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Review

Role of obesity-associated dysfunctional adipose tissue in cancer: A molecular nutrition approach ☆

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ABSTRACT

Obesity is a complex disease caused by the interaction of a myriad of genetic, dietary, lifestyle and environmental factors, which favors a chronic positive energy balance, leading to increased body fat mass. There is emerging evidence of a strong association between obesity and an increased risk of cancer. However, the mechanisms linking both diseases are not fully understood. Here, we analyze the current knowledge about the potential contribution that expanding adipose tissue in obesity could make to the development of cancer via dysregulated secretion of pro-inflammatory cytokines, chemokines and adipokines such as TNF-α, IL-6, leptin, adiponectin, visfatin and PAI-1. Dietary factors play an important role in the risk of suffering obesity and cancer. The identification of bioactive dietary factors or substances that affect some of the components of energy balance to prevent/reduce weight gain as well as cancer is a promising avenue of research. This article reviews the beneficial effects of some bioactive food molecules (*n*-3 PUFA, CLA, resveratrol and lipoic acid) in energy metabolism and cancer, focusing on the molecular mechanisms involved, which may provide new therapeutic targets in obesity and cancer. This article is part of a Special Issue entitled: Bioenergetics of Cancer.

1. Energy balance and obesity

The concept of energy balance involves the exact equilibrium between caloric intake and energy utilization. Energy expenditure takes the form of physical activity, basal metabolism, and adaptive thermogenesis [1]. Physical activity refers to all voluntary movement, while basal metabolism includes the myriad biochemical processes necessary to sustain life. Adaptive thermogenesis refers to energy dissipated in the form of heat in response to environmental changes, such as diet or exposure to cold. In this context, it should be pointed out that the boundary between what is considered basal metabolism versus adaptive thermogenesis is not always clear-cut [1]. Obesity is defined as an abnormal or excessive fat accumulation that involves a risk to health. The fundamental cause of overweight or obesity is a positive energy balance, in which energy intake exceeds energy expenditure over a prolonged time leading to the increased body mass including the accumulation of subcutaneous and visceral fat [2]. However, obesity is a complex disease caused by different factors such as genetic, diet, lifestyle and environmental factors [3]. Some studies estimated that 40–70% of the variation in obesity-related phenotypes could be heritable [4]. In most of cases, obesity appears as a polygenic condition that is additionally affected by a myriad of environmental factors. In fact, the development of overweight and obesity is a consequence of the easy and cheap availability of high-calorie yielding foods, which is combined with sedentary lifestyle changes, occurring in modern societies and affecting genetically predisposed subjects (Fig. 1).

The prevalence of obesity among children, adolescents and adults has been dramatically increasing during the last decades [5,6]. The World Health Organization (WHO) estimates that there are currently more than 1.6 billion overweight adults and at least 400 million of these are obese. Moreover, they predict that by 2015 approximately 2.3 billion adults will be overweight and more than 700 million will be obese [7]. Thus, obesity is acquiring the characteristics of an authentic pandemia and it has been recognized as one of the major global health problems. Indeed, this health hazard is linked to several types of common diseases including cardiovascular disease [8], type 2 diabetes mellitus [9,10], hypertension, dyslipidemia, liver disease and also various types of cancer [9,11,12]. Therefore, the health consequences of obesity are huge and varied, ranging from an increased risk of premature death to several non-fatal but debilitating diseases that have adverse effects on the quality of life.

Furthermore, obesity typically leads to insulin and leptin resistance and a shift to dysfunctional adipose tissue. These conditions cause metabolic dysregulation with elevated circulating fatty acids and an increased secretion of pro-inflammatory adipokines. When left

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untreated, these conditions cause lipotoxicity, chronic inflammation, hypertension, atherosclerosis and cardiovascular disease [13,14]. The association between hypertension and obesity is well documented. Both systolic and diastolic blood pressure increase with BMI (Body Mass Index). Thus, obese people present higher risk to develop hypertension in comparison with lean people [15]. Obese individuals are frequently characterized by an impaired lipid profile, in which plasma triglycerides are raised, HDL-cholesterol concentrations are reduced and low-density lipoprotein apo B (LDL-apoB) levels are raised. This disturbed metabolic profile is more often seen in obese patients with a high accumulation of intra-abdominal fat and has consistently been related to an increased risk of cardiovascular diseases [16,17]. A positive association between obesity and the risk of developing type 2 diabetes mellitus has been also repeatedly reported in different studies. Intra-abdominal fat accumulation, has been associated with an increased risk of prediabetic conditions such as impaired glucose tolerance and insulin resistance [18].

Nonalcoholic fatty liver disease (NAFLD) is another of the consequences of the current obesity epidemic and the hepatic manifestation of the metabolic syndrome. This term encompasses a clinicopathologic spectrum of disease ranging from isolated hepatic steatosis to nonalcoholic steatohepatitis (NASH), the more aggressive form of fatty liver disease and characterized by steatosis, inflammation and progressive fibrosis, ultimately leading to cirrhosis and end-stage liver disease [19]. The most widely accepted theory that explains the pathogenesis of NASH is titled the 'Two Hit Theory' resulting from fatty infiltration of the liver due to obesity and insulin resistance, followed by inflammatory insults, potentially due to oxidative stress [20]. Recent studies estimate that NAFLD affects 30% of the general population and as high as 90% of the morbidly obese [21]. Furthermore, obese patients are at particularly high risk for NASH in view of the frequent co-existence of other features of the metabolic syndrome; thus, the prevalence of NASH in those patients ranges from 20%–30% against 5%–7% in the general population [22]. Although patients with isolated steatosis generally have a benign prognosis, some 26–37% of patients with NASH demonstrate progression of fibrosis over time period of up to 5.6 years, with up to 9% progressing to cirrhosis [23]. BMI and diabetes constitute independent risk factors associated with the progression of fibrosis [24]. Thus, it has been reported that about 40%–62% of patients with NASH-related cirrhosis develop a complication of cirrhosis after 5–7 years of follow-up [25]. The increase in the prevalence of childhood obesity results in a rising prevalence of metabolic syndrome and type 2 diabetes in populations. NASH was first observed in children in 1983 as a pattern of liver injury and it can even develop in obese children under 10 years of age [26]. The significant relation between fasting insulin, insulin resistance and NAFLD in obese children underlines the clinical dimension of these metabolic disturbances [27].

On the other hand, obesity is considered a major risk factor for the development and progression of sleep apnea [28]. Sleep apnea can be a problem with serious implications for anesthetic management, surgery, effect on pulmonary hypertension, stroke coronary artery disease and cardiac arrhythmias [29]. In addition, sleep apnea has a strong correlation with glucose metabolism [30]. Recently, the association between obesity and kidney disease onset has been accepted since several epidemiological and pathological studies support this relationship. A number of epidemiological studies have also provided sufficient evidence of a positive association between obesity and the incidence of cancer, particularly of hormone-dependent and gastrointestinal cancers. Modulation of energy balance, through increased physical activity, reduced the risk of many cancers, including cancers of the colon, breast and endometrium. In this context, it has been shown that weight loss by dietary and physical activity interventions partially reverse metabolic, endocrinal, inflammatory, and renal alterations associated with obesity [31].

2. Obesity and cancer

Energy imbalance is associated with obesity and different studies have observed a relationship between obesity and cancer [32–35].

The concept of a relationship between dysregulated metabolism and carcinogenesis was first enunciated by Otto Warburg [36]. In 2002, the International Agency for Research on Cancer (IARC) expert panel evaluated the link between weight and cancer [37] and concluded that some cancers could be prevented by avoiding weight gain. Since the IARC report, many observational and epidemiological studies have further investigated the association between adiposity and cancer, suggesting that obesity is associated with a significantly

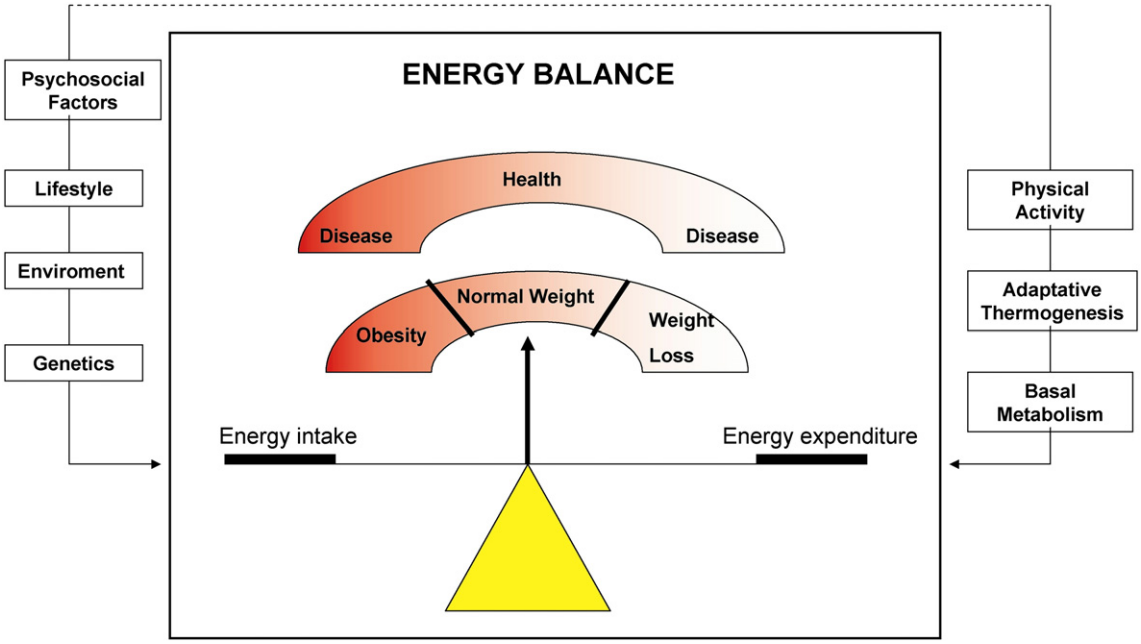

Fig. 1. Fundamental principles of energy balance. A positive energy balance occurs when energy intake is greater that energy expenditure and promotes weight gain/obesity. Conversely, a negative energy balance promotes weight loss.

increased risk of developing several cancer types including those of colon [38], esophagus, breast (in postmenopausal women) [39], endometrium, kidney, liver, gallbladder and pancreas [5,11,35,39,40].

Obesity management is an opportunity for cancer prevention [41], and adipose tissue has been suggested as a target organ in the treatment of hormone-dependent breast cancer and other types of cancer.

2.1. Obesity and breast cancer

Breast cancer is the second most common cancer in the world and the most common neoplasia among women. The association between indicators of body size and risk of breast cancer has been examined in numerous studies [42–44]. Obesity increases breast cancer risk in postmenopausal women by around 50%, probably by increasing serum concentrations of free estradiol [42,43,45]. Interestingly several studies established that the association between body size and the risk of breast cancer differed according to menopausal status [46,47]. In fact, BMI and body weight have been found to be positively related to the risk of breast cancer among postmenopausal women whereas some studies found inverse associations [11]. Furthermore, abdominal adiposity has been found to be positively associated with a higher risk of breast cancer in postmenopausal women, this relationship being stronger among nonhormone-replacement therapy users than among hormone replacement therapy users [48,49].

However, the mechanisms that underlie the association between obesity and breast cancer risk are not completely understood. Several hypotheses have been proposed, including alterations in sex hormones, growth factors and cytokines [11]. Another mechanism by which obesity may induce the development of breast cancer involves insulin and/or Insulin-like growth factors (IGFs) [50].

2.2. Obesity and endometrial cancer

There is convincing and consistent evidence from both case–control and cohort studies that overweight and obesity are strongly associated with endometrial cancer [51,52]. In fact, the risk of developing endometrial cancer is about 2 to 3-fold higher in obese women than in lean women [53] and about 40% of endometrial cancer incidence has been estimated to be attributable to excess body weight [54]. As with breast cancer, the potential mechanism for the increase risk of endometrial cancer associated with obesity is the increase in circulating estrogens [6].

2.3. Obesity and colorectal cancer

Colorectal cancer is the third most common cancer in the world. Incidence rates are approximately 10-fold higher in developed than in developing countries [53]. A possible association between an excess of body weight and risk of colon cancer has been examined in many epidemiological and cohort studies which have concluded that obesity is related with a higher risk of colorectal cancer [33,54,55]. Different studies have suggested that waist circumference and the waist/hip ratio are also strongly related to a higher risk of colorectal cancer and large adenomas in men, as supported by European Prospective Investigation into Cancer and Nutrition (EPIC), whereas body weight and BMI are associated with colon cancer risk in men but not in women [56,57]. The reasons for the gender difference are speculative. One hypothesis is that abdominal adiposity, more common in men than in women, is a stronger predictor of colon cancer risk than peripheral adiposity [58]. However, the mechanisms involved in the association between abdominal obesity and increased colon cancer risk remains still unclear. Another possible explanation is the protective role of exogenous estrogens on the risk of colorectal cancer [59].

2.4. Obesity and prostate cancer

Prostate cancer is the cancer most frequently diagnosed in men in Europe [60]. More than 40 studies, including prospective and case–control studies, examining the association between obesity and risk of prostate cancer have provided conflicting results [61]. However, a recent meta-analysis has suggested a weak significant positive association with an estimated increase in prostate cancer risk (5% excess risk per 5 unit increment of BMI) [62]. The association between waist circumference or waist hip-ratio and risk of prostate cancer has been examined in only a very few studies with most studies reporting no significant associations [62,63].

2.5. Obesity and esophageal cancer

Obesity is associated with a 3-fold increase in risk for adenocarcinoma of the esophagus [6,64]. The link between obesity and risk of esophageal cancer has recently been confirmed by quantitative meta-analysis that included twelve case–control studies and two cohort studies [65]. High BMI is associated with gastroesophageal reflux and frequent reflux is very strongly associated with esophageal adenocarcinoma [66,67]. Thus the increased occurrence in gastroesophageal reflux itself is considered to be a major risk factor for esophageal cancer.

2.6. Obesity and liver cancer

Primary liver cancer is one of the most common and deadly cancers worldwide. Incidence is increasing and hepatocellular carcinoma (HCC) has risen to become the fifth most common cancer and the third leading cause of cancer death [68,69]. Obesity has been established as a significant risk factor for liver diseases. A large prospective mortality study, demonstrated that high BMI was significantly associated with higher rates of liver cancer-related death. Compared to patients with normal BMI, the relative risk of mortality from liver cancer was 1.68 times higher in women and 4.52 times higher in men with BMI>35 kg/m^2 [51]. Similarly, data obtained from the United Network of Organ Sharing (UNOS) database on all liver transplantation from 1991 to 2000 carried out in the United States showed that the overall incidence of HCC in patients undergoing liver transplantation was 3.4% with a slightly higher prevalence among obese patients at 4.0%. Moreover, in this study obesity was confirmed to be an independent risk factor for HCC in patients with alcoholic cirrhosis (odds ratio [OR], 3.2) and cryptogenic cirrhosis (OR, 11.1) [70]. Obesity has definitively been established as a risk factor for the development of HCC. It is likely that this association represents the progression of underlying NAFLD to cirrhosis, but it remains unclear whether cirrhosis is a necessary prerequisite for the development of HCC [71]. Animal models of NAFLD support the hypothesis that obesity-related metabolic abnormalities, rather than cirrhosis, initiate the hepatic neoplastic process during obesity [72].

2.7. Other types of cancer

Obesity has also been linked to other types of cancer, although overall the amount of studies or data available is still limited. Several recent studies have suggested that high BMI may be associated with approximately a doubling of risk for pancreatic cancer in men and women [6]. Moreover, a recent meta-analysis supports a positive relationship between BMI and risk of pancreatic cancer [73]. However, in the study from the EPIC cohort, the BMI was not found to be significantly associated with pancreatic cancer. Two further studies have found some evidence for a positive association with waist circumference in men but not in women [74,75].

The role of obesity on ovarian cancer survival is unclear but it has been suggested that obesity may affect ovarian cancer survival by

having a negative impact on optimal surgical and cytotoxic treatment and increasing the likelihood of postoperative complications [76].

Few studies have investigated the association of BMI with cancers of gallbladder, stomach and uterine cervix but data are limited and inconsistent [32,77].

In summary, these studies have demonstrated that there is a clear association between obesity and different types of cancer (specially, breast, esophageal, colorectal…). However, the biological mechanisms that link overweight and obesity to different forms of cancer, other than those with an endocrine component, are poorly understood. Thus, further research to define the causal role of obesity in these types of cancers is needed.

3. Role of dysfunctional adipose tissue

Obesity is strongly associated with changes in the physiological function of adipose tissue, leading to insulin resistance, chronic inflammation, and altered secretion of adipokines [78]. White adipose tissue (WAT) is a complex and metabolically active organ, with a relevant important role in regulating whole-body metabolism. WAT is the largest energy storage organ, having an important lipid storing capacity in periods when energy input exceeds energy expenditure and with a lipolytic function (release of NEFA) during energy deprivation [1,79]. In addition to its primary role as a fuel reservoir, white adipose tissue has been confirmed as a major endocrine organ, since the tissue synthesizes and secretes an array of sex steroids, and bioactive peptides termed 'adipokines', involved in the physiological regulation of fat storage, energy metabolism, food intake, insulin sensitivity, and immune function among others [80]. In fact, adipose tissue dysfunction might play a crucial role in the different obesity-linked diseases including inflammation, insulin resistance and cancer. Several of these factors, such as insulin resistance, chronic inflammation, decreased levels of adiponectin, increased levels of plasminogen activator inhibitor-1 (PAI-1), endogenous sex steroids, visfatin and leptin, could be involved in carcinogenesis and cancer progression. In this section, we will review the pathophysiological mechanisms linking obesity to cancer, focusing on adipose tissue dysfunction as a potential unifying causal factor [78].

3.1. Sex steroids

WAT is an active organ that secretes different sex steroids. Obesity has an important impact on the synthesis and bioavailability of endogenous sex steroids. Indeed, obesity is associated with an increased serum concentration of estradiol and estrone and a decreased serum concentration of testosterone. Increased levels of estradiol are the result of the peripheral conversion of androgens to estradiol by an overall increased aromatase activity in WAT, secondary to the enhanced total adipose tissue mass [81]. In addition, obesity is associated with increased insulin and bioactive IGF-1 levels which downregulate the concentration of the circulating sex hormone-binding globulin, resulting in an increased fraction of bioavailable estradiol, but decreased testosterone production [82]. Prospective studies suggest this increased bioavailability of sex steroids, especially estrogen which is strongly associated with risk of endometrial and postmenopausal breast cancer [52]. The proliferative effect of estrogen on epithelial tissue of both breast and endometrium is believed to be the underlying mechanism.

3.2. Inflammation

It is well recognized that inflammation is involved in the promotion and progression of cancer [83–85]. Obesity is associated to systemic low-grade inflammation, which has been suggested to have an important role in the pathogenesis of some disorders such as insulin resistance, atherosclerosis and cancer [61,86]. In obesity, the expanding WAT makes a substantial contribution to the development of obesity-linked inflammation via dysregulated secretion (from both by adipocytes and the non-adipocyte fraction) of pro-inflammatory cytokines (Interleukin (IL)-6 and 1 and tumor necrosis factor alpha, TNF-α), chemokines (monocyte chemotactic protein 1, MCP-1) and adipokines (haptoglobin, PAI-1, leptin, visfatin, resistin and vascular endothelial growth factor, VEGF) and the reduction of anti-inflammatory adipokines (e.g. adiponectin, IL-10, antagonist IL-1) [87,88]. The precise role of these inflammatory components in carcinogenesis is not completely understood and therefore continues to be an appealing avenue of research.

TNF-α plays an important role in adaptive responses of the immune system and other organ systems. The anti-tumor effects of TNF-α have been related to activation of Caspase 3 and induction of apoptosis [89]. However, recent studies have suggested that TNF-α is involved in carcinogenesis because of its ability to activate NF-κB [90]. In almost all cell types, when exposed to TNF-α, NF-κB is activated and leads to the expression of a variety of inflammation-related genes. Also TNF-α appears to contribute to the development of the tissue architecture necessary for tumor growth and metastasis [91,92]. It also induces other cytokines, angiogenic factors and matrix metalloproteinases (MMPs) and thus drives to the increased growth and survival of tumor cells [93]. These tumor-promoting activities suggest that inhibition of TNF-α is an effective strategy for cancer therapy. Indeed, clinical trials with several TNF-α antagonists have shown promising effects. For example, D2E7 (a fully humanized anti-TNF-α monoclonal antibody), infliximab (a chimeric immunoglobulin G1 monoclonal antibody against TNF-α), pegylated recombinant humanized sTNF-R1, pegylated humanized anti-TNF-α fragment (CDP870) and TNF-α synthesis inhibitors (p38 kinase inhibitors) have been used to treat various tumors [94].

On the other hand, IL-6 is a pleiotropic inflammatory cytokine, involved in the maturation of B cells, with described cancer-stimulatory [95] and also cancer-inhibitory properties [96]. IL-6 is an important regulator of immune cell growth and differentiation. Recent studies have demonstrated that IL-6 regulates chronic inflammation, which can create a cellular microenvironment beneficial to cancer growth [95]. High circulating IL-6 concentrations in obesity correlated with overall cancer death and increased risk of cancer precursor lesions [78]. The activation of the IL-6 complex activates Janus kinases (JAK) and the signal transducer and activator of transcription 3 (STAT3) pathways, which regulate cell proliferation and apoptosis [97].

Obesity-induced inflammation involves other inflammatory components that could contribute to the development of cancer. These components include MMPs, which are associated with cancer-cell invasion and metastasis [78], suggesting that the strongly induced mRNA levels of several MMPs in obesity, as well as their role in adipocyte differentiation, might represent a potential molecular link between obesity and cancer.

3.3. Adipokines

3.3.1. Adiponectin

Adiponectin is a hormone mainly secreted by adipose tissue, and to a small degree is also produced by cardiac myocytes, muscle cells and endothelial cells [98]. The most important functions of adiponectin identified so far are anti-atherogenic, anti-inflammatory and insulin-sensitivity effects. In contrast to other adipokines, circulating levels of adiponectin are negatively associated with obesity, BMI, visceral fat accumulation and insulin resistance [99]. Several case–control studies have observed that serum adiponectin levels were significantly decreased in breast cancer patients [100]. One study described that adiponectin levels were significantly reduced in postmenopausal women with breast cancer, but not in premenopausal women and, most importantly, this inverse association with

adiponectin was independently associated with BMI [101]. However, another study observed reduced adiponectin levels in both premenopausal and postmenopausal women with breast cancer, and found that patients with serum adiponectin levels in the lowest tertile exhibited significantly larger tumors [102]. Moreover, *in vitro* studies have demonstrated that adiponectin treatment suppressed cell proliferation and caused cell growth arrest and apoptosis in breast cancer cells [103]. Moreover, Brakenhielm et al. [104] reported that adiponectin-induced antiangiogenesis and antitumor activity involves caspase-mediated endothelial cell apoptosis. The role of adiponectin in cancer etiology is not yet fully understood. Although it is possible that adiponectin provides indirect protection against carcinogenesis, by affecting insulin sensitivity and the inflammatory state, adiponectin may have direct anti-carcinogenic effects. The pathway that involves adiponectin and the adiponectin receptors, AdipoR1 and R2 mediates the activation of AMP-activated protein kinase (AMPK). Activated AMPK plays an important role in the regulation of growth arrest and apoptosis by stimulating p53 and p21 [105]. Independent of AMPK activation, adiponectin decreases the production of reactive oxygen species (ROS), which may result in decreased activation of mitogen-activated protein kinases (MAPK) and thereby inhibition of cell proliferation [78,100].

Moreover, the important anti-inflammatory and immunomodulatory properties of adiponectin could also contribute to its anti-carcinogenic effects. Thus, adiponectin has been shown to inhibit endothelial NF-κB signaling and to markedly reduce TNF-α production in cultured macrophages. Moreover, adiponectin also induces the production of anti-inflammatory cytokines IL-10 and IL-1RA in human leukocytes [106].

In conclusion, the decreased plasma levels of adiponectin in obesity may be associated with the increased risk of cancer in obesity. Thus, it has been proposed that upregulation of adiponectin levels might be of therapeutic use in the prevention or treatment of some cancers [100].

3.3.2. PAI-1

PAI-1 is a serine protease inhibitor produced by endothelial cells, stromal cells and adipocytes mainly in visceral adipose tissue. PAI-1 affects adipocyte differentiation and insulin signaling. Furthermore, increased PAI-1 levels have been associated with obesity, as the result of increased PAI-1 production from obese adipocytes [107].

Moreover, PAI-1 inhibits urokinase plasminogen activator (uPA), which acts as an inducer of fibrinolysis and extracellular matrix degradation, and is associated with tumor cell invasion and metastasis [108]. Paradoxically, PAI-1 is involved in tumor growth, invasion, metastasis, and angiogenesis by interacting with vitronectin, integrins, and other components of the uPA system and by affecting the extracellular matrix [78].

PAI-1 is a poor prognostic indicator for a number of cancers including breast cancer. However, there is no single mechanism to explain why an elevation in PAI-1 protein results in decreased patient survival [109]. In this context, there are a number of studies that suggest alternative roles for PAI-1 outside of the traditional protease inhibitor role. Specifically, several studies have indicated that PAI-1 promotes tumor growth through an inhibition of apoptosis [110], regulation of angiogenesis, as well as increased cell adhesion, and increased migration. In addition to the role of PAI-1 in breast cancer migration and invasion, it has been implicated in an inflammatory response. Taking together the current knowledge, it has been proposed that inhibition of PAI-1 might be a potential target in cancer therapy [109].

3.3.3. Visfatin/ NAMPT/PBEF

Visfatin was identified as an adipokine highly expressed in visceral fat of human subjects and rodents, whose plasma circulating levels were positively correlated with the size of visceral fat depots. Besides, this adipokine seemed not to be correlated with subcutaneous fat depots and consequently, it was termed visfatin (from visceral fat) [111]. This adipocytokine was initially discovered as pre-B cell colony-enhancer factor (PBEF), because it favored the development of lymphocyte B colonies [112]. Later on, it was described as nicotinamide phosphoribosyltranferase (NAMPT), a key enzyme that catalyses the first step in NAD biosynthesis from nicotinamide, which widens considerably its biological perspective [113].

The role of visfatin in obesity and linked metabolic disorders remains controversial [98]. Thus, several studies showed increased levels of visfatin in obesity, diabetes mellitus, and cardiovascular disease [114,115]. However, other studies reported lower levels of visfatin in these diseases [116–118]. The discrepancies in clinical studies may be attributed to the multifactorial regulation of visfatin as well as to the lack of concordance between commercially available visfatin assays [119]. Thus, more research is needed to better define the role of visfatin in metabolic diseases.

Moreover, several studies have shown an increased expression of Nampt/PBEF/visfatin in different types of cancers [120]. Thus, a recent study suggests that visfatin plays a role in prostate cancer progression, with particular relevance and emphasis in an obese population [121]. Furthermore, Wang et al. [122] described that NAMPT is prominently overexpressed in human prostate cancer cells and that elevation of NAMPT expression occurs early for the prostate neoplasia. Moreover, the inhibition of NAMPT significantly suppresses cell growth in culture and growth of xenografted prostate cancer cells in mice. Furthermore, they demonstrated that NAMPT knockdown sensitizes prostate cancer cells to chemotherapeutic treatment [122]. Nakajima et al. [123] observed that visfatin levels were gradually increased with stage progression in gastric cancer patients. Visfatin has also been related with breast cancer. In fact, visfatin has been shown to stimulate proliferation of MCF-7 human breast cancer cells [124]. Moreover, FK866/APO866 and CHS828/GMX1777 are two known inhibitors of visfatin and have been evaluated as anticancer agents in the clinic [120].

3.3.4. Leptin

Leptin, a 16 kDa adipokine produced by WAT, plays a critical role in the regulation of body weight and energy balance by inhibiting food intake and stimulating energy expenditure. Circulating leptin levels are actively transported through the blood-brain barrier and activates the hypothalamic anorexigenic neurons POMC/CART (pro-opiomelanocortin; cocaine and amphetamine regulated transcript) while inhibiting orexigenic NPY/AgRP (neuropeptide Y; agouti related peptide) neuropeptides leading to decreased appetite [125]. The key role of the leptin system in regulating body fat in animals and humans is demonstrated by the severe hyperphagia and obesity caused by leptin deficiency. However, leptin concentrations positively correlate with total body fat mass. Thus, leptin serum levels are high in obese subjects, suggesting that resistance to leptin action develops with chronic overfeeding and obesity. Leptin circulating levels rapidly decline under caloric restriction and weight loss [126].

Leptin has also shown to be involved in the inflammatory response, the regulation of insulin sensitivity as well as with carcinogenesis [127]. Leptin plays an important role in both adaptive and innate immunity. Accordingly, the leptin receptor is found to be expressed on a variety of immune cells. The most evident effects of leptin on the modulation of adaptive immune responses have been shown in leptin-deficient mice (*ob*/*ob*) and humans, which exhibited impaired immunity in parallel to metabolic disturbances [128]. These alterations are reversed by the administration of recombinant leptin [106]. With regard to innate immunity, leptin is a direct potent chemoattractant for monocytes and macrophages and also upregulates the phagocytic function of these leukocytes [127].

Leptin has also been shown to be a growth factor in cancer cell lines [129]. Indeed, leptin caused stimulation of normal and tumorous

cell growth as well as migration, invasion and enhancement of angiogenesis [130]. Moreover, elevated circulating leptin levels have been identified in patients with different types of cancer [128].

Numerous studies have investigated the complex mechanisms involved in the relationship between obesity, leptin and different cancers. Thus, Fig. 2 summarizes the potential pathways directly linking dysfunctional adipose tissue to obesity and cancer.

3.3.4.1. Leptin and breast cancer. It has been suggested that leptin induced proliferation of breast cancer cell lines, by activating JAK2–STAT3, PI3K–Akt–GSK3, ERK1/2, and AP-1 pathways, increasing the expression of proteolytic enzymes that are essential in metastatic process and stimulating angiogenesis, which is needed for tumor growth [131,132]. Specifically, in estrogen receptor-positive human breast cancer cell lines, leptin exerts its effects through activation of MAPK pathway [133,134]. Leptin itself can also enhance aromatase activity in MCF-7 cells and increase the production of estradiol or activate the telomerase which also promotes cell proliferation [135]. High levels of VEGF and leptin are strongly linked. Thus, leptin signaling upregulates VEGF in human and mouse mammary tumor cells (MT), which has been linked to worse prognosis of breast cancer, but the specific molecular mechanisms are largely unknown. A recent study demonstrated that leptin signaling regulates VEGF mainly through HIF-1alpha and NF-κB, and suggested that disruption of leptin signaling could be used as a novel way to treat breast cancer [136]. However, different studies exploring serum leptin levels in women with breast cancer showed inconsistent data. Thus, while some studies observed elevated plasma leptin levels and increased leptin gene expression and leptin receptor expression in breast cancer patients, other investigations do not support a relationship between systemic leptin levels and risk of breast cancer [87,131]. Further studies are needed in order to investigate the relationship between leptin and breast cancer as well as the underlying mechanisms.

3.3.4.2. Leptin and endometrial cancer. A close association between high leptin levels, as a consequence of obesity, and endometrial cancer has been described [137,138]. A recent study has shown that leptin may promote cell proliferation of endometrial cancer cells by the functional activation of cyclooxygenase-2 (COX-2) through JAK2/STAT3, MAPK/ERK, and PI3K/AKT-dependent pathways, suggesting that COX-2 may be a critical factor of endometrial carcinogenesis in obesity [139].

3.3.4.3. Leptin and colorectal cancer. There is accumulating evidence that leptin signaling might be involved in the development of colon cancer. Thus, data from a cohort study detected an almost 3-fold increased risk of colon cancer among people with high leptin levels [140]. Another case–control study in Japanese women also suggested that leptin substantially increases the risk of colorectal cancer [141]. Several *in vitro* experiments have also demonstrated a significant mitogenic activity of leptin in colonic epithelial cells [142,143]. Leptin can induce proliferation through the activation of the NF-κB and ERK1/2-dependent pathways [142,143], as well as by upregulating the c-fos expression in colon cancer cells [144].

Diverse nutritional trials demonstrated that diets rich in fats that increase circulating leptin promote carcinogenesis by stimulating colon cell proliferation [131,144]. Other studies carried out in animals supported the hypothesis that leptin is a growth factor in colonic epithelium and therefore that hyperleptinemia promotes epithelial dysplasia, which in turn promotes colorectal tumorigenesis. However, the relationship between leptin and colorectal cancer is not fully understood. Indeed, other research studies in rodents suggested that leptin treatment may have some protective effects against colon carcinogenesis [145]. Furthermore, controversial data were found regarding the association between serum leptin and colorectal cancer risk [128].

3.3.4.4. Leptin and prostate cancer. Several studies showed association between moderately elevated or high leptin levels with prostate cancer risk [146]. Leptin levels have also been significantly correlated with testosterone and specific prostatic antigen [147]. Leptin may interact with markers related to abdominal obesity such as sex hormones or IGF-1 increasing the risk of developing prostate cancer [131]. Several *in vitro* and *in vivo* studies reported that leptin increased cell proliferation, via JNK activation, and induced suppression of apoptosis, favoring tumor cell progression, invasion and metastasis [147], corroborating the role of this adipokine on prostate cancer.

3.3.4.5. Leptin and esophageal cancer. Several authors proposed a link between leptin and esophageal adenocarcinoma. *In vitro* studies reported that leptin stimulates cell proliferation on human esophageal cancer cells (OE-33, OE-19, KYSE-410) through activation of ERK and epidermal growth factor receptor system and through a reduction of apoptosis [128]. However, no studies have examined the association between serum leptin and esophageal cancer risk. In this sense, two recent case–control studies examined serum leptin concentrations in patients with Barrett's esophagus [148] describing a 3-fold increased risk of Barret's among men in the highest quartile of serum leptin. However, Francois et al. [149] did not find any association between plasma leptin with the risk of Barrett's.

In summary, all the previous studies support the important contribution of some key adipokines in the control of growth and proliferation of different types of tumors (see Table 1).

3.4. Insulin resistance, obesity and cancer

Dysfunctional adipose tissue in obese subjects makes a key contribution to the development of obesity-linked hyperinsulinemia and insulin resistance. Insulin upregulates hepatic production of IGF-1 and both act as growth factors able to promote cancer cell proliferation and decrease apoptosis [150]. These IGF-1 effects are mediated through several downstream signaling networks, including the phosphatidylinositol 3-kinase (PI3K)–AKT system and the Ras/Raf/MAPK systems, respectively [151]. Moreover, clinical studies have shown that patients with high levels of IGF-1 have an increased risk of several types of cancer, including colorectal, prostate, and postmenopausal breast cancer. Hyperinsulinemia is also an independent risk factor for breast cancer in postmenopausal women and increases the risk of colorectal and endometrial cancer; however, some controversial results have been found (reviewed by van Kruijsdijk et al. [78]).

3.5. Oxidative stress, obesity and cancer

Oxidative stress is generating much recent interest mainly because of its accepted role as a major contributor to the etiology of several pathologies with serious public health implications such as obesity and cancer [152,153]. Oxidative stress can result from an imbalance between reactive species production and body antioxidant defences. ROS primarily originate in mitochondria during oxidative phosphorylation. The study of Furukawa et al. [152] found that increased oxidative stress in accumulated fat is an early instigator of metabolic syndrome and that controlling the redox state in adipose tissue is a potentially useful therapeutic target for obesity-associated metabolic syndrome. In fact, this and other trials have observed that oxidative stress caused dysregulated production of adipokines, cytokines and chemokines including adiponectin, leptin, resistin, PAI-1, IL-6, and monocyte chemotactic protein-1 in adipocytes [154,155].

The role of oxidative stress in cancer is controversial. In fact, both pro- and anti-cancer effects have been attributed to ROS. Thus, increased ROS production control tumor cell proliferation and enhance metastatic potential of tumor cells [156]. However, several studies have suggested that a pharmacological regulation in favor of increasing intracellular ROS and/or depleting protective reducing

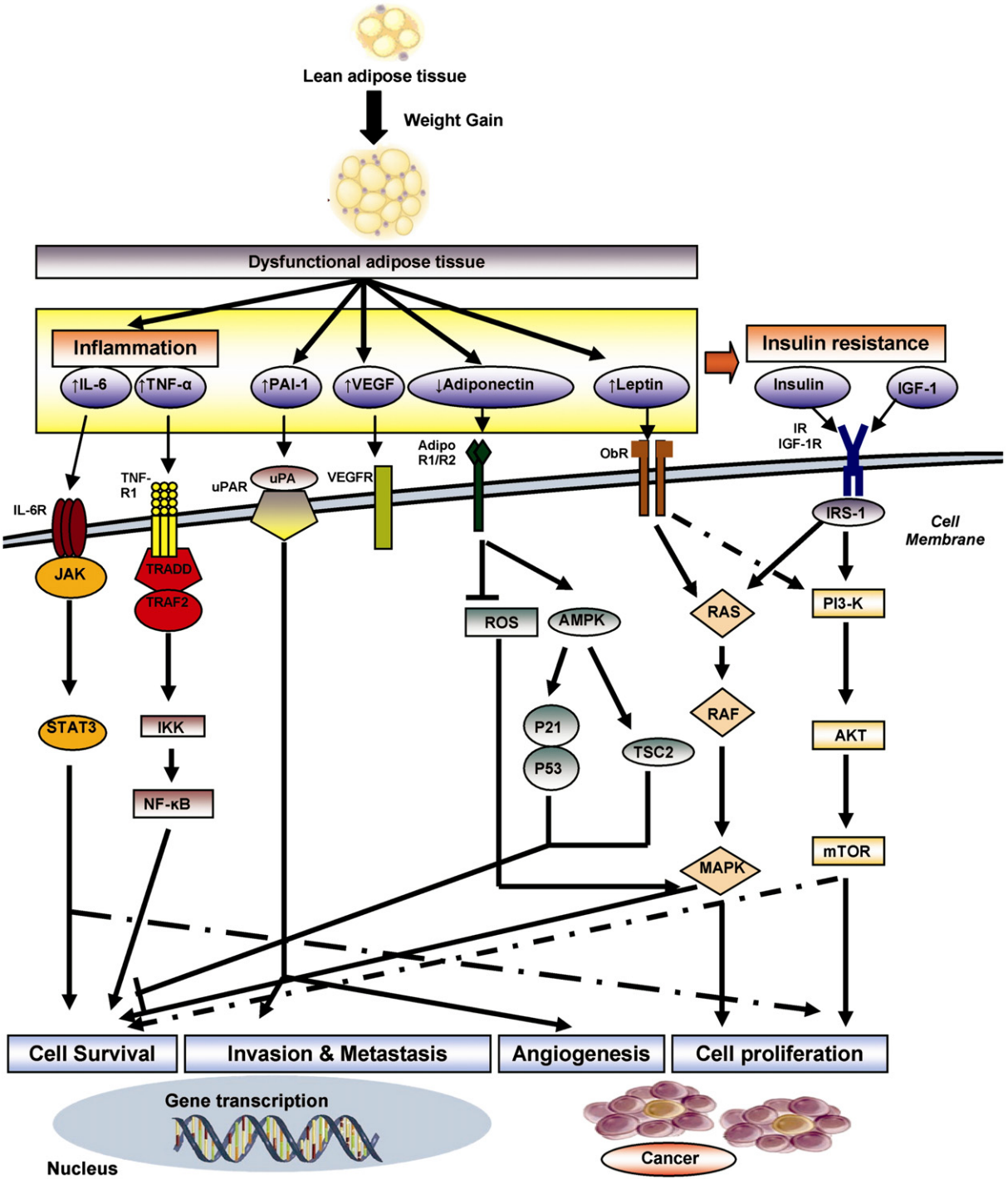

Fig. 2. Potential pathways directly linking obesity with cancer. AdipoR1/R2, adiponectin receptor 1/2; AMPK, 5′-AMPactivated protein kinase; IGF-1, insulin-like growth factor-1; IGF-1R, insulin-like growth factor-1 receptor; IKK, IκB kinase; IL-6, interleukin-6; IL-6R, interleukin-6 receptor; IR, insulin receptor; IRS-1, insulin receptor substrate-1; JAK, Janus kinase; MAPK, mitogen-activated-protein-kinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-κB; ObR, leptin receptor; PAI-1, plasminogen activator inhibitor-1; PI3K, phosphatidylinositol 3-kinase; ROS, Reactive oxygen species; STAT3, signal transducer and activator of transcription 3; TNF-α, tumor necrosis factor-α; TNF-R1, tumor necrosis factor-receptor 1; TRADD, TNFRSF1A-associated via death domain; TRAF2, TNF receptor-associated factor 2; TSC2, tuberous sclerosis complex 2; uPA, urokinase-type plasminogen activator; uPAR, urokinase-type plasminogen activator receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.
Modified with permission from van Kruijsdijk et al. [78].

metabolites may lead to oxidative stress and resultant induction of apoptosis for the treatment of cancer [157].

Uncoupling protein-2 (UCP2) is expressed widely including in white adipose tissue, skeletal muscle, pancreatic islets, and central nervous system. Although the function of UCP2 is controversial, UCP2 may play a role in lipid metabolism as well as in energy expenditure Moreover, it has been suggested that UCP2 may function as a sensor of mitochondrial oxidative stress, being activated by ROS and providing protection against ROS production [158]. In fact, loss of UCP2 function may result in increased generation of ROS and reduced antioxidant capacity, whereas UCP2 overexpression conveys cytoprotection to various tissues by limiting oxidative injury [159,160]. These findings suggest a role for UCP2 in physiological states associated with oxidative stress including cancer [161]. In fact, cancer cell survival

depends on adaptive mechanisms that include modulation of oxidative stress. UCP2 expression has been found to be increased in different types of cancer, including human colon cancers, supporting the idea that UCP2 is part of a novel adaptive response by which oxidative stress is modulated in cancer [160]. However, it has been considered that the physiologically significant roles of UCP2 in the protection against reactive oxygen species remain still circumstantial [162].

3.6. Mitochondrial biogenesis, obesity and cancer

Mitochondrial dysfunction can lead to the development of several metabolic diseases such as obesity and cancer. In this sense, several studies have demonstrated that adipose mitochondrial biogenesis was overwhelmingly suppressed in both genetic and high-fat diet-induced rodent models of diabetes/obesity [163,164]. Peroxisome proliferator-activated receptor gamma coactivator (PGC-1α) and the NAD-dependent deacetylase SIRT1 have been characterized as master regulators of mitochondrial biogenesis [165]. Both, the expression of PGC-1α and SIRT1 are reduced in adipose tissue of obese subjects [166,167].

Therefore, developing therapeutics to improve mitochondrial function and/or biogenesis is an attractive strategy for preventing these disorders (reviewed by Pérez-Matute et al. [168]). In this sense, it has been recently demonstrated that the insulin sensitizer actions of pioglitazone could be due, at least in part, to its stimulatory effects on mitochondrial biogenesis in human subcutaneous adipose tissue [169]. Moreover, it has been observed that part of the mitochondrial dysfunction can be triggered by adverse nutrition conditions [170], and that bioactive food components may contribute to improve adipose tissue failure and mitochondria [171].

4. Molecular nutrition, energy metabolism and cancer

Cancer is known to be caused by a variety of factors including sedentary lifestyle, infections, radiation exposure and hormonal factors. Furthermore, breast, prostate, colorectal, esophageal and liver cancers seem to be also associated with dietary patterns. In fact, dietary factors account for approximately 30% of tumors in industrialized countries [172]. However, and despite these studies, there are some inconsistencies caused by the multi-factorial and complex nature of cancer as well as the different genetic background of individuals. In addition, not all macronutrients affect genes and oncogene expression in the same way [171]. Variation in cancer incidence among and within populations with similar dietary patterns suggests that an individual's response may reflect interactions with genetic factors, which may have ramifications in gene, protein and metabolite expression patterns (reviewed by Davis and Milner [173]).

Nutrigenomics considers the relationship between a specific nutrient or a diet and gene expression, whereas nutrigenetics determines how genetic variability affects the response to dietary pattern, functional food or supplement for a specific health outcome [174]. The specific fields of genome-health nutrigenomics and genome health nutrigenetics are proposed on the premise that a more useful approach to the prevention of diseases caused by genome damage is to take into consideration that (a) inappropriate nutrient supply can cause sizeable levels of genome mutation and alter expression of genes required for genome maintenance and (b) common genetic polymorphisms may alter the activity of genes that affect the bioavailability of micronutrients and/or the affinity for micronutrient cofactors in key enzymes involved in DNA metabolism or repair. Supplementation of the diet with appropriate minerals and vitamins could, in some cases, help to overcome inherited metabolic blocks in key DNA maintenance pathways [175,176].

In fact, during the last few years, research focused on the study of the mechanisms underlying the beneficial effects of bioactive food in energy metabolism and cancer. It is important to remember that an excess body weight is generally linked to enhanced cancer risk [32,33,35]. Thus, a large number of bioactive food components occurring in food may provide protection at several stages of the cancer process. Representative bioactive components found in food that are protective against cancer include essential nutrients (i.e., calcium, zinc, selenium, folate, Vitamins C, D and E) as well as non-essential food components (i.e., carotenoids, flavonoids, indoles, allyl sulfur compounds, conjugated linoleic acid, *n*-3 fatty acids, and lipoic acid) [177]. These bioactive food components may modify

Table 1
Effects of different adipokines on cancer cells.

Cancer type	Adipokines	Model of study	Effects and proposed mechanism of action	Reference
Breast cancer	Adiponectin	Breast cancer MDA-MB-231 cells	Induced growth arrest and apoptosis	[103]
	Visfatin	MCF-7 breast cancer cells	Stimulated cell proliferation by upregulating cyclin D1 and cdk2 and MMP-2, MMP-9, and VEGF	[124]
	PAI-1	MDA-MD-435 cell and human breast cancer cell	Promoted tumor growth by inhibition of apoptosis, regulation of angiogenesis and by increasing cell adhesion and migration	Reviewed by [109]
	Leptin	MCF-7 breast cancer cells	Proliferation of breast cancer cells by activation of JAK2–STAT3, PI3K–Akt–GSK3, ERK1/2, MAPK and AP-1	[131–133]
		MCF-7 breast cancer cells	Promoted cell proliferation by upregulating telomerase activity	[135]
		MCF-7 breast cancer cells	Enhanced aromatase expression via AP-1	[134]
Endometrial cancer	Leptin	Human endometrial cancer cells	Promoted cell proliferation by activation of COX-2, JAK2/STAT3, MAPK/ERK, and PI3K/AKT	[139]
Colorectal cancer	Leptin	Human colon cancer HT-29 cells, colonic epithelial cells	Stimulated proliferation of colon cancer cell lines by activating p42/44 MAPK	[142]
		Human colon cancer HT-29 cells treated with sodium butyrate	Induced proliferation by activation of NF-κB and ERK1/2	[143]
		Human colon cancer HT-29 cells, colonic epithelial cells	Stimulated growth and proliferation and upregulation of c-fos expression	[144]
Prostate cancer	Leptin	DU145 and PC-3 human prostate cancer cells	Increased cell proliferation through JNK, PI3K/Akt or ERK1/2 pathways, and suppression of apoptosis	Reviewed by [147]
	Visfatin	Human prostate cancer cells	Overexpression of NAMPT increased prostate cancer cell by increasing FOXO3 and oxidative stress resistance	[122]
		Human prostate tissue and Ln CaP or PC-3 cells	Increased PC-3 cell proliferation and the expression and activity of MMP-2 and -9 by activating MAPK, ERK 1/2 and p38.	[121]
	PAI-1	Human prostate cancer PC-3 cells	Promoted tumor growth through inhibition of apoptosis	[110]
Esophageal cancer	Leptin	Esophageal cancer cells (OE-33, OE-19, KYSE-410)	Stimulates cell proliferation by activation of ERK and epidermal growth factor receptor system. Suppression of apoptosis.	[128]

simultaneously more than one cancer development mechanism such as hormonal balance, cell signaling, cell-cycle control, apoptosis, and angiogenesis [178].

4.1. Dietary fatty acids, obesity and cancer

Dietary factors that potentially increase the risk of cancer include low fruit, vegetable, or fiber intake, high red meat or saturated fat consumption, and exposure to caffeine or alcohol [179]. Some case–control and cohort studies have also found positive associations between dietary glycemic index (a physiological assessment of a food's carbohydrate content through its effect on postprandial blood glucose concentrations), and risk of various cancers, including those of the colon, breast, and prostate [180]. Among the numerous dietary compounds that have been related to cancer, dietary lipids have been revealed as significative ones. Epidemiological and especially experimental studies have established a relationship between dietary fat and breast, colon and rectum tumors and, to a lesser extent, prostate [181,182]. A growing body of evidence suggests that not only the total amount of fat ingested, but also the type of fat included in the diet contribute to the development of obesity and insulin resistance [98]. Moreover, an expanding number of retrospective case–control investigations have also found an increase in cancer risk with increasing fat intake, especially with animal and saturated fat intake [183]. Thus, the association of high red meat or saturated fat consumption with increased colorectal cancer risk is supported by the preponderance of observational data [184]. In contrast to diets high in saturated fat, diets high in fish oil appear to prevent or attenuate the development of obesity and insulin resistance [185–187] and cancer [181].

4.1.1. n-3 Polyunsaturated fatty acids (n-3 PUFAs)

The *n*-3 PUFAs present in fish oil, are known to have numerous beneficial effects on health. These include improvement of endothelial function, anti-arrhythmic effects, reductions in platelet aggregation and serum triglyceride concentrations, and amelioration of pathological conditions such as inflammatory diseases, hypertension and cancer. Diets containing high levels of *n*-3 PUFAs have been shown to reduce WAT and adipocyte size and to prevent non-insulin-dependent diabetes in rats. Indeed, eicosapentaenoic acid (EPA) [20:5 (*n*-3)], one of the prominent *n*-3 PUFAs contained in fish oil, has been reported to be useful in preventing the onset of insulin resistance and diabetes in animal models of obesity and diabetes [188].

Regarding the mechanisms underlying the beneficial effects of marine *n*-3 PUFA consumption, it was demonstrated that *n*-3 PUFA are important regulators of key metabolic transcription factors including the peroxisome proliferator-activated receptors (PPARs) and sterol regulatory element binding protein (SREBP) [98]. *n*-3 PUFAs have anti-inflammatory effects in a range of chronic inflammatory conditions, because their ability to decrease the production of classic inflammatory mediators such as arachidonic acid-derived eicosanoids and inflammatory cytokines. Moreover, it was recently described that *n*-3 PUFAs serve as substrates for the conversion to a novel series of lipid mediators designated resolvins and protectins, with more potent anti-inflammatory properties than their *n*-3 precursors [189].

AMPK activation could be also involved in *n*-3 PUFA-induced improvements on energy metabolism and insulin sensitivity. A recent study of our group has demonstrated that EPA strongly stimulates AMPK phosphorylation in 3T3-L1 adipocytes [190]. Moreover, two recent trials have described the ability of *n*-3 PUFAs to *in vivo* activate AMPK [191,192]. *n*-3 PUFAs have also been shown to upregulate mitochondrial biogenesis and induce beta-oxidation in white fat in mice, associated with a three-fold stimulation of the expression of genes encoding regulatory factors for mitochondrial biogenesis and oxidative metabolism such as PGC-1α and nuclear respiratory factor-1 (Nrf-1) [193].

Furthermore, the beneficial properties of *n*-3 PUFAs may also partially result from the modulation of WAT metabolism and the secretion of bioactive adipokines that directly regulate energy homeostasis, insulin sensitivity and carcinogenesis. Thus, different studies of our group and others have shown that *n*-3 PUFAs are important regulators both *in vitro* and *in vivo* of the secretion and gene expression of leptin [188,194], adiponectin [194–196], visfatin [118,190] and apelin [118,197], among other adipokines.

The proposed mechanisms for the anticancer actions of *n*-3 PUFAs include suppression of neoplastic transformation, inhibition of cell proliferation, enhancement of apoptosis, and antiangiogenic. A recent study suggests that *n*-3 PUFAs inhibit hepatocellular carcinoma cell growth through blocking beta-catenin and cyclooxygenase-2 [153]. Another investigation suggests that DHA induce apoptosis in human MCF-7 breast cancer cells both *in vitro* and *in vivo*. The induction of apoptosis in these cells is selectively mediated via caspase 8 activation [198]. Recently, it has been suggested that resolvins biosynthesized from *n*-3 PUFAs may play a role as anti-inflammatory and proresolving mediators in colon cancer [199].

4.1.2. Conjugated linoleic acid (CLA)

CLA was initially discovered in 1987 by Ha et al. [200] and it was first identified as an anticarcinogen molecule. Several studies have indicated that CLA exert anti-obesity effects in rodents, although its effects in humans are controversial. The potential mechanisms responsible for the antiobesity properties of 10,12-CLA isomer in rodent models include decreased energy intake by suppressing appetite, increased energy expenditure, decreased lipogenesis and adipogenesis, increased lipolysis and apoptosis [201,202]. Several studies have also shown that CLA regulates both leptin and adiponectin *in vivo* [203] and *in vitro* [194]. Furthermore, it has been suggested that this inhibition of leptin and adiponectin induced by CLA may contribute to the insulin resistance observed in some CLA-treated animals and humans [204].

On the other hand, a number of assays have demonstrated that CLA exerts chemopreventive and therapeutic activities in a number of rodent and human tumor models. Thus, the 10t, 12c isomer of CLA inhibits tumorigenesis and tumor growth in human breast (MCF-7), colon (HT-29) and prostate (LNCaP) cancer cell lines. This inhibitory effect of CLA on tumor growth is mediated in part by its pro-apoptotic activity [205,206].

4.2. Antioxidants, obesity and cancer

The attenuation or complete suppression of oxidative stress as a way to improve several diseases has flourished as one of the main challenges of research in the last years. A number of trials have examined the effects of supplementation with different antioxidants on oxidative stress associated to obesity and/or cancer [205–213]. However, and although several positive effects have been found [207–209] there are some controversial results, specially in the field of antioxidant supplementation and cancer. Thus, a trial found a statistically significant reduction in total and specific cancer incidence and mortality after supplementation with antioxidants [210]. However, other studies observed a lack of effect of supplementation with antioxidants on cancer [211,212]. Furthermore, the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC) and the β-Carotene and Retinol Efficacy Trial, especially on lung cancers did not observe reduction in the incidence of lung cancer among male smokers after five to eight years of dietary supplementation with alpha-tocopherol or beta carotene. In fact, these trials raise the possibility that these supplements may actually have harmful as well as beneficial effects [213,214]. Vitamin C also seems to have a controversial role in cancer [215]. Possible reasons for these discrepancies in relation to the efficacy of antioxidant to counteract oxidative stress and improve health relate to (1) the type of antioxidant used (some of the

antioxidants examined were ineffective and nonspecific and dosage regimen or duration of therapy were inefficient), (2) patient cohort included in trials, (3) the trial design itself and (4) inappropriate or insensitive methodologies to evaluate oxidative state (reviewed by Pérez-Matute et al., 2009 [168]).

4.3. Resveratrol, obesity and cancer

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a well-known polyphenolic compound of red wine with numerous beneficial activities, including cardioprotective actions [216], anti-cancer effects [217] and anti-inflammatory and antioxidant properties [218]. Recently, this broad spectrum of effects is enlarged by new data demonstrating a great potency of this compound in relation to obesity and diabetes. It is well established that resveratrol exerts beneficial effects in rodents fed with a high fat diet, substantially reducing visceral fat and body weight gain [219,220]. The mechanisms underlying these resveratrol effects include: induction of genes for oxidative phosphorylation and mitochondrial biogenesis (reviewed by Szkudelska and Szkudelski [221]), inhibition of preadipocyte proliferation and adipogenic differentiation, stimulation of basal and insulin-stimulated glucose uptake, and inhibition of *de novo* lipogenesis [222]. Resveratrol may also influence the secretion and plasma concentrations of some adipokines such as adiponectin and TNF-α and inhibits leptin secretion from rat adipocytes [223,224]. However, data regarding the effects of resveratrol on adipokines are still insufficient to be conclusive.

Several studies have suggested that activation of SIRT1 and AMPK plays a key role in the metabolic effects of resveratrol [225,226]. A recent research has also shown that resveratrol modulates tumor cell proliferation and protein translation via SIRT1-dependent AMPK activation [227]. In this context, resveratrol has been proposed as a potential dietary compound against various cancers including breast and colon tumors. Resveratrol may affect all three discrete stages of carcinogenesis (initiation, promotion, and progression) by modulating signal transduction pathways that control cell division and growth, apoptosis, inflammation, angiogenesis, and metastasis [228]. Recently, it has been shown that resveratrol suppresses IGF-1 induced cell proliferation and elevates apoptosis in human colon cancer cells, via suppression of IGF-1R/Wnt and activation of p53 signaling pathways [217].

4.4. Lipoic acid, obesity and cancer

α-Lipoic acid (LA) or 1,2-dithiolane-3-pentanoic acid is a promising dietary bioactive molecule because of its recognized therapeutic potential on several diseases such as diabetes, vascular disease, hypertension and inflammation [229]. Both LA and its reduced form dihydrolipoic acid (DHLA) exert powerful antioxidant properties although DHLA seems to be a more effective [230]. Their antioxidants functions involve: quenching ROS (reactive oxygen species), regeneration of endogenous and exogenous antioxidants involving vitamin C, vitamin E and glutathione, chelation of redox metal including Cu (II) and Fe (II) and repair of oxidized proteins. LA can be found in different foods such as spinach and cabbage, liver and meat, whole wheat and yeast of beer, but it is also endogenously produced by the liver through the lipoic acid synthase (LASY) machinery. Deficiency of LASY results in an overall disturbance in the antioxidant defence network, leading to increased inflammation, insulin resistance and mitochondrial dysfunction [231].

LA is an important cofactor for mitochondrial bioenergetic enzymes, and therefore, plays a critical role in mitochondrial energy metabolism [232,233]. In addition, there are increasing scientific and medical interests in the potential therapeutic uses of LA. In this sense, several studies have described the putative benefits of LA on obesity and associated complications. Thus, LA reduces body weight and adiposity in rodents [234,235] and humans [236]. Several mechanisms may contribute to the anti-obesity effects of LA including the suppression of hypothalamic AMPK activity [237], which in turn leads to a reduction on food intake, and the stimulation of energy expenditure by increasing Ucp-1 mRNA levels in brown adipose tissue [234] and by enhancing adenosine monophosphate-activated protein kinase (AMPK)-peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α) signaling in the skeletal muscle [238]. Furthermore, the inhibitory action of LA on intestinal sugar transport could also contribute to a lower feed efficiency observed in LA-treated animals [235].

In addition, LA has also beneficial actions in both glucose and lipid metabolism, and it has been proposed as a potential therapy for insulin resistance and type 2 diabetes [239–241]. LA positively interacts with the insulin pathway and glucose handling in muscle and adipocytes, by modulating the IR/PI3K/Akt pathway and GLUT4 translocation [229]. LA also promotes mitochondrial biogenesis in adipocytes and muscle through a stimulation of PGC-1α, contributing to improve the defective mitochondrial function associated to diabetes/obesity [242,243].

Several trials have also suggested the potential use of LA in cancer therapy [244] due to its ability to induce apoptosis in cancer cells [245,246]. However, the molecular mechanisms underlying the apoptotic effect of LA are not well understood. Shi et al. [246] suggested that the inhibition of ROS generation mediated LA-induced apoptosis in hepatoma cells. Moreover, LA, through scavenging ROS, inhibits PI3K signaling and induces mitochondrial pathway mediated apoptosis [246]. However, Moungjaroen et al. [247] demonstrated that LA induced-ROS generation mediates caspase activation and apoptosis in human lung epithelial cancer cells through Bcl-2 downregulation.

A recent study have suggested that LA exerts an inhibitory effect on cell proliferation via EGFRs and Akt signal transduction and induces cancer cell apoptosis in MDA-MB-231 human breast cancer cells [248]. Further studies are needed to better characterize the mechanisms involved in the anti-carcinogenic action of LA.

5. Perspectives

There is emerging evidence of strong associations between obesity and the incidence of cancer. In obesity, the expanding adipose tissue could make a clinically relevant contribution to the onset and development of cancer via dysregulated secretion of pro-inflammatory cytokines, chemokines and adipokines such as TNF-α, IL-6, leptin, adiponectin and PAI-1. More investigation in order to better understand the molecular mechanisms that link dysregulated adipose tissue function and cancer is worth pursuing, as it may provide new therapeutic targets to prevent or treatment in cancer. Nevertheless, tackling obesity is a priority for reducing the incidence in addition to mortality of certain cancers. The identification of bioactive dietary factors or substances that affects some of the components of energy balance to prevent/reduce weight gain is a promising avenue of research. However, the mechanisms by which dietary components modulate obesity and cancer are not fully understood, partly because of the lack of appropriate research tools to identify the complex mechanisms involved. With the emergence of Nutrigenomics, it is now possible to exploit genome-wide changes in gene expression profiles related to molecular nutrition in obesity and cancer. Evolution of '-omics' epigenomics, transcriptomics, proteomics, and metabolomics will allow a better understanding of how dietary factors may affect both energy metabolism and carcinogenesis, leading to healthier foods and, in turn, healthier people and lifestyles.

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