress conditions [238, 239]. Enhanced hypoxia in white adipocytes of obese mice was shown to correlate with increased production of unfolded proteins, and overexpression of ER stress factor CHOP [221]. In turn, CHOP activation attenuated the expression of adiponectin by interfering with the activity of its promoter, revealing potential links between ER stress and low circulating adiponectin levels seen in obesity [221]. Cumulatively, above-described results indicate that the crosstalk between ER stress, HIF signaling and tumor metabolism might be critical driver of tumor cell survival and chemoresistance (Figure 1).

Adipocyte artillery and their effects on metabolism

Few studies have demonstrated the effects of adipocyte-derived factors on tumor metabolism. The majority of reported studies focus on TNF-α, leptin, and lipids or lipolysis products [240, 241]. A study utilizing genetically obese *ob/ob* mice showed an association between TNF-α secretion and OxPhos dysregulation [242]. A marked decrease in mitochondrial respiratory chain activity in liver cells of *ob/ob* mice was reported. Also reported were elevated levels of TNF-α, inducible nitric oxide synthase (iNOS), and tyrosine nitrated proteins correlated with increased adiposity. It was determined that *ob/ob* mice not only have diminished activity of OxPhos system, but also a reduction in the assembly of the OxPhos subunits in the mitochondria to about 50–60% [243]. Most of the decreases were seen in subunits transcribed by mitochondrial DNA, which was reduced by approximately 60% relative to control mice.

Along with TNF-α, white adipocyte-secreted factors such as leptin and Wnt peptides can also cause mitochondrial impairment [244, 245]. The observed effects of leptin appear to not only result from canonical leptin signaling, but also from its non-canonical signals associated with crosstalk with both the phosphatidylinositol 3-kinase (PI3-K) pathway and

the Ras-dependent pathways [246]. These pathways are both commonly deregulated in cancers and affect cellular survival, growth, and metabolism [247, 248]. PI3-K activation leads to subsequent activation of the downstream target protein Akt, and PI3-K/Akt signaling has been shown to directly regulate cellular metabolism [248]. Induction of this pathway leads to the expression of glucose, amino acid, lipoprotein, and iron transporters at the cellular surface [156]. Additional effects include stimulation of glycolytic enzymes hexokinase and phosphofructokinase, increased transcription of glycolytic genes, and relative increases in protein synthesis essential for rapid cellular division [249, 250].

It has been recently demonstrated, that Wnt signaling, which, when elevated, is commonly associated with tumorigenesis and tumor survival, suppresses mitochondrial respiration and cytochrome C oxidase activity [251]. An enhanced Wnt signaling through the β-catenin pathway leads to the inhibition of cytochrome C oxidase subunits COXVIc, COXVIIa, and COXVIIc, and this inhibition of mitochondrial activity results in an enhanced glycolytic phenotype. It has been postulated that with higher white adipocyte content, levels of Wnt ligands are increased, leading to enhanced positive correlation with Wnt signaling in neighboring cells [252, 253].

Little is known to date on how adipocyte-derived lipids directly influence tumor metabolism; however, there is increasing evidence that lipids generated by the tumor cells during lipogenesis modulate metabolic pathways in cancer cells and stimulate the Warburg Effect. One consequence of the Warburg Effect is an increase in lipid biosynthesis, and de novo lipogenesis is, in fact, performed at high rates in cancer cells [243]. An example of a bioactive lipid with implications for prostate tumorigenesis is sphingosine-1/2 phosphate (S-1/2P) [254, 255]. S1P is activated by the phosphorylation of sphingosine by sphingosine kinase 1 or 2 (SK1 or SK2). S1P has been shown to induce cell growth, survival, and migration and to play a role in variety of cancers [256]. Similarly, upregulation of SK1 has been associated with glioblastomas, lung, thyroid, and breast cancers [257–261]. Notably, S1P has also been shown to highly present in obese patients compared to lean patients [262] and its potential involvement in obesity-driven tumorigenesis calls for further investigations.

Current therapeutic options in targeting tumor metabolism

Tools to regulate glycolysis

Because tumor metabolism is deregulated in almost all cancers, targeting glycolytic intermediates has become a hot topic in therapeutic research. One of the first inhibitors developed to target glycolysis was 2-deoxyglucose (2-DG), a glucose analog that downregulates glucose metabolism through competitive inhibition [263]. 2-DG is transported into the cell and phosphorylated by hexokinase to 2-deoxyglucose-phosphate (2-DG-P). 2-DG-P cannot be further metabolized and accumulates in the cells, leading to competitive inhibition of hexokinase during glycolysis [264]. *In vitro* studies have shown that this effect causes a decrease in cellular ATP production, and leads to the blockage of cell cycle progression and subsequent cell death [265]. A recent study has demonstrated that a combination of 2-DG treatment with photodynamic therapy induces tumor cell death in a synergistic manner [266]. Decreased cellular proliferation and increased apoptosis of cancer cells was also demonstrated upon 2-DG treatment in the N-diethyl-nitrosamine-induced rat

hepatocarcinoma model [267]. Along with a decrease in glycolysis, there was an observable decrease in the tricarboxylic acid (TCA) cycle activity, fatty acid and cholesterol biosynthesis, and ATP production, all pathways associated with tumor progression and metabolism. Other studies have shown that inhibiting glyoxylase 1, an enzyme responsible for the conversion of the glycolysis byproduct methylyglyoxyl to D-lactate, in a highly metabolically active tumor cells leads to an increase in apoptosis and a decrease in cellular proliferation [268, 269].

Targeting glycolysis in order to reverse the Warburg Effect has sparked interest as a potential anti-cancer therapy and has led to recent breakthroughs in therapeutics. One particularly intriguing target gaining a significant amount of attention from the pharmaceutical industry is LDH-α, an enzyme converting pyruvate to lactate, and a biomarker of advanced disease, poor prognosis, and resistance to therapy in many different cancers [270–272]. LDH-α inhibitors have a high specificity for cancer cells because of the high demand for lactate production in cancer cells during aerobic glycolysis [273]. It was recently reported that inhibition of LDH-α reduced ATP levels and led to an accumulation of ROS in lymphoma cells [274]. This accumulation of ROS resulted in increased incidence of apoptosis, suggesting that LDH-α is critical for tumor maintenance and cancer cell metabolism [274, 275]. These results have been recapitulated in a variety of diverse cancer types including lung cancer, renal cancer, breast cancer, hepatocellular carcinoma, nasopharyngeal carcinoma, and pancreatic cancer [274, 276–282].

There has been clinical success with drugs designed to target other enzymes in the glycolysis pathway, such as hexokinase II (HKII), phosphofructokinase (PFK), glyceraldehyde-3 phosphate dehydrogenase (GAPDH), and pyruvate kinase M2 (PKM2). Lonidamine, a selective HKII inhibitor, reached phase III trials in the 1990s as a therapeutic option for patients with lung cancer and was mildly successful but had toxic side effects [283, 284]. A novel approach by Wang et al. used the natural compound curcumin as a potential drug that could target HKII specifically and was shown to have anti-cancer effects in vitro [285]. The authors reported that colorectal cancer cells treated with curcumin in vitro have decreased mitochondria-associated anti-apoptotic HKII, leading to enhanced cell death. 3-bromopyruvate (3-BrPA), a selective inhibitor of another glycolytic enzyme, glyceralaldehyde-3-phosphate dehydrogenase (GAPDH), has been shown to downregulate PI3K/Akt signaling axis, leading to induced apoptosis in breast cancer cells [286, 287]. This finding suggests potential benefits of dual targeting of glycolysis enzymes and PI3K/Akt-mediated cellular metabolism. 3-BrPA has been FDA approved for phase I clinical trials as a selective glycolysis inhibitor [288–290] and was shown to induce ER stress, inhibit global protein synthesis and thereby induce tumor cell death [291]. Attempts have also been made to target phosphofructokinase, particularly PFKB3, the isoform commonly upregulated in cancers. Specifically, the use of selective PFKB3 inhibitors, such as 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one (3PO) shown that inhibition of PFKB3 leads to autophagy and could be an effective anti-tumor therapy [292]. 3PO is currently being tested in clinical trials [293].

Metabolic transporters as targets for therapy

Monocarboxylate transporters (MCTs) are proteins over-expressed in most cancers and responsible for the import (MCT1) and export (MCT4) of lactate [294]. MCTs are strong contributors to high production and secretion of lactate resulting from the Warburg effect, which makes them attractive targets for anti-cancer therapies. MCT-targeting agents showed significant anti-cancer effects, and a novel inhibitor developed by AstraZeneca, AZD3965, is currently being developed in a phase I clinical trial in patients with advanced cancer [295]. Significant efforts have recently been made to selectively target the glucose transporters, the proteins responsible for the uptake of glucose to be utilized in glycolysis [296, 297]. Promising results with WZB117, a small molecule inhibitor of glucose transporter one (GLUT1) showed in vitro and in vivo inhibition of glucose uptake by WZB117 [298]. Treatment with WZB117 caused down-regulation of glycolysis, reduced cellular ATP, reduced levels of cell cycle genes, and a more than 70% reduction in tumor size in mice injected with human lung cancer cells [298].

Modulating tumor metabolism with nanoparticle-based therapies

A newly developing field in cancer therapeutics, nanomedicine, revolves around the use of synthesized targeting molecules that can “carry” an encapsulated or bound drug for specific delivery to its target site without toxic effects on non-target tissues. The use of nanomolecules to target glycolysis specifically in tumor cells has been a growing area of research. Ryland et al. used C6-ceramide nanoliposomes to target the Warburg Effect in chronic lymphocytic leukemia (CLL) [299]. Their results demonstrated that treatment of CLL cells in vitro and in vivo with the C6-ceramide nanoliposomes leads to a marked decrease gene and protein expression of GAPDH, a reduction in cellular ATP, and a consequent tumor regression [299].

New approaches to anti-cancer therapies have revolved around finding novel ways to repurpose traditional compounds. Of interest, shikonin, a natural napthoquinone, along with its traditional role as an anti-inflammatory medicine, has been shown to alter cellular metabolism as an anti-cancer therapeutic [300]. Shikonin-loaded antibodies-armed nanoparticles have been developed specifically as a targeted therapy for ovarian cancer [301]. Shikonin was shown to target PKM2 and to have a necroptotic effect on cancer cells [302, 303]. Furthermore, a study by Matthaiou et al., reported that shikonin-loaded antibody-armed nanoparticles exhibit selective cytotoxicity against ovarian tumor cells in vitro [301]. Shikonin was also shown to induce autophagy in human pancreatic cancer cells in a PI3-K-dependent manner [303]. Cancer cells treated with shikonin had increased expression of autophagy-associated genes LC3-II/LC3-I and a marked reduction in phosphorylation and activation of the phosphoinositol 3-kinase (PI3-K)/Akt signaling pathway [303].

Targeting PI3-K in tumor metabolism

Since the discovery of PI3-K in the 1980s and the demonstration of its clinical importance for tumor survival, significant research efforts have been aimed at inhibiting this cancer-favoring signaling pathway. One of the original inhibitors to target PI3-K was wortmannin, a compound shown to inactivate this kinase by covalent interactions with Lys-802, leading to the inability to transfer a phosphate group [304]. The rationale is that by inhibiting PI3-

K/Akt signaling – which, when active, induces glycolytic genes – there would be an observed decrease in glycolysis and production of ATP and lactate, with a subsequent increase in cell death and chemoresistance. Indeed, studies with glycolytic glioma cells have shown that wortmannin treatment leads to suppression in glycolytic migration and an increase in glycogenic phenotype [305]. Additionally, the use of PX-866, a selective PI3-K inhibitor, has shown promising in vitro and in vivo anti-cancer effects and has had success in initial phase I studies in the clinic [306–311]. A treatment with PI3-K inhibitor, LY294002, resulted in a decrease in levels of glycolytic enzymes in human colorectal cancer cells and an increase in apoptosis, suggesting that PI3-K inhibitors have the potential to negatively regulate cancer cell metabolism and to be therapeutically beneficial. Unfortunately, although wortmannin and LY294002 have been effective in vitro, the associated toxicities kept these compounds from being translated to the clinic [312, 313]. However, there have been 15 different PI3-K inhibitors that have successfully entered clinical trials and idelalisib, a selective PI3-K-delta inhibitor was recently approved by the FDA [314]. Idelalisib, used in combination with CD20 antibody rituximab has shown promising results in patients with CLL, which is known to be associated with high rates of glycolysis [315–317].

c-MYC as a potential metabolic target

The transcription factor, c-MYC is regulated by mammalian target of rapamycin (mTOR), which is activated downstream of PI3-K/Akt and has well-established effects on cellular metabolism [318–320]. Studies utilizing mouse embryonic fibroblasts have demonstrated that mTOR signaling leads to induction of genes involved in glycolysis, the pentose phosphate signaling pathway, and lipogenesis, all pathways upregulated during aerobic glycolysis [321–323]. Treatment with rapamycin, the mTOR inhibitor, revealed significant decrease in the glycolytic capacity of cancer cells [324, 325]. The glycolytic inhibitor 2-DG has shown efficacy in downregulating HIF-1α and c-MYC in non-Hodgkin lymphoma cells, enhancing tumor cell sensitivity to methylprednisolone, resulting in cell cycle arrest and apoptosis, and showing a positive feedback between glycolysis and c-MYC induction [326]. Interestingly, a study using, diclofenac, a nonsteroidal anti-inflammatory drug, showed suppression of c-MYC. This down-regulation of c-MYC that resulted in significantly reduced levels of GLUT1, LDH-α, MCT1 and coincident decrease in glucose import and lactate secretion by human melanoma cells in vitro, validating the importance of targeting this transcription factor for anti-cancer therapy [327–329]. The most current, ongoing clinical trials targeting various aspects of metabolism in cancer cells are listed in Table 1.

Conclusions

With obesity toll spreading to pandemic levels, it is critical that the underlying mechanisms linking obesity to metabolic pathologies and tumorigenesis are elucidated. It is clear that factors and lipolysis products derived from any type of adipocyte have the capacity to alter cellular homeostasis in neighboring cells. Abnormal adiposity and chronic inflammation in obesity can lead to the secretion of a multitude of factors, all of which can influence tumor metabolism. Our understanding of tumor metabolism over the last century has revealed a complex, integrated network of enzymes and metabolites cooperating together to facilitate tumor cell growth and survival. The dynamic functions of metabolic proteins make tumor

metabolism an intricate and attractive field of research. Further understanding of the interactions between these metabolites and their oncogenic nature will provide insight into elucidating targetable mechanisms and development of novel therapies. Many leaps have been made in cancer therapies in a context of tumor metabolism. It remains crucial to advance our understanding of adipose tissue and disease in order to determine the molecular mechanisms behind adiposity and pathologies and, specifically, cancer.

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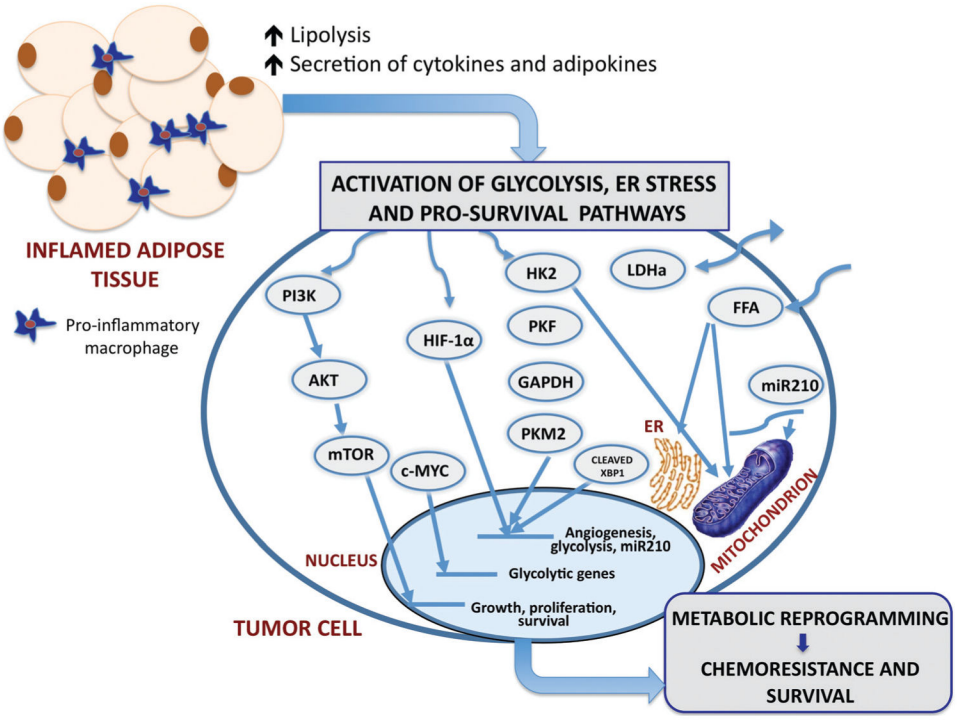

Figure 1.

The proposed schematic of possible mechanisms of metabolic regulation of tumor cells by dysfunctional adipocytes in obesity The major consequence of obesity is adipose tissue inflammation and associated increases in circulating levels of lipolysis-generated lipids and pro-inflammatory cytokines and adipokines. Through paracrine, autocrine, and endocrine effects, adipocyte-derived factors activate metabolic pathways in tumor cells and facilitating growth and survival. Pathways of interest include the following: phosphoinositol 3-kinase (PI3-K) signaling cascade, hypoxia-inducible factor 1α (HIF-1α), increased glucose uptake and enhanced glycolysis, and the potentially oncogenic endoplasmic reticulum (ER stress) pathway. The stimulation of PI3-K pathway leads to downstream activation of Akt and mTOR, enhancing the transcription of genes involved in growth, proliferation and survival. PI3-K signaling can also activate c-MYC and lead to the induction of glycolytic genes. A potential crosstalk between the glycolysis pathway and the HIF-1α signaling axis potentiates HIF activity, and exacerbates the glycolytic and hypoxic phenotypes. HIF-1α signaling leads to the expression of miRNA-210, which disrupts mitochondrial integrity, affecting cellular metabolism. Additionally, FFA have the ability to disrupt mitochondrial and ER membrane integrity and cause mitochondrial dysfunction and ER stress. The interactions of the ER stress response protein, XBP-1, with HIF-1α drive the expression of HIF- and glycolysis-targeted genes. This adipocyte-driven dynamic network of events results in metabolic adaptation of tumor cells, implicating adiposity in tumor aggressiveness and chemoresistance to therapy. PI3K, phosphoinositide 3-kinase; AKT, protein kinase b; mTOR, mammalian target of rapamycin; c-MYC, myc proto-oncogene; HIF-1α, hypoxia-inducible factor 1; HK2, hexokinase 2; PKF, phosphofructokinase; GAPDH,

glyceralaldehyde-3-phosphate dehydrogenase; PKM2, pyruvate kinase isoform; LDHα, lactate dehydrogenase; FFA, free fatty acids; miR-210, micro RNA 210.

Table 1

Current, on-going clinical trials targeting different aspects of cellular metabolism in different cancer types.

Target	Drug	Clinical trial cancer	Clinical trial reference ID
Phosphofructokinase Isoform 3 (PFK3B)	ACT-PFK-158	Advanced solid malignancies [330]	NCT02044861
Myc	Lenalidomide	B-cell lymphoma [331]	NCT02213913
		Multiple myeloma [332]	NCT01380106
		Hodgkin's lymphoma [333]	NCT01460940
Pyruvate dehydrogenase kinase 1 (PDK1)	Dichloroacetate	Head and neck cancer [334]	NCT01163487
mTOR	Rad001	Prostate cancer [335]	NCT00657982
		Triple negative breast cancer [336]	NCT01939418
		Glioma [337]	NCT00823459
		Gastric cancer [338]	NCT01514110
Hexokinase II (HK2)	Curcumin	Breast cancer [339]	NCT01975363
		Prostate cancer [340]	NCT01917890
		Leukemia/lymphoma [341]	NCT02100423
Phosphoinositol 3-kinase	GDC-0980/GDC-0941	Breast cancer [342]	NCT01437566
		Advanced solid tumors [343]	NCT01540253
	BKM120	Head and neck cancer [344]	NCT01816984
Wnt	LGK974	Multiple cancers [345]	NCT01351103
	CWP232291	Acute myeloid leukemia [346]	NCT01398462
	PRI-724	Advanced myeloid malignancies [347]	NCT01606579
TNF-α	L19TNFα	Advanced solid tumors [348]	NCT02076620
HIF-1α	Digoxin	Breast cancer [349]	NCT01763931
	Ganetespib	Multiple cancers [350]	NCT02192541
	CRLX101	Ovarian/tubal/peritoneal cancer [351]	NCT01652079
	Phenelzine	Prostate cancer [352]	NCT01253642