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Review

Obesity and cancer: the role of adipose tissue and adipo-cytokines-induced chronic inflammation

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Abstract

Adipose tissue in addition to its ability to keep lipids is now recognized as a real organ with both metabolic and endocrine functions. Recent studies demonstrated that in obese animals is established a status of adipocyte hypoxia and in this hypoxic state interaction between adipocytes and stromal vascular cells contribute to tumor development and progression. In several tumors such as breast, colon, liver and prostate, obesity represents a poor predictor of clinical outcomes. Dysfunctional adipose tissue in obesity releases a disturbed profile of adipokines with elevated levels of pro-inflammatory factors and a consequent alteration of key signaling mediators which may be an active local player in establishing the peritumoral environment promoting tumor growth and progression. Therefore, adipose tissue hypoxia might contribute to cancer risk in the obese population. To date the precise mechanisms behind this obesity-cancer link is not yet fully understood. In the light of information provided in this review that aims to identify the key mechanisms underlying the link between obesity and cancer we support that inflammatory state specific of obesity may be important in obesity-cancer link.

Key words: adipocytes inflammation, adipocytokine, obesity, cancer.

Introduction

Obesity, defined as abnormal excess accumulation of fat in adipose tissue, is a chronic low-grade inflammation. It is associated with a high risk of developing type 2 diabetes, metabolic syndrome cardiovascular disease, and several types of cancer [1-5]. In tumors of breast, colon, liver and prostate, obesity represents a poor predictor of clinical outcomes. [6–9]. The precise mechanisms underlying this obesity–cancer link are not yet well understood. The definition of overweight and obesity according to WHO is defined by body mass index (BMI, weight/height m^2): BMI = 25-29 kg/m^2 for overweight and BMI ≥ 30 kg/m^2 for obesity, Table 1 [10]. The adipose tissue in addition to its ability to keep lipids is now recognized as a real organ with both metabolic and endocrine functions [11]. The knowledge about the structural and functional principles of adipose tissue has evolved considerably over the last ten years to get to today's conception of the adipose organ [12,13]. At the cellular level it shows considerable heterogeneity, being constituted only half from mature adipocytes, and for the rest from preadipocytes, fibroblasts, endothelial cells, nerve cells and macrophages [14,15]. (Figure 1). The adipose tissue is divided in brown adipose (BAT) and in white adipose (WAT). The BAT is only a minimal part of the body, which in an adult is approximately 50 grams compared to kilograms of the white adipose tissue. The most important knowledge we have today on the white adipose tissue regarding its role. Recently several studies have clearly demonstrated that the white adipose tissue is a true endocrine organ, a secretory organ metabolically active, and far from being inert tissue [16,17]. It consists of different

cell types and produces a number of adipokines and cytokines [18]. Both stem cells (one every 50 adipocytes) that the pre-adipocytes are found in adipose tissue. These cells, when stimulated and activated, have the capacity to divide and give rise to new adipocytes. Once formed, the new white adipocytes will remain so until the death of the individual: they can then increase or decrease in volume but not in number [19]. It is therefore important to prevent an excessive increase of adipose tissue and the number of adipocytes, especially in children, in which this phenomenon would condemn them, with high probability, to remain obese for the rest of life [20].

Table 1 Diagnostic criteria for obesity in according to WHO classification.

Category	BMI value (kg/mq)
Underweight	≤ 18.5
Normal Weight	18.5-24.9
Overweight	25-29.9
Obesity Type 1	30-34.9
Obesity Type 2	≥ 35

Adipocytes: hypertrophy and hyperplasia

Body fat is stored in white adipose tissue into smaller fat cells, adipocytes, whose number and size varies greatly from individual to individual. Adipocytes, to ascertaining which of lipids, vary their size (diameter 20-200 μm): they are able changing of 20 times their diameter and out several thousand times their volume. Adipocytes modulate a variety of physiological responses which include the metabolism of lipids and glucose, inflammation, blood pressure and ultimately angiogenesis and homeostasis [21]. Body fat may increase in two ways (Figure 2):

- Hypertrophy: increase in the volume of adipocytes
- Hyperplasia: increase in the number of adipocytes

The hyperplasia of adipose tissue occurs during certain periods of life (last half of pregnancy, the first year of life and the beginning of puberty) or in special situations, such as obesity. In all other cases remain the phenomena of hypertrophy [22,23]. It is important to remember that the hyperplasia, unlike hypertrophy, is an irreversible process, so even in the event of slimming exasperated cells does not decrease in number but, only in their volume [24]. When an obese person slimming, fat cells lose a certain amount of fat, reducing their volume, but the number of adipocytes cannot be reduced. That's the reason a person with obesity regained in the short term much of body fat lost when suspending the crash diet. An excessive accumulation of triglyceride inside white adipocytes causes a progressive increase of their volume. The adipocyte hypertrophy creates the risk of compromising the integrity of the adipocytes themselves who do not have unlimited power to increase the volume; therefore reached a certain limit an adipocyte excessively hypertrophic undergoes events of hypoxia and necrosis [25]

As a result there has been an alteration of adipose tissue with changing in the production of steroid hormones and adipokines, development of metabolic disorders, and the onset of chronic subclinical inflammation [26,27]. These alterations are implicated in the mechanism of carcinogenesis, progression and tumor metastasis [28] (Figure 3). Recent studies demonstrated that in obese animals is established a status of adipocyte hypoxia and in this hypoxic state interaction between adipocytes and stromal vascular cells contribute to tumor development and progression [29]. In obesity, adipose tissue hypoxia may cause cellular mechanisms that lead to the development of insulin resistance, to a state of chronic inflammation with infiltration of macrophages, the reduction of adiponectin and increased of leptin, adipocyte death, ER stress and mitochondrial dysfunction [30-34]. Therefore, adipose tissue hypoxia might contribute to cancer risk in the obese population [35,36]. Hypoxia-inducible factor 1 alpha (HIF-1a), is an important

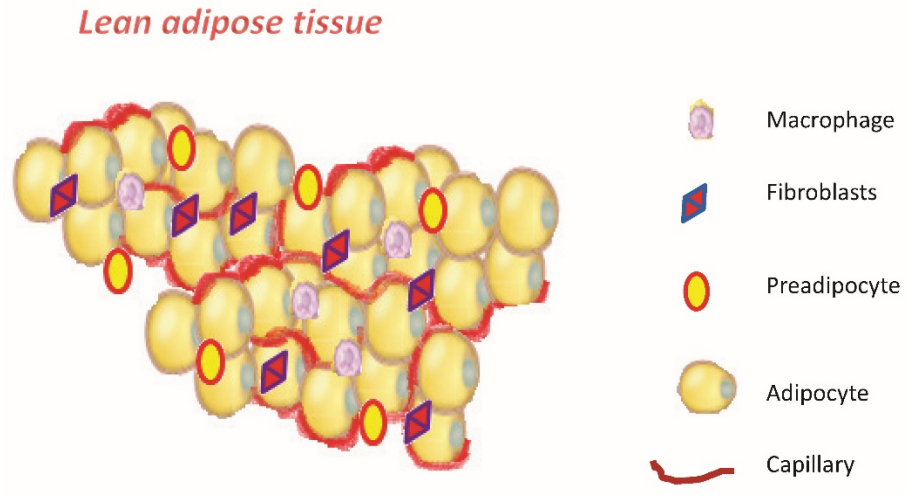

Figure 1 Schematic representation of adipose tissue.

transcription factor that is regulated by hypoxia and in tumors leads to increased vascularization. HIF-1a is involved in the regulation of transcription of genes implicated in the mechanisms of carcinogenesis. These include angiogenesis, cell survival, invasion and metabolism of glucose. Finally, HIF-1a was associated with an increase occurrence of metastases. Furthermore HIF-1a inhibition might improve sensitivity of tumors to radiation [37,41].

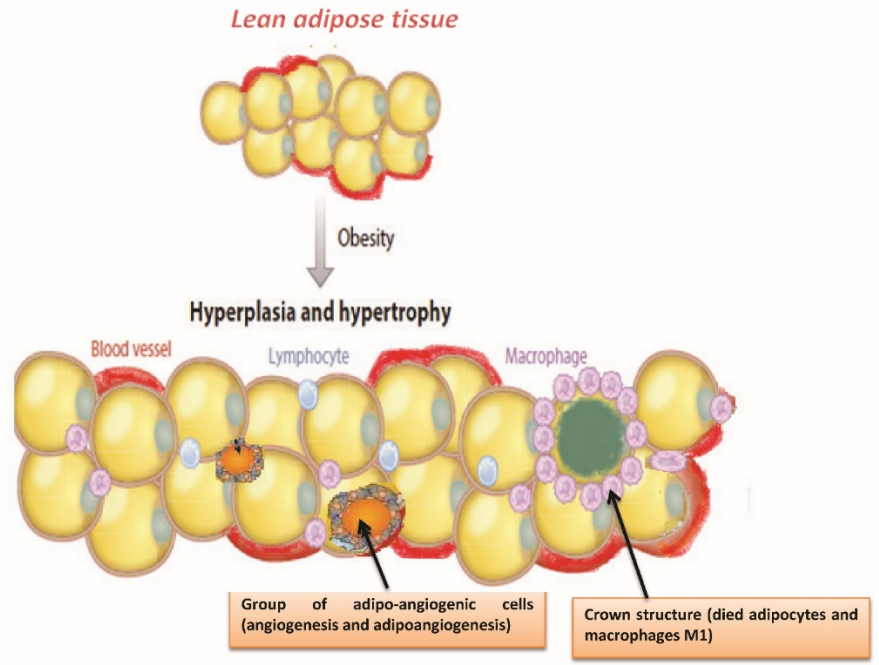

Figure 2 Adipocyte hypertrophy and hyperplasia induces an inflammatory cascade and accumulation of immune cells, activation of leukocytes, endothelial cells coupled with angiogenesis, adipogenesis and death of adipocytes.

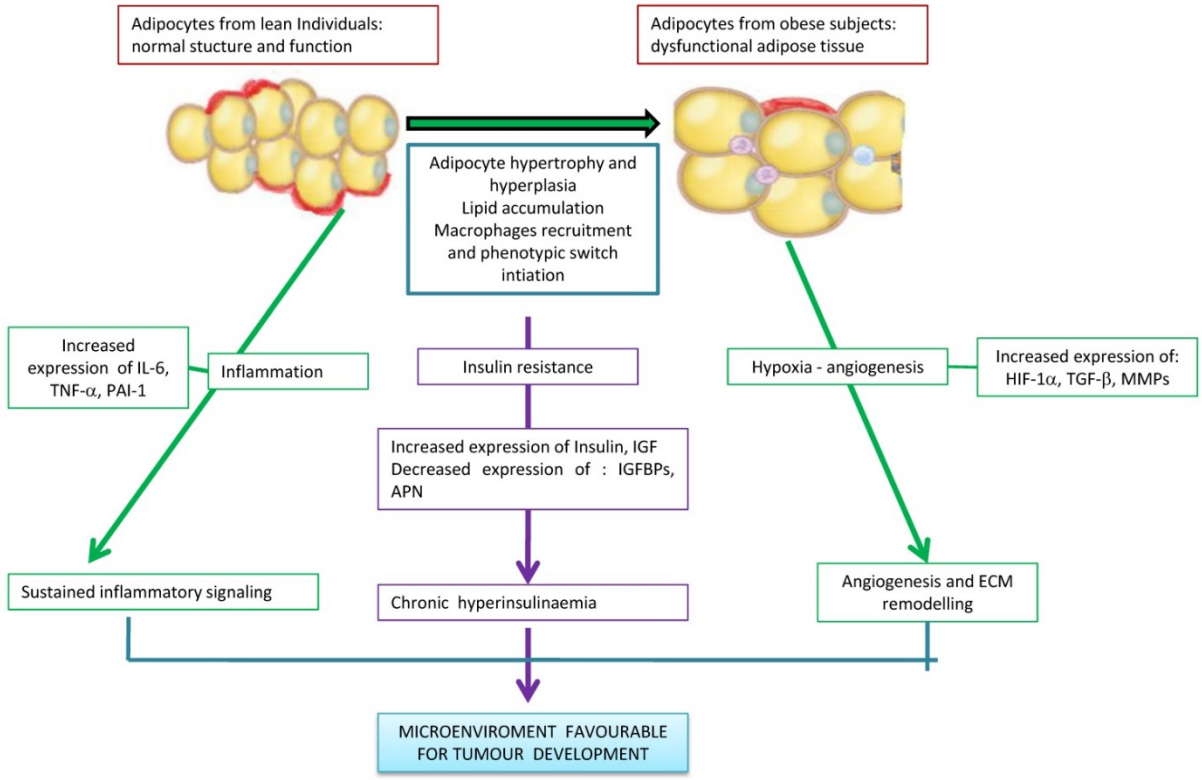

Figure 3 The different mechanisms linking obesity and cancer. Excessive adipose tissue is related to the changes of the lipids concentrations in the circulation, levels of species reactive oxygen as well as to secretion of adipokines and circulating hormones. The hypertrophy and hypoxia of adipose tissue cause chronic inflammation. Thus, cytokines secreted by inflamed adipose tissue, production of angiogenic factors, infiltration of macrophages M1 and insulin resistance associated with obesity may favor stimulation of a favorable microenvironment for tumorigenesis.

To block hypertrophy, each fat cell realizes two actions [42,43]:

- amends its protein synthesis by producing and secreting cytokines, inflammatory proteins and hormones which are able to prevent further entry of fatty acids on the inside;
- stimulates the increase of the number of new adipocytes in order to accumulate triglycerides that are continuously introduced with the daily nutrition.

Adipocytokines

The white adipocytes produce and secrete a large number of molecules, collectively called adipocytokines or adipokines. The adipocytes have a robust protein synthesis capable of producing specific proteins in norm-volume condition, but in the presence of hypertrophy undergo a change in their protein synthesis, with production of inflammatory proteins (cytokines) [44-46]. While the majority of adipokines, such as tumor necrosis factor-α, IL-6, PAI-1 are pro-inflammatory, adiponectin on the contrary is an adipokine with anti-inflammatory, anti-diabetic, cardio protective and anti-tumor actions [47,49]. Dysfunctional adipose tissue in obesity releases a disturbed profile of adipokines with elevated levels of pro-inflammatory factors and reduced adiponectin [50]. (Figure 4)

This variation in the pathophysiology of adipocytes is the key to understanding the relationship between obesity, insulin resistance status, metabolic syndrome, diabetes mellitus type 2, atherosclerosis and several types of cancer (breast, prostate, colon, liver) [51-54].

However, it acquired the close relationship between the production of inflammatory proteins and the degree of hypertrophy of adipocytes [55,56].

Follows is a summary of the various proteins secreted by adipocytes both in conditions of normal volume and in hypertrophic adipocyte (Figure 5):

- Cytokines: TNF-α, IL-1, IL-6, IL-10.
- Transforming Growth Factor- b (TGF-b).
- Leptin, resistin, adiponectin.
- Monocyte Chemoattractive Protein-1 (MCP-1).
- CXCL5
- Haemostatic Proteins: Plasminogen Activator Inhibitor-1 (PAI-1)
- Proteins involved in blood pressure regulation: angiotensinogen.
- Angiogenic proteins: vascular endothelial growth factor (VEGF).

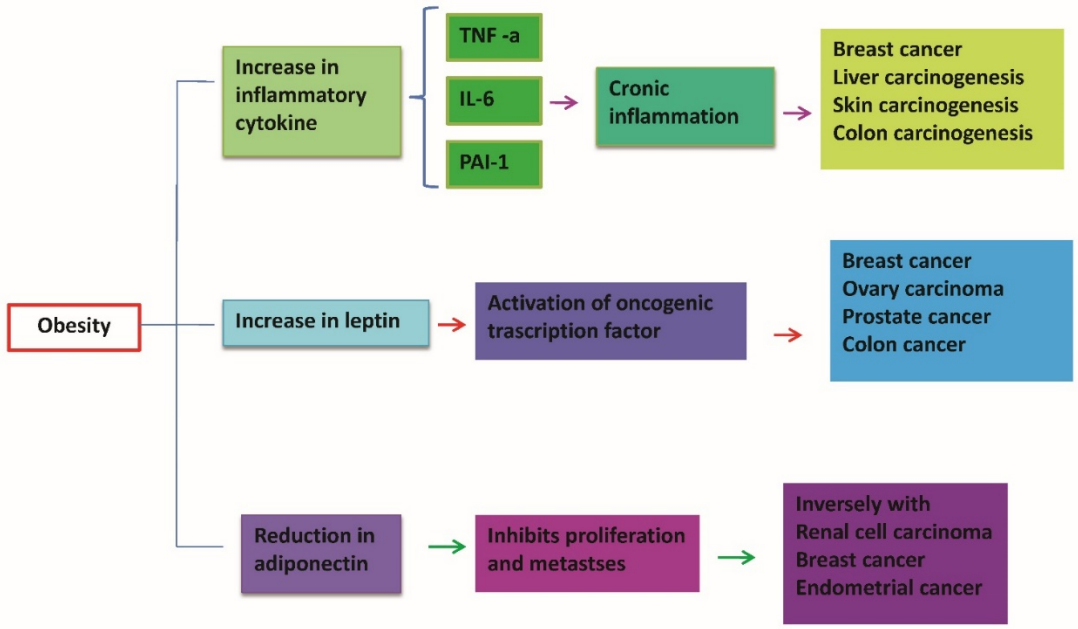

Figure 4 Dysfunctional adipose tissue in obesity is associated with disturbed profile of mediators released from this tissue establishing a state of chronic inflammation. An increase of pro-inflammatory cytokines and leptin causes a down regulation of adiponectin. This results in a reduction of anti-inflammatory and anti-tumor activity explicated by adiponectin. In obesity high levels of pro-inflammatory cytokines such as TNF-α and IL-6 act systematically and could induce oncogenic effects in distant sites such as colon, liver, breast.

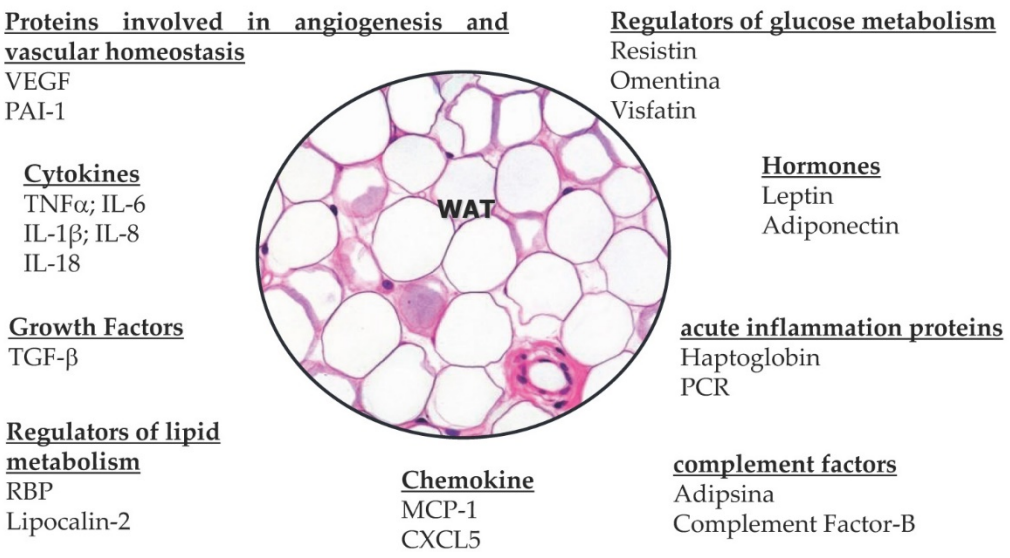

Figure 5 Summary of the various proteins secreted by white adipocytes both in conditions of normal volume and in hypertrophic adipocytes. Adipose tissue play an active role in controlling the physiological and pathological process through various adipokines. Dysfunctional adipose tissue in obesity releases a disturbed profile of adipokines with elevated levels of pro-inflammatory factors like leptin, IL-6 and TNF-alfa and reduced adiponectin that is protective against tumourigenesis. These adipokines have been implicated in cancer development and progression through their effects on insulin resistance, lipolysis and various inflammatory pathways. In the context of obesity, the hypertrophic expansion of adipose tissue induces local hypoxia, inflammatory activation and reactive angiogenesis, changes which favour tumourigenesis.

The adipokines constitute a class of proteins extremely heterogeneous, both in structural and functional terms, but have some common characteristics. From the functional viewpoint adipokines are polyvalent molecules, involved in a large number of physiological and pathological processes in fact modulate the sensitivity of peripheral tissues to insulin, regulate appetite, energy expenditure, and glucose and lipids metabolism, homeostasis, angiogenesis, blood pressure and all the axis of endocrine and reproductive systems [57-59]. In addition, many appear to be strongly related to immunity and inflammation [60,61]. Within this wide range of signals and protein factors, it is evident how the white adipose tissue plays an active role in controlling the physiological and pathological processes, in particular the metabolism and energy homeostasis [62,63]. It is precisely through the various adipokines that the white adipose tissue communicates directly with the peripheral tissues and in particular with the skeletal muscle. And above all there is an intense cross-talk between white adipocytes and brain through leptin and the sympathetic nervous system [64-66]. Following describes the two best-known hormones secreted by white adipocytes: adiponectin and leptin.

Adiponectin is the main hormone produced by mature not hypertrophic white adipocytes. It carries a powerful anti-inflammatory action, in addition to its role in modulating insulin sensitivity improving it in the liver, muscle and adipocytes [67,68]. Increase the oxidation of lipids in tissues by promoting weight loss, improves endothelium-dependent vasodilatetion, reduces the production of oxygen free radicals, has anti-inflammatory action: reduces the expression of adhesion proteins, the production of TNF-alpha and counteracts the effects on endothelial function, inhibits the differentiation of monocytes into macrophages, inhibits the activity of metalloproteases wall, inhibits the effects of LDL (low density lipoprotein) oxidized on endothelial cells of the capillaries of the microcirculation content in 'adipose organ and systemic vascular network [69,70]. Plasma levels of adiponectin are reduced in obesity in the abdomen, in the male, in postmenopausal women, in high blood pressure, hypertriglyceridemia in type 2 diabetes mellitus and coronary artery disease [71-77]. Adiponectin expression is decreased by TNF-a and IL-6, increased by PPARy agonists [78] (Figure 6). Adiponectin exerts a reduction in the proliferation of adipocyte cells, endothelial cells and tumor cells [79,80]. In addition to inhibit tumor growth and survival, adiponectin blocks angiogenesis by decreasing the expression of VEGF and Bcl-2 (anti-apoptotic) and increasing the activity of p53, Bax and caspase (pro-apoptotic), with resulting in apoptosis of endothelial cells. Likewise, adiponectin was shown to reduce TNF-α induced effects on cell proliferation and migration [81,82]. In fact, it has been shown that the reduced concentrations of adiponectin observed in obesity may represent one of the mechanisms that connect obesity with the development and progression of cancer [83-86]. importantly, adiponectin levels are decreased in

obesity-associated insulin resistance and cancer [87]. Insulin resistance is increased, with resultant elevation in insulin and bioavalible IGF1 levels, which enhance tumor cellular proliferation [88,89]. Low levels of adiponectin exert pro-inflammatory effects by means of the rise of the production of various proinflammatory cytokines including TNF-α and IL-6, favoring in this manner the onset of a permissive tumor microenvironment facilitating tumor promotion [90-92]. In several studies has been observed a negative correlation between circulating adiponectin levels and the risk of developing certain types of cancer such as colorectal, breast, pancreatic, liver and prostate cancer [93-96]. Low adiponectin levels are potentially associated with carcinogenesis [97-99]. The adiponectin protective effects in tumors also include the inhibition of leptin proliferative signaling and inducing cell apoptosis [100-101].

Leptin is produced by white "normal" adipocytes and hypertrophic adipocytes, acts as a key mediator in body weight regulation [102]. Once entered into the blood stream, reach the brain, where it provides a critical hormonal signal to the hypothalamus in the regulation of appetite and energy expenditure: inhibition of appetite [103]. The production of this hormone is closely related to adipose tissue mass and volume of adipocytes: an increase in body fat, especially visceral fat, as well as a diet high in calories is associated with an increase in circulating levels of leptin where weight loss results in a reduction of the same [104,105]. The production of leptin is to limit the continuous entry of fatty acids in adipocyte hypertrophic, choice of defense needed to prevent cell death by excessive volume. Under conditions of obesity can develop a state of leptin resistance and therefore the actions ensured by this adipocyte hormone cannot be exercised [106,107] (Figure 7). Leptin is currently at the centre of the obesity-cancer link, as it is produced in proportion to fat mass and potently induces cell mitogenesis, growth and motility [108-110]. Mature adipocytes secrete both adiponectin and leptin with preadipocytes showing a primarily secretion of high leptin levels [110-112]. An increase of preadipocyte pool in obese subjects is related to an increase in leptin levels, with proangiogenic and promitogenic properties [113,114]. Simultaneously, high levels of leptin leads other inflammatory cells stimulating the differentiation of monocytes into macrophages favoring in this manner the state of chronic inflammation obesity-associated [115]. In summary, leptin has an important role in the development of a large variety of malignancies increasing the expression of anti-apoptotic proteins, inflammatory markers (TNF-a, IL-6), angiogenic factors (VEGF), and also the hypoxia-inducible factor-1a (HIF-1a) [116,117]. These processes promote cancer cell survival, proliferation and migration [118,119].

The activation of the inflammatory process occurs in the case of hypoxia or when the availability of oxygen is not adequate to the demands of white and brown adipose tissue. This results in a decrease in oxygen tension that activates the transcription factor HIF-1 (Hypoxia Inducible Factor-1) and generates a number of negative effects [120]:

- Inhibition of adiponectin production by white adipocytes;
- Induce a state of insulin resistance;
- Ischemia and necrosis of white adipocytes;
- The production of angiogenic factors;
- The release of inflammatory cytokines;
- Increased production of free radicals can also damage the DNA of the same adipocytes.

In conclusion, hypoxia of adipocytes is the key link between the initial cell damage and activation of the inflammatory process [121,122].

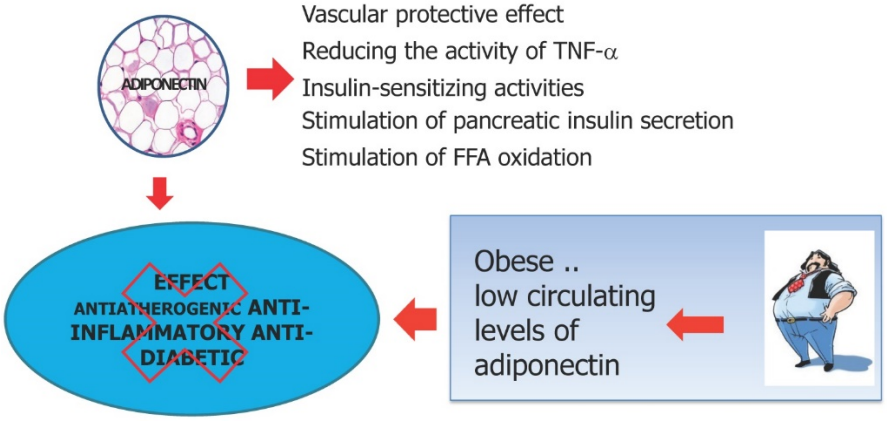

Figure 6 In obese subjects lower adiponectin levels lead to a reduction of the anti-inflammatory antidiabetic and antitumor power explicate by adiponectin. Decreased levels of adiponectin leads to a state of insulin resistance by cytokine-mediated inflammation contributing to the tumor permissive microenvironment that facilitates tumourigenesis.

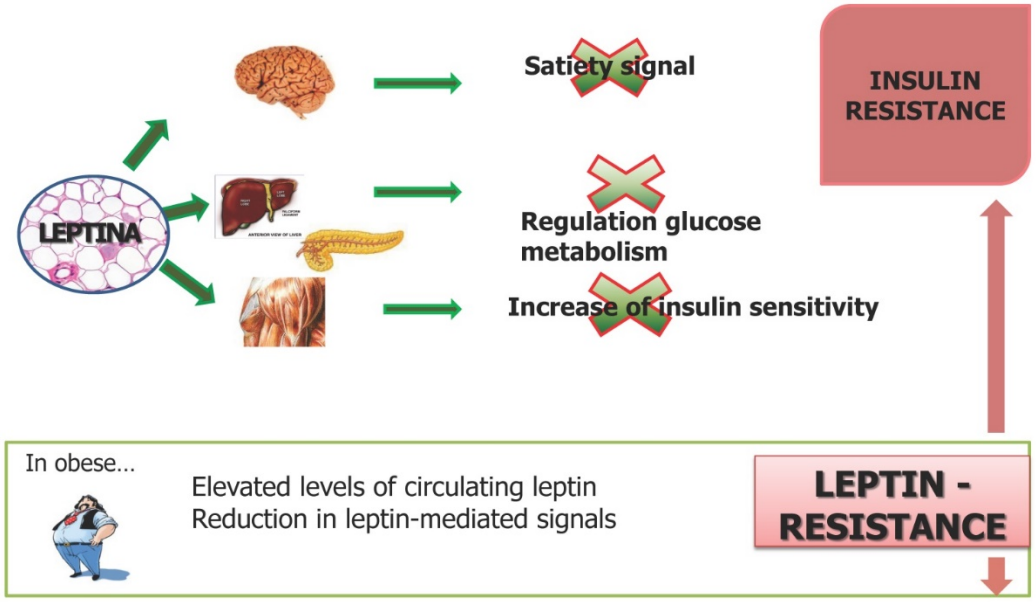

Figure 7 Leptin plays important action in regulating glucose metabolism, in the satiety signal and increase insulin sensitivity. Under conditions of obesity can develop a state of leptin resistance and therefore the actions ensured by this hormone cannot be exercised. In obese subjects an increase of adipocytes is related to an increase in leptin levels that activates inflammatory cell response and induces pro-inflammatory cytokine production maintaining the obesity-associated state of chronic inflammation. In this context increased leptin levels lead to increased expression of anti-apoptotic, pro-inflammatory and angiogenic factors that promote proliferation and migration of cancer cells.

White adipocytes and inflammation: the inflammatory Triad

The hypertrophic hypoxic white adipocytes present alteration of the extracellular matrix and collagen. In this condition activating their capacity to adapt to aggressive situations, changing their natural protein synthesis and directing the production of their proteins to cytokines, inflammatory proteins damaging cells and entire systems anatomy of the body [123]. Hypertrophy associated with subsequent hypoxia, is therefore the functional transition to generate a "change" of protein synthesis to local and systemic inflammatory agents [124]. There is an axis between white hypertrophic adipocytes secreting inflammatory proteins and functional status of the endothelium of the capillaries and systemic fat [125]. The inflammatory proteins secreted by hypertrophic and hypoxic white adipocytes are the primary cause of atherosclerosis, state of insulin resistance, high blood pressure, type 2 diabetes mellitus, metabolic syndrome, bone joint and muscle tendon degeneration [126-128]. Furthermore links between obesity and inflammation and between chronic inflammation and cancer may suggest that inflammation may be important in linking obesity to cancer [129-132]. Virchow over 100 years ago, emphasized the link between chronic inflammation and cancer development. He observed the increased presence of leukocytes in neoplastic tissue [133,134]. Since then, the role of chronic inflammation has been observed in multiple cancer types. Like adipose tissue, tumor microenvironment is composed of multiple cell types including epithelial cells, fibroblasts, mast cells, and cells of the innate and adaptive immune system that favors a pro-inflammatory and pro-tumorigenic environment [135,136].

Belong to the group of inflammatory cytokines:

- Tumor Necrosis Factor-alpha (TNF-α)
- Interleukin-1 (IL-1)
- Interleukin-6 (IL-6)

which constitute a "triad inflammatory" that acts in adipose tissue and of all the other cells of the whole organism [137]. Obesity causes chronic inflammation silent that is without symptoms, in charge of related diseases with functional and aesthetic decay of the whole organism [138]. The triad inflammatory (TNF-α, IL-1, IL-6) shall set up actions aimed at integrity adipocyte hypertrophy and hypoxic in the organ fat and aggressive actions whole body level with inflammatory degenerative diseases [139,140].

Tumor necrosis factor-a. Another pro-inflammatory cytokine secreted by adipocytes is TNF-α, increased secretion of this cytokine is found in obese subjects [141]. More than two decades ago TNF-α was first described as a cytokine with antitumor properties but later when its antitumor activity was tested on cancer patients became apparent its active role in promoting cancer [142]. Thereafter has been observed that the proinflammatory role of TNF-a becomes involved in

all stages of tumorigenesis that include tumor cell transformation, survival, proliferation, invasion, angiogenesis and metastasis [143]. Animal models have shown a positive relationship between TNF-α and tumor development and progression in liver and colorectal cancer with elevated circulating concentrations in different tumor types [144-146]. In addition, TNF-α is not only produced by a wide variety of tumor cells but also by adipocytes. Levels of TNF-α are increased in obesity, indicating a role for this cytokine in the obesity-associated inflammation and particularly in insulin resistance and diabetes [147,148].

Interleukin-6 Another cytokine produced by adipose tissue belonging to the group of pro-inflammatory cytokines is IL-6 whose levels are increased in obese subjects [149,150]. IL-6 is a key modulator in inflammation-associated carcinogenesis, regulates the expression of genes involved in the different steps of tumor growth and progression via the JAK/STAT signaling pathway [151,152]. In fact a relationship between IL-6 and carcinogenesis has been shown for several types of cancer and elevated circulating level correlate with disease aggressiveness and poor prognosis [153-157].

Interleukin-1 Interleukin-1 is a regulatory cytokine expressed in both normal tissues and in tumor cells. IL-1 can lead to the activation of transcription factors such as NF-kB and AP-1, and promote the expression and promote the expression of genes that regulate the mechanisms of survival, proliferation and tumor angiogenesis [158]. In obesity-related inflammation, IL-1 over-regulates HIF-1a protein through a classical NF-kB/COX-2 inflammatory signaling pathway culminating in up-expression of the angiogenic factor VEGF needed for tumor growth and metastasis [159].

The following summarizes the actions of inflammatory triad:

1. Reduction and block of capillaries lipoprotein lipase synthesis. The reduction and the absence of this enzyme on the wall of the capillaries in the adipose organ prevents the release of triglycerides from circulating VLDL in the blood, and then the non-entry of fatty acids into adipocytes; the value of triglycerides and cholesterol in the blood increases [160,161].

2. Blocking of insulin receptors of adipocytes. This block implies a state of insulin resistance initially in the fat organ, subsequently of the whole body, particularly in muscles with increased glucose and insulin in the blood until the onset of diabetes mellitus type 2 [162-163].

3. Activation of lipoprotein lipase hormone sensitive in adipocytes with breakdown of triglycerides accumulated in hypertrophic white adipocyte, output of free fatty acids (FFA) with a consequent reduction in volume. Excess of FFA in the blood cause fatty liver and insulin resistance in the muscles, increasing glucose and insulin in the blood until the onset of diabetes mellitus type 2 [164].

4. Endothelial Inflammation. Exists an axis between hypertrophic and hypoxic white adipocytes secreting inflammatory proteins and functional status of capillaries endothelium of the adipose organ tissue and systemic vascular with the entire systemic vascular network (atherosclerosis and vein diseases) [165,166]. (Figure 8)

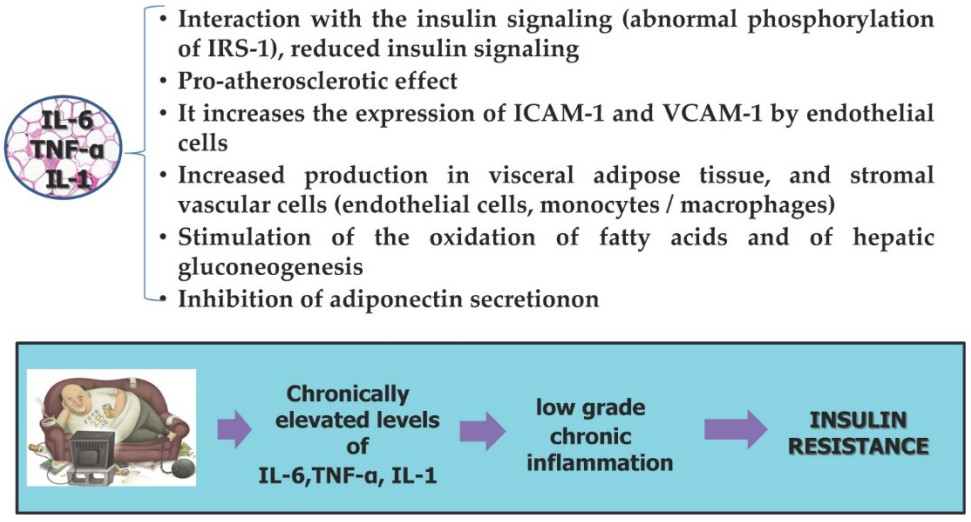

Figure 8 Actions of inflammatory triad. Obesity causes chronic silent inflammation with subsequent increased secretion of inflammatory triad cytokines and decreased production of adiponectin that make unable adipose tissue to store the surplus of free fatty acids contributing to a development of insulin resistance, type 2 diabetes, and obesity-related cardiovascular disease. The mitogenic and anti-apoptotic environment caused by elevated levels of insulin in obesity accelerates the stepwise accumulation of mutations and, hence, favor carcinogenesis. TNF-a, IL-6 and IL-1 signaling, enhancing carcinogenesis by increasing cell proliferation and neoangiogenic cell properties. In addition, the inflammatory enhancing expression of VEGF, ICAM-1 and VCAM-1 by endothelial cells.

Adipocytes, inflammation and insulin resistance

One of obesity-related diseases is insulin resistance considered a major risk factor for cancer development and has been associated with poor prognosis for several cancers [167,168].

The hypoxic hypertrophic adipocytes and macrophages in addition to an increase of the production of inflammatory cytokines TNF-α, IL-1, IL-6 also reduce the production of adipocyte hormones protective, including adiponectin [169,170]. The whole of these pathological changes leading to the appearance of a state of insulin resistance, which is established through different mechanisms still only partly elucidated:

- direct mechanism that includes the deactivation of the substrate of the insulin receptor (ISR-1) by phosphorylation of serine and threonine residues by inflammatory mediators such as IL-6 and TNF-α [171];
- Indirect mechanism caused by the increase in free fatty acids (FFA) in the circulation, which cause an increase of other mediators of inflammation (e.g. NF-KB), implicated in insulin resistance [172,173].

The insulin resistance is a condition characterized by not active insulin that is due to reduction of the receptors located in the cell membranes of adipose tissue and muscle, with an increase of blood glucose and insulin [174,175]. The defect of insulin action makes the fatty tissue less able to store glucose and fatty acids and fatty tissue as a compensatory response seeks to expand further through hypertrophy, but mostly hyperplasia [176]. In patients with insulin resistance there is an increase in glucose and insulin levels due to a reduced sensitivity of tissues to insulin [177]. In chronic hyperinsulinaemia it is observed increased secretion of IGF-1 and a reduced production of binding proteins so it results a further increase in circulating levels of IGF [178]. Through the IGF receptor, IGF activates downstream signaling pathways that promote mitogenic and proangiogenetic pathways and inhibit apoptosis [179]. The insulin and adipokine cancer hypotheses overlap, since he insulin-resistant state is mediated, at least in part, by cytokine-mediated inflammation [180]. The cytokines promote the insulin resistance which in turn leads to a state of chronic low-grade inflammation of the adipose tissue by establishing a favorable microenvironment for tumor promotion [181,182].

White adipocytes: hypoxia, ischemia and oxidative stress

The adipocyte hypertrophy generates obstruction of capillaries with hypoxia and ischemia both individual white adipocytes (hypertrophic and hypossic) that the brown adipocytes [183]. For hypoxia means a pathological condition caused by a lack of oxygen in the blood or in adipose tissue, while ischemia is a condition caused by an inadequate blood flow [184]. Hypertrophy of white adipocytes damages the microcirculation, the vascular network of the entire organ adipose creating conditions of obstruction and constriction of capillaries with endothelial damage in the white and brown adipose tissue [185,186]. Furthermore, the progressive hypertrophy of white adipocytes and the expansion of the white adipose tissue make the same adipocytes more away from the vascular network, with reduction of the volumes of oxygen available [187]. The adipose organ is a major consumer of oxygen and the condition of hypoxia/ischemia generates a greater state of oxidative stress, able to direct the white adipocytes hypertrophic/hypoxic and towards the secretion of inflammatory proteins and brown adipocytes towards a situation of dysfunction [188,189]. The brown adipocyte is much richer in capillaries and requires significant volumes of oxygen to ensure adequate oxidation of fatty acids and ensure proper body temperature [190]. A hypoxic condition in brown adipocytes promotes the reduction of thermo genesis, i.e. the production of heat, and oxidation of fatty acids, with sensation of cold and continuous weight gain because the fatty acids are deposited in white adipocytes [191-193]. Moreover, in conditions of hypoxia and ischemia the brown adipocytes produce significant amounts of reactive oxygen radicals (Radical Oxygen Species, ROS) that damage their mitochondrial functionality [194-196]. Hypoxia occurs when oxygen availability is not adequate to the demand of both white and brown adipose tissue [197]. This results in a decrease in oxygen tension that activates the transcription factor HIF-1 (Hypoxia Inducible Factor-1) and generates a series of negative effects:

- inhibition of production of adiponectin by white adipocytes;
- induction of a status of insulin resistance;
- ischemia and necrosis of white adipocytes;
- production and release of inflammatory cytokines and angiogenic factors;
- Increased production of free radicals which are able to also damage the DNA of the same adipocytes.

In conclusion, hypoxia and ischemia of adipocytes are the key link between the initial cell damage and activation of the inflammatory process [198-207].

Adipocytes and cancer

Adipose tissue is composed by a heterogeneous cell population mostly represented by adipocytes. Other cellular components including endothelial cells, macrophages, pericytes and adipocytes progenitor cells [208,209]. In adipose tissue interaction between adipocytes and stromal vascular cells contribute to tumor development and progression. Some types of tumors such as breast develop in proximity of adipocytes and metastasize in an environment mainly dominated by adipocytes such as the abdominal cavity [210]. Growth and metastasis of these tumors reflect the important role of the numerous adipocytes present in the microenvironment for tumor maintenance progression [211,212]. Microenvironment within local adipose deposits clearly provides a tumor permissive niche for transformed, infiltrating cells. During cancer progression cancer associated adipocytes undergo considerable morphological and functional alterations acquiring a fibroblast-like phenotype [213,215]. This phenotypic change involves a loss of expression of adiponectin and leptin the markers of terminal adipocyte differentiation. As a result an increase in the secretion of pro-inflammatory cytokines such as IL-6, TNF-α and PAI-1 that create a favorable environment inducing tumor cells to acquire a phenotype with major invasiveness and aggressiveness [216-220]. Alterations of the signaling mechanisms of the key mediators in obesity could represent determining factors for the establishment of a peritumoral environment to promote the development and tumor progression. In the light of information provided in this review we support that inflammatory state specific of obesity may be important in obesity-cancer link. Nevertheless, the molecular basis of the interactions that exist between the key mediators of tumor cells and adipocytes, which promote the establishment of a permissive tumor microenvironment is still unclear.

Conclusion

The results led to the hypothesis that an unfavorable adipokines profile with a reduction of adipokines with anti-inflammatory or anti-tumor activity could provide a comprehensive insight into the understanding of the molecular mechanisms involved in carcinogenesis related to obesity. This can provide the specific targets that are involved in those mechanisms whereby obesity leads to tumor progression. In conclusion, in obese subjects may become useful to follow a path to preventing cancer and its progression reduction plan to stop the inflammatory cascade, improve insulin sensitivity and contrast the factors that induce hypoxia.

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Conflict of interest

None declared.

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