Metabolic Syndrome, Type 2 Diabetes, and Cancer: Epidemiology and Potential Mechanisms

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Abstract

Obesity is associated with multiple metabolic disorders that drive cardiovascular disease, T2D and cancer. The doubling in the number of obese adults over the past 3 decades led to the recognition of obesity as a "disease". With over 42 million children obese or overweight, this epidemic is rapidly growing worldwide. Obesity and T2D are both associated together and independently with an increased risk for cancer and a worse prognosis. Accumulating evidence from epidemiological studies revealed potential factors that may explain the

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association between obesity-linked metabolic disorders and cancer risk. Studies based on the insulin resistance MKR mice, highlighted the roe of the insulin receptor and its downstream signaling proteins in mediating hyperinsulinemia's mitogenic effects. Hypercholesterolemia was also shown to promote the formation of larger tumors and enhancement in metastasis. Furthermore, the conversion of cholesterol into 27-Hydroxycholesterol was found to link high fat diet-induced hypercholesterolemia with cancer pathophysiology. Alteration in circulating adipokines and cytokines are commonly found in obesity and T2D. Adipokines are involved in tumor growth through multiple mechanisms including mTOR, VEGF and cyclins. In addition, adipose tissues are known to recruit and alter macrophage phenotype; these macrophages can promote cancer progression by secreting inflammatory cytokines such as TNF-α and IL-6.

Better characterization on the above factors and their downstream effects is required in order to translate the current knowledge into the clinic, but more importantly is to understand which are the key factors that drive cancer in each patient. Until we reach this point, policies and activities toward healthy diets and physical activities remain the best medicine.

Keywords
Cancer · Hyperinsulinemia · Obesity

1 Introduction

Growing evidence, over the past decade or more, has provided us with the knowledge that obesity and type 2 diabetes (T2D) are associated with an increased risk of many types of cancer and more importantly, perhaps, increased mortality in these individuals. The major emphasis today is focused on the epidemic of obesity and, secondarily, T2D and the metabolic derangements of these metabolic disorders. In addition, there are numerous ongoing studies attempting to understand the etiology of the vascular complications resulting from obesity and T2D, as well as potential preventative medications. On the other hand, given the increase in cases of obesity and T2D worldwide, focus should also be directed towards a major complication, namely, cancer risk and cancer mortality, which undoubtedly increases in parallel with the obesity/T2D epidemic.

In this review we present the epidemiological evidence for the association between these metabolic disorders and cancer risk, we will describe the studies identifying causative factors, and we will try to relate the metabolic aspects of both obesity and T2D and how they impact on cancer.

2 Epidemic of Obesity and T2D and the Increased Cancer Risk

The epidemic of obesity is now recognized as a worldwide problem. While the USA still leads the world in the percent of overweight and obese individuals, many westernized countries are fast catching up, and developing countries are increasingly being affected. According to the World Health Organization, in 2008, over 1.4 billion adults (11%) worldwide are overweight, of which ~300 million were obese (Haslam and James 2005), and the incidence is rising rapidly. The universally accepted definition of overweight and obesity is a body mass index (BMI) of >25 and >30 kg/m^2, respectively. Using these criteria, more than 60% of adults in the USA are overweight and at least half of these are obese. In Southeast Asian countries, due to different body habitus, it is clearly more appropriate to define obesity using waist circumference, >40 inches in men and >35 inches in women. These measurements correlate better with visceral adiposity, and visceral adiposity closely tracks with elements of metabolic syndrome such as dyslipidemia, hypertension, and glucose intolerance.

The concern over the growing epidemic of obesity and the health ramifications has recently motivated the American Medical Association to designate obesity as a "disease," whereas previously it was considered a "disorder," a condition that carries less concern. The clear evidence that obesity predisposes to cardiovascular disease and cancer, for example, warrants this refocus on obesity as a disease entity.

This obesity epidemic is driving a similar trend in T2D, and the International Diabetes Federation (IDF) data suggests that ~8% of the world's population has diabetes with levels as high as ~10% in the Middle East and North Africa. By the year 2030, this number will more than double, since many obese individuals are unaware they have diabetes.

2.1 Obesity and Cancer

The increased association of obesity and metabolic syndrome with cancer risk and cancer mortality has become evident over the past decade, from numerous epidemiological studies. Thus, in countries where obesity prevalence has increased rapidly, such as the USA, a significant proportion (~20%) of all new cancers may be attributable to obesity (Calle et al. 2003; Jemal et al. 2007). Specific examples of common cancers include breast, endometrial, colon, and prostate cancers. In one study of over 33,000 men, the presence of metabolic syndrome was associated with a 56% enhanced risk of cancer mortality over the following 14 years of follow-up (Jaggers et al. 2009; Pothiwala et al. 2009). While the Nurses' Health Study suggested that central adiposity determined by waist circumference and waist to hip ratio was associated with an increased risk of postmenopausal breast cancer (Huang et al. 1999), more recent studies have claimed that premenopausal obesity is also a risk factor for breast cancer risk (Pierobon and Frankenfeld 2013; Robinson et al. 2014). The Million Women Study in the UK and the Cancer Prevention Study

II in the USA similarly reported increased cancer mortality in obese individuals (Petrelli et al. 2002; Reeves et al. 2007).

Strong supporting evidence for the association of obesity and cancer risk and mortality was obtained from a number of bariatric surgery studies, which dramatically reverse obesity. In the Swedish Obesity Subjects (SOS) study, following more than 30% weight loss, a reduction of cancer in women of about 41% was recorded (Sjostrom et al. 2009). A similar effect was seen in the Utah obesity study (Adams et al. 2009). Furthermore, in the Women's Intervention Nutrition Study (WINS), a 24% reduction in breast cancer was seen after only a 4% reduction in weight over 5 years (Prentice et al. 2006). The actual mechanisms involved in this effect are as yet undefined, but most likely reflect a correction of factors that are abnormal in cases of obesity and metabolic syndrome.

2.2 Children/Adolescents

The obesity epidemic has not spared children and adolescents. While definitions of obesity and metabolic syndrome are less well defined in children and adolescents, the increase is clear (Cook et al. 2003; Weiss et al. 2004). Furthermore, nonalcoholic fatty acid liver disease (NAFLD, another complication of obesity) is increased from 2.6% in normal weight children to 77% in overweight children (Franzese et al. 1997; Schwimmer et al. 2006). In line with this increase in NAFLD is the increase in adult hepatocellular carcinoma (HCC) in individuals who were obese during their childhood years, with a hazard ratio (HR) of 1.2–1.3 (Berentzen et al. 2014). Other studies have shown that BMI in the upper quartile in children from 2 to 14 years of age was associated with increased cancer risk in adulthood by 40% (Park et al. 2012), particularly colorectal, ovarian, cervical, and kidney cancer.

2.3 T2D Epidemic

The obesity epidemic is driving an epidemic of T2D worldwide. While there exists a group of healthy obese individuals, the majority demonstrate features of metabolic syndrome or prediabetes and, in genetically predisposed, progress to frank T2D (Cornier et al. 2008). Different manifestations of metabolic syndrome have different diagnostic criteria, but most include an increased waist circumference, dyslipidemia, hypertension, and even elevated fasting plasma glucose. Almost 70–80% of individuals with T2D are obese; moreover, several long-term prospective studies have shown a higher risk of T2D with increasing body weight. A National Health and Nutrition Examination Survey (NHANES) 25 years ago highlighted an association between being overweight and suffering from diabetes (Van Itallie 1985). Recently, it has been discovered that even apparently metabolically healthy overweight or obese men are still at significantly higher risk of developing T2D (Arnlov et al. 2011).

2.4 T2D and Cancer

Evidence is now emerging for a direct association between T2D and a higher risk of cancer mortality independent of the effects of obesity. (Coughlin et al. 2004; Verlato et al. 2003; Yancik et al. 2001a, b). It was found that hyperinsulinemia and insulin resistance, as shown by elevated levels of circulating C-peptide (a commonly used biomarker for insulin secretion in T2D), were significant risk factors for breast cancer (Bruning et al. 1992; Gunter et al. 2009; Verheus et al. 2006). A prospective study in Sweden of 80,000 women (average age 64.2 years) found that individuals with T2D had an increased incidence of breast cancer (Weiderpass et al. 1997). In another prospective study in 2003, an increased risk of estrogen receptor-positive breast cancer, postmenopausally, was found to be associated with T2D (Michels et al. 2003). Although T2D patients are known to be at high risk of developing pancreatic cancer (Coughlin et al. 2004; Pisani 2008; Rousseau et al. 2006), it has also been discovered that pancreatic cancer precedes diabetes (Isaksson et al. 2003; Permert et al. 1994). Colorectal cancer is also positively associated positively with T2D. A case-control study of around 10,000 adults in the UK showed that the risk of both colonic and rectal cancers is increased in both male and female diabetic patients (odds ratio = 1.42) (Yang et al. 2005), as was also shown in the Physicians' Health Study, where the relative risk of colorectal cancer in men with T2D was 1.5 (Sturmer et al. 2006). Endometrial cancer risk has also been shown to be associated with high circulating insulin or C-peptide levels, and mortality risk is relatively high in diabetes compared to some other cancers (relative risk $\geq$2) (Folsom et al. 2004).

In contrast to most epithelial cancers, T2D has been found in several meta-analyses to be inversely associated with prostate cancer risk (Bonovas et al. 2004; Coughlin et al. 2004; Kasper and Giovannucci 2006). On the other hand, obese males with high levels of circulating C-peptide, who develop prostate cancer, are at higher risk of dying from the disease, suggesting a relationship between insulin and aggressive, high-grade prostatic tumors specifically (Ma et al. 2008).

3 Potential Mechanisms

Following the numerous observations that obesity and diabetes are clearly associated with an increased risk of cancer and cancer-related mortality, there has been increased interest in establishing the causal factors involved in this effect. Some of the possible factors are listed in Table 1. In-depth analyses of the observational studies have strongly suggested that insulin, insulin-like growth factor 1 (IGF-1) and insulin-like growth factor 1 receptor (IGF-1R), leptin, inflammatory cytokines, caloric intake, and lipids are examples of potential causal factors that may explain the association between metabolic disorders and cancer risk. To study these various factors, a number of groups have developed appropriate mouse models for these preclinical experiments.

Table 1 Potential causal factors of the association between metabolic disorders and cancer risk

Factor	Associated with	References
Hyperinsulinemia	Insulin resistance	Ferguson et al. (2013), Novosyadlyy and LeRoith (2010), Xu et al. (2014)
IGF-1/IGF-1R	Nutrition	Djiogue et al. (2013), Lee and Yee (1995), Levine et al. (2006)
Leptin	Obesity	Ntikoudi et al. (2014), Uddin et al. (2014), Vansaun (2013)
Adiponectin (low)	Obesity	Grossmann and Cleary (2012), Vansaun (2013)
Glucose	Diabetes	Noto et al. (2013), Sciacca et al. (2013), Tseng and Tseng (2014)
Inflammatory cytokines	Inflammation	Del Prete et al. (2011), Elinav et al. (2013), Landskron et al. (2014)
Estrogen and androgens	Breast, endometrial, and prostate cancers	Crawford (2009), McNamara and Sasano (2015), Rizner (2013), Wang and Di (2014)

4 Animal Models

4.1 Obesity

High-fat diet (HFD)-induced obesity has been used extensively in mice to study the ramifications on cancer growth. Using this model it was demonstrated that the growth of Lewis lung carcinoma and mouse colon 38 adenocarcinoma cell lines was increased. This was associated with insulin resistance, hyperinsulinemia, glucose intolerance, and hyperleptinemia. Male mice demonstrated more severe metabolic derangements compared to female mice, and the effect on tumor growth was more pronounced. Interestingly, when female obese mice underwent ovariectomy, they developed the same degree of metabolic derangement as the male obese mice, and the effect on tumor growth was markedly enhanced. This suggested that estradiol was protective against metabolic derangements in the face of HFD-induced obesity (Yakar et al. 2006). Similarly, in ovariectomized mice fed with a HFD or a calorie-restricted (CR) diet, HFD-induced obesity had the largest tumors whereas CR mice had the smallest (Rondini et al. 2011). In other models of diet-induced obesity and CR diet, it was demonstrated that prostate, pancreatic, and skin, in addition to colon and breast, cancers are affected by these manipulations of the metabolic changes (Blando et al. 2011; Ford et al. 2013; Lashinger et al. 2013; Moore et al. 2012; Olivo-Marston et al. 2014). The factors mediating these effects include hyperinsulinemia, leptin, inflammatory cytokines, and, as recently demonstrated, hypercholesterolemia.

4.2 Hypercholesterolemia

In mice fed with HFD to induce obesity, Nelson et al. showed that mammary tumor growth was increased and dependent on a metabolite of cholesterol, namely, 27-OH cholesterol, as well as the presence of the estrogen receptor. The conversion of cholesterol to its 27-OH metabolite occurred both in tumor-associated macrophages and tumor cells as well (Nelson et al. 2013). In a separate study, ApoE knockout (ApoE-/-) mice, which demonstrate hypercholesterolemia and hypertriglyceridemia, were shown to have enhanced mammary tumor growth and lung metastases (Alikhani et al. 2013). Interestingly, ApoE-/- mice are insulin sensitive and have normal glucose homeostasis, making them an excellent model to study the isolated effects of lipid abnormalities as their circulating insulin levels are also normal if somewhat lower than wild-type controls (Kawashima et al. 2009). These observations, along with studies in prostate cancer cells (Pelton et al. 2012), have identified cholesterol as tumor promoters and support the epidemiological studies that show an association of hyperlipidemia and cancer growth and mortality and the reduction of mortality in statin users (Nielsen et al. 2012).

4.3 Hyperinsulinemia

The MKR mice were developed by engineering muscle insulin resistance through a transgenic overexpression of a defective IGF-1R that interferes with insulin receptor (IR) as well, through hybrid receptors, resulting in severe insulin resistance. Male MKR mice are diabetic with severe hyperglycemia, hyperinsulinemia, and hyperlipidemia, but without being obese, since the diabetes is not brought about by HFD-induced obesity and diabetes. Female MKR mice, on the other hand, do not demonstrate hyperlipidemia and hyperglycemia but still have hyperinsulinemia; thus they are extremely useful for studying the effect of isolated hyperinsulinemia on cancer. Using multiple oncogenic-induced mouse tumor models, both by orthotopic injections of cancer cell lines and crossing with mammary tumor transgenic mice (Table 2), we were able to demonstrate that hyperinsulinemia was causative in the growth and progression of mammary tumors as well as metastases to the lungs. The role of hyperinsulinemia was demonstrated by reducing the circulating levels of insulin. This was achieved by the use of a β_3-adrenergic receptor agonist (CL-316,243) previously shown to improve the insulin resistance and hyperinsulinemia in male MKR mice (Kim et al. 2006). The reduced insulin levels led to a marked reduction in breast tumor growth (Fierz et al. 2010a). Since insulin may affect tumor growth via IR or IGF-1R, we blocked the tyrosine kinase activity of these receptors using a small molecule tyrosine kinase inhibitor (BMS-536924). Receptor activity inhibition resulted in reduced tumor growth. A similar result was obtained with the use of low-dose picropodophyllin (PPP), a compound designed as an IGF-1R-specific inhibitor, but in our hands PPP inhibits both IR and IGF-1R (Rostoker et al. 2013).

Table 2 Mouse mammary tumor models

Chemicals	Cell lines	Transgenic mice	Oncogenes	References
DMBA				Middleton (1965)
MPA				Lanari et al. (2009)
Nitrosourea compounds (MNU, ENU, etc.)				Williams et al. (1981), Imamura et al. (1984)
	MVT-1		c-myc/VEGF	Pei et al. (2004)
		MMTV-c-myc	c-myc	Stewart et al. (1984)
	Met-1		PyVMT	Borowsky et al. (2005)
		MMTV-PyVMT		Guy et al. (1992)
	MCNeuA		NeuA	Campbell et al. (2002)
		rtTA-Neu (tetracycline inducible)		Gunther et al. (2002), McHenry et al. (2010)
		MMTV-c-Neu	NeuC	Muller et al. (1988)
	M-Wnt mesenchymal E-Wnt epithelial		Wnt	Dunlap et al. (2012)
		MMTV-Wnt1		Tsukamoto et al. (1988)
	E0771			Ewens et al. (2005), Sirotnak et al. (1984)
		MMTV-v-Ha-ras	v-Ha-ras	Sinn et al. (1987)
		WAP-TGF-α		Sandgren et al. (1995)
		WAP-IGF-1		Hadsell et al. (1996)
		WAP-Tag	SV40	Tzeng et al. (1993)

DMBA 7,12-dimethylbenz-(a)anthracene, *ENU* *N*-ethylnitrosourea, *MMTV* mouse mammary tumor virus, *MNU* *N*-methyl-*N*-nitrosourea, *MPA* medroxyprogesterone acetate, *PyVMT* polyoma-virus middle T antigen, *rtTA* reverse tetracycline-dependent transactivator, *SV40* Simian virus 40, *Tag* SV40 T antigen, *TGF-α* transforming growth factor-α, *VEGF* vascular endothelial growth factor, *v-Ha-ras* Harvey rat sarcoma viral oncogene, *WAP* whey acidic protein promoter

Since mTOR is activated by insulin and is a central mediator of tumor progression (Fig. 1), we studied the impact of mTOR inhibition (by rapamycin) on mammary tumor progression and the metabolic state of the mice. Mammary tumor progression was studied in the double transgenic, MMTV-PyVmT/MKR, and two orthotopic models using the Met-1 and MCNeuA cells. In both the wild-type and MKR (insulin-resistant, hyperinsulinemic) mice, glucose intolerance and hypertriglyceridemia worsened significantly after rapamycin treatment. Nonetheless, tumor growth was inhibited in all three mammary tumor models, despite the worsening of insulin resistance and higher levels of circulating insulin (Fierz et al. 2010b). Inhibition of phosphatidylinositol 3-kinase (PI3K) alone, using the

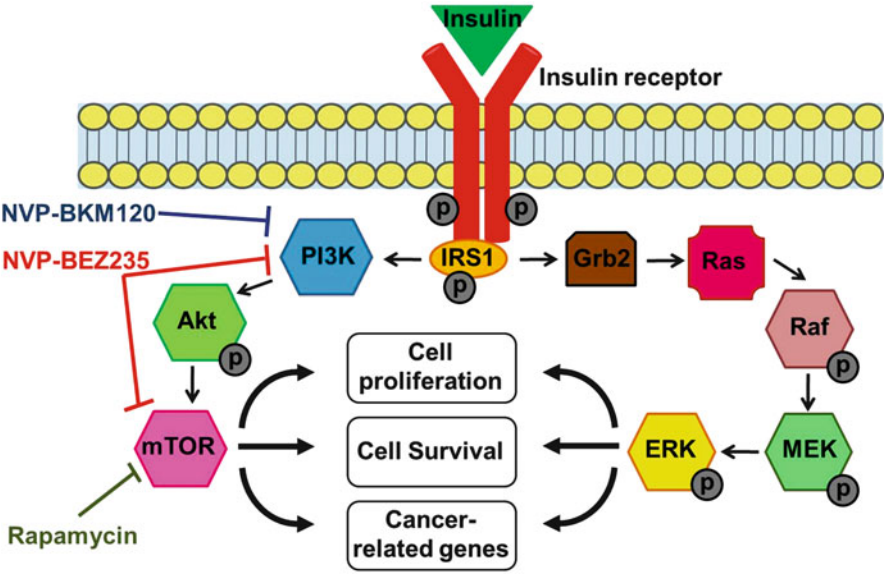

Fig. 1 Insulin receptor/PI3K/mTOR signaling pathway. *ERK* extracellular signal-regulated kinase, *Grb2* growth factor receptor-bound protein 2, *IRS-1* insulin receptor substrate 1, *MEK* mitogen-activated protein kinase kinase, *P* phosphate, *Raf* rapidly accelerated fibrosarcoma kinase, *Ras* rat sarcoma protein

oral pan-class I PI3K inhibitor (NVP-BKM120), or together with mTOR, using NVP-BEZ235, inhibited tumor growth. However, in regard to the metabolic effects, inhibiting PI3K alone led to more severe metabolic derangements with increased insulin resistance, hyperinsulinemia, and hyperglycemia, in comparison to the dual inhibitor of PI3K/mTOR (Gallagher et al. 2012).

4.4 Adipokines

Circulating adipokines are commonly altered in obesity and T2D (Nalabolu et al. 2014). Leptin is classically elevated in these conditions, whereas adiponectin is reduced. Leptin has been shown to stimulate cancer cell growth in cell cultures, suggesting a role in the effect of obesity in enhancing cancer growth and prognosis (Park and Scherer 2011; Somasundar et al. 2003). The role of leptin in cancer progression has been studied in genetically induced obese mouse models. The Lep^{Ob}/Lep^{Ob} mice are obese, insulin resistant, and hyperinsulinemic, with *low* leptin levels. These competing features may explain the varying results when studying cancer in these mice. On the other hand, Lep^{db}/Lep^{db} mice, carrying a leptin receptor mutation that results in obesity with elevated leptin levels, show more marked cancer growth and metastases. Interestingly, serum from Lep^{Ob}/Lep^{Ob} induces a mesenchymal phenotype in the B16 melanoma cells that may explain

the enhanced pulmonary metastases in the absence of increased primary tumor growth (Kushiro and Nunez 2011).

On the other hand, adiponectin has been shown to induce cancer cell apoptosis and may explain the effect of low adiponectin levels in obesity and T2D on cancer prognosis (Kelesidis et al. 2006; Körner et al. 2006). In a model of chemical (azoxymethane, AOM)-induced colon carcinogenesis and adiponectin and adiponectin receptor knockout mice, HFD increased the AOM effect (Fujisawa et al. 2008). Adiponectin administration inhibited tumor growth through multiple mechanisms, including inhibition of cell proliferation and inhibition of mTOR, VEGF, and cyclins (Moon et al. 2013).

Interestingly, there seems to be an interplay between the effect of adiponectin and cholesterol on tumor growth (Liu et al. 2013). In bigenic mice (MMTV-PyVmT and adiponectin deficient) fed with high-fat high-cholesterol diet, the resultant hypercholesterolemia and increased expression of the low density lipoprotein (LDL) receptor (LDLR) increased tumor cholesterol content and enhanced tumor growth. Adiponectin downregulated the LDLR in vitro and in vivo and demonstrated anti-cancer effects. Thus, the potential effects of adiponectin deficiency in obesity and T2D on both metabolism and enhanced cancer growth may be explained by a number of mechanisms. Insulin resistance associated with reduced adiponectin may secondarily lead to enhanced LDLR expression in cancer cells and increased uptake of cholesterol, leading to enhanced cancer growth. This may partially explain the increased LDLR expression seen in triple negative breast cancers and the worse prognosis (Antalis et al. 2011; Rudling et al. 1986).

4.5 Inflammatory Cytokines

Both obesity and T2D have been labeled "inflammatory disorders." Adipose tissue from obese individuals shows a marked increase in macrophage infiltration and dysregulation of these macrophages in the tumor environment, suggesting that local tumor-associated macrophages (TAM) may regulate tumor progression (Fig. 2). TAMs are recruited by monocyte chemotactic protein-1 (MCP-1) found in tumor tissues and are generally of the M1 macrophage phenotype that is pro-inflammatory. The switch from M2 (anti-inflammatory) to M1 macrophages is commonly seen in obese individuals and rodents. These macrophages are also capable of secreting pro-inflammatory factors that affect the adipose tissue and cancer cells leading to cancer progression. Thus, in the case of breast cancer, obese women have increased circulating levels of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). Elevated levels of these cytokines are associated with increased cancer progression. Moreover, local breast adipose tissue may similarly affect tumor growth via cytokines. Reversal of these effects was seen with low-calorie diets, low-fat diets, and weight loss. Similarly, cyclooxygenase (COX) and prostaglandin E_2 (PGE_2) inhibitors may prove to be useful as they inhibit the elevated levels of COX-2 and PGE_2 found in white adipose tissue inflammation (Howe et al. 2013). These drugs have additional relevant effects,

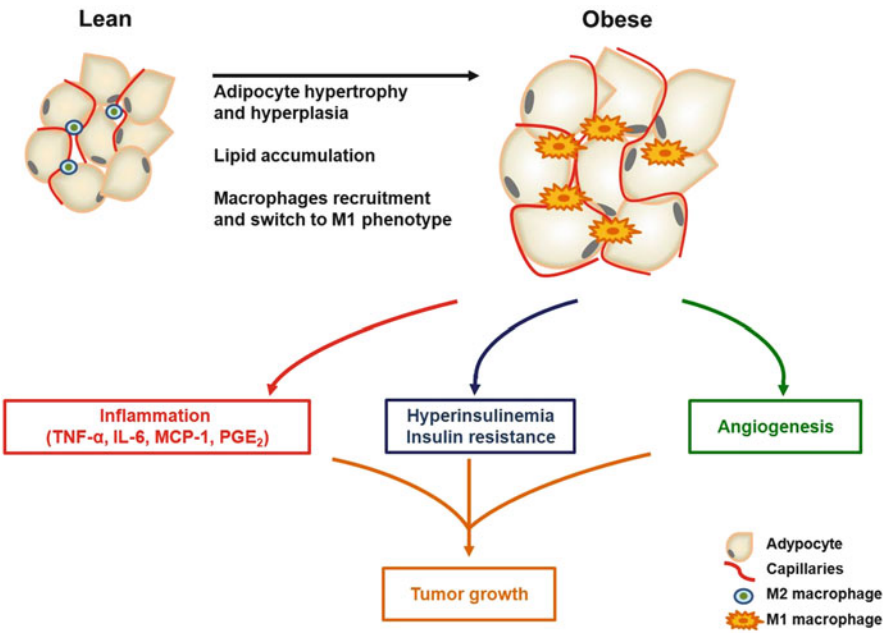

Fig. 2 Adipocyte and macrophage dysregulation favor tumor development

including activation of adenosine monophosphate-activated protein kinase (AMPK, which inhibits mTOR) and nuclear factor-κB (NF-κB) antagonism that may be important in inhibiting the inflammatory processes.

5 Metformin, Insulin, and Cancer

Metformin is a biguanide that has multiple biological properties, many of which may be beneficial in reducing cancer risk or cancer progression. Metformin reduces the activity of complex I in the respiratory chain in hepatocytes, causing energetic stress, which in turn activates liver kinase B1 (LKB1)/AMPK pathway and inhibits gluconeogenesis (Shaw et al. 2005). Reduced hepatic gluconeogenesis lowers blood glucose levels and, secondarily, circulating insulin concentrations. Since hyperinsulinemia has been shown to be associated with cancer and cancer-related mortality in obese and pre-diabetic individuals, this may be one explanation for metformin's reduction of cancer risk and mortality in these situations, as demonstrated by epidemiological studies (Wang et al. 2014; Zhang et al. 2013). Other effects of metformin on adipokines and inflammatory cytokines were recently revealed. These include resistin and adiponectin (Gomez-Diaz et al. 2012; Singh et al. 2012). What effect these may have on insulin resistance and secondarily on cancer remains to be determined.

Effects of metformin on cancer may also be via direct mechanisms. Otto Warburg demonstrated increased glycolysis in cancer cells, also known as the Warburg effect (Warburg 1956); however, a significant amount of ATP is derived from oxidative phosphorylation, the latter being affected by metformin-induced stress and AMPK activation. AMPK, in turn, inhibits cancer cell growth by inhibiting fatty acid synthesis and mTOR-induced protein translation (Algire et al. 2010; Larsson et al. 2012). p53 mutations in certain cancers may make them more sensitive to biguanides, due to increased oxidative phosphorylation. Finally, metformin may play a role in inhibiting tumor-initiating cells that are commonly resistant to therapy (Zhu et al. 2014).

6 Conclusions

While the epidemiological documentation of a relationship between obesity, metabolic syndrome, T2D, and cancer risk and prognosis is becoming clearer, the causal factors remain to be defined. Specific animal models and human studies have identified strong contenders, such as hyperinsulinemia, hyperlipidemia, IGF-1, and leptin levels; the relevance of each of these may vary depending on the model. Identifying, quantifying, and proving which factors are of greater importance are critical if investigators wish to target molecules to be used as adjunct chemotherapy, especially for chemoresistant- or radiation-resistant cancers.

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