Obesity and Increased Risk for Atherosclerosis and Cancer

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Abstract

During obesity and overweight is present in adipose tissue an imbalance in macrophage activation polarization with prevalence of M1 phenotype. This functional phenotype promotes a proinflammatory state characterized by Th1 type response sustained with a mechanism of cross-talk between macrophages and adipocytes. Obesity-related dysregulation in adipokines secretion and derangement in sex steroid hormone metabolism such as insulin may concur also. These changes may contribute to the development of atherosclerosis and cancer.

Keywords: Obesity; Macrophages; Adipocytes; Atherosclerosis; Cancer

Introduction

The International Agency for Research on Cancer (IARC) has determined that people who are overweight or obese are at increased risk of developing several cancer types. The proposed mechanisms are chronic hyperinsulinemia linked to the insulin resistance obesity-related, increased circulating levels of insulin-like growth factor-1 and oestrogens adiposity-related. The Atherosclerosis Risk in Communities studies (ARIC study) shows that obesity is risk for the development of carotid artery intima-media thickness: this is an index of generalized atherosclerosis. The proposed mechanisms are some immunomodulatory cytokines/chemokines and adipokine dysregulation obesity-related. The aim of the study is to suggest a general hypothesis in pathogenic mechanism of the increased risk for atherosclerosis and cancer obesity-related.

Macrophages and Adipocytes: General Aspects

Tissue macrophages have a broad role in the maintenance of tissue homeostasis through the clearance of senescent cells, the invading microorganisms, the remodeling and repair of tissue after inflammation so they play an important role in both the innate and acquired immune response: this heterogeneity reflects the specialization function that is adapted by macrophages in different anatomical locations. This macrophage heterogeneity in different organs is linked to their activation which includes distinct phenotypes (polarization) and physiological activities [1-3].

The classical activation (M1) is associated with high microbicidal activity, pro-inflammatory cytokines production, generation of ROS and cellular acquired immunity (Th1-type response). This activation is mediated by ligation of the inflammatory stimuli to the receptors such as Toll-like receptors. The alternative activation (M2) is associated with tissue repair, anti-inflammatory cytokine production and acquired humeral immunity (Th2-type response). This activation is mediated by ligation of the stimuli to the receptors such as CD200 or CD172a. This phenotype is further subdivided into M2a, M2c [4,5].

Therefore the plasticity and differentiation of macrophages into M1 and M2 functional phenotypes represents extremes of a continual spectrum of differential pathways depending on the recognition receptors used and subsequent intracellular signal pathway transduction induced by receptor activation. The pattern of macrophage recognition receptor include the so called mannose receptor and scavenger receptor [6,7] (Table 1).

<table>
<thead>
<tr>
<th>Activating Signals</th>
<th>Classical (M1)</th>
<th>Alternative (M2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptor Activation</td>
<td>IFNgamma/LPS</td>
<td>IL-4/IL-13</td>
</tr>
<tr>
<td>Signal transduction</td>
<td>TLR-4/INFgamma-R</td>
<td>ILR</td>
</tr>
<tr>
<td>Chemokine Production</td>
<td>CXCL8/CXCL10/MPI-1/ RANTES</td>
<td>CCL22/CCL17</td>
</tr>
<tr>
<td>Cytokine Production</td>
<td>TNFalpha/IL-6/IL-12</td>
<td>IL-1/IL-10/IL-4/IL-13/ TGFbeta</td>
</tr>
<tr>
<td>Metabolic Factors</td>
<td>NO/ROS/MMP-1,2,3</td>
<td>Enzyme Arginase 1(upregulated)</td>
</tr>
<tr>
<td>Th1 Response</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Th2 Response</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Physiological Effect</td>
<td>host defense/cellular immunity</td>
<td>antiinflammatory/wound repair</td>
</tr>
<tr>
<td>Pathological Effect</td>
<td>chronic cancer inflammation/ allergy/DTH</td>
<td></td>
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</tbody>
</table>

Table 1: Comparison of macrophage activation states and functions. The M1 and M2 macrophage phenotype polarization represents extremes of a continual spectrum of differential pathway depending on the recognition receptors activated with subsequent intracellular signal pathway transduction induced. During obesity is present an increase in M1 macrophage polarization. Every macrophage phenotype may have physiological and pathological effect. The M1 macrophage physiological effects are proinflammatory such as host defense, cellular immunity, and direction of adaptive immune system whereas pathological effects are chronic inflammation, cancer, type I autoimmune disease. The M2 macrophage physiological effects are...
anti-inflammatory such as wound repair, remodeling and tumoral immunity whereas pathological effects are allergy, asthma, delayed type hypersensitivity. Chemokines are so named because they are cytokines that induces chemotaxis, or directed migration, of leukocytes subsets by binding to specific G-protein-coupled cell surface receptors on target cells.

IFN: Interferon; LPS: Lipopolysaccharide; IL: Interleukin; TLR: Toll Like Receptor; Ifn-gamma-R: Interferon Gamma Receptor; ILR: Interleukin Receptor; NfkB: Nuclear Factor Kappa B; ESRK: Extracellular Signal-Regulated Kinase; TNF: Tumor Necrosis Factor; RANTES: Regulated on Activated Normal T-Cell Expressed and Secreted; TGF: Transforming Growth Factor; NO: Nitric Oxide; ROS: Reactive Oxygen Species; MMP: Matrix Metalloproteinase; Th1: T Helper Cell Response Type 1; Th2: T Helper Cell Response Type 2; DTH: Delayed Type Hypersensitivity

Adipose tissue is generally considered to exist in “brown” and “white” forms which together constitute the “adipose organ” but recently has been described an intermediate type [8].

Adipose tissue is composed of many cells types, mature adipocytes being the most abundant whereas the other cell types present are included in the stromavascular fraction [9]. White adipose tissue is the site of energy storage as triglycerides being specialized for the production of heat through the presence of the mitochondrial uncoupling proteins whereas the main role of brown tissue is nonshevering thermogenesis [10].

White adipose tissue is not only an energy store but it is involved in a number of functions as an endocrine organ and can secrete immune system-related proteins (adipocytokines, ASP, MIF, TNF-alpha) and vascular function-related proteins(angiotensinogen,PAI-1,VEGF) [11].

Analysis of the scientific literature revealed that the adipocytes and macrophages have many features in common [12-14].

The macrophages can infiltrate adipose tissue by diapedesis from the systemic circulation as monocytes or can transdifferentiate from local adipose tissue preadipocytes and mesenchimal stem cells. The molecular basis for diapedesis is provided by the fact that the adipocytes secrete a wide variety of chemoattractants that direct monocytes from the circulation into fat stores and the adipose tissue can support locally the differentiation and maturation of monocytes into macrophages.

**Obesity and Macrophages**

Macrophages accumulate within the white adipose tissue of obese mice proportionally to adipocyte size and number.

In lean mice adipose macrophages are polarized toward an alternatively activated state M2 whereas in obese mice have an M1 profile (proinflammatory state) [15]. How does obesity switch adipose macrophages from M2 to an M1 activation state characterized by Th1 type response (proinflammatory response)?

Adipose tissue becomes hypoxic in obesity and adipocyte cellular hypoxia may be a basis for the proinflammatory response in obesity [16,17]. Hypoxia may affect other cellular components of adipose tissue such as macrophages: these cells are capable of increasing their inflammatory response in the face of hypoxia [18] and more recently in the specific context of adipose tissue [19]. The finding that macrophages are present around areas of hypoxic adipocytes in adipose tissue may suggest that tissue hypoxia could provide a means of macrophage recruitment [20]. The increased productions of monocyte chemoattractant protein-1(MCP-1) and macrophage inhibitor factor-1(MIF-1) have been proposed as key determinants of macrophage infiltration and enhanced inflammatory response [21].

The identification of fatty acids, LDL, ox-LDL as endogenous ligands for peroxisome proliferator-activated receptors (PPARs) has provided a unique approach to study lipid homeostasis at the molecular level in higher organisms [22]. Adipocyte PPAR gamma activation by fatty acids, LDL, ox-LDL is essential for lipid storage inside adipocytes playing an important role in lipid flux and efflux [23]; in obesity major lipid influx inside the adipocyte cell leads to the inflammatory pathways by the intracellular stresses such as endoplasmic reticulum stress or excess of ROS production by mitochondria with activation of signaling cascades JNK/IKK inducing lipolysis and adipocyte releasing fatty acids that activate macrophages [24]. Macrophages PPR gamma activation by fatty acids, LDL, ox-LDL controls alternative activation of macrophages in adipose tissue and is required for maturation of alternatively activated macrophages [25]; the PPAR gamma activation induces the expression of the adipocyte fatty acids binding protein gene in human monocytes also. Macrophage activated secretes proinflammatory cytokines such as TNF that may stimulate the TNF-R1 (TNF receptor 1) on adipocytes inducing NF-kB activation pathway inside the adipocyte cell.

Adipocyte PPAR gamma activation by fatty acids, LDL, ox-LDL is also essential for lipid storage inside adipocytes so the adipocyte play an important role in lipid flux and efflux: in obesity the major lipid influx inside the adipocyte cell leads to the adipocyte inflammatory pathways activation by the intracellular stress such as endoplasmic reticulum stress or excess of reactive oxygen substance production by mitochondria with activation of signaling cascades JNK/IKK inducing lipolysis and adipocyte release of fatty acids that activate macrophages.

Finally the activation of the adipocyte and macrophage Toll like receptors signaling system (such as TLR4) by fatty acids results in NF-kB activation via ESRK/JNK signaling pathway with subsequent release of cytokines, chemokines and adipokines [26,27]. This activation could be also obtained by lipopolysaccharide (LPS) circulating in plasma which during obesity is increased because of is continually produced within the gut by the death of gram-negative bacteria and is absorbed into intestinal capillaries and transported by lipoproteins as observed in experimental model of obesity in mice (metabolic endotoxinemia).

These mechanisms could be named a paracrine cross-talk between macrophages and adipocytes during obesity that leads to the proinflammatory state.

This obesity proinflammatory state is sustained by the white visceral adipose tissue that as an endocrine organ induces in obesity a change in plasma level of immunomodulatory adipokines such as adiponectin and leptin and by macrophages switch polarization in M1 phenotype that produces proinflammatory cytokines and chemokines such as TNF-alpha and interleukin-6.

**Macrophages, Obesity and Atherosclerosis**

Many factors contribute to the development of atherosclerosis. Under normal conditions, the vessel wall has its own machinery to maintain vascular homeostasis. However, the balance is broken when repetitive metabolic stimuli resulting from hypertension, insulin...
resistance or obesity strike the vessel wall. Most of these stimuli disturb homeostasis through the initiation of inflammation that is the recruitment of inflammatory cells, the increased adhesion molecules, secretion of chemoattractant and proinflammatory cytokines from the endothelial cells and the migration and proliferation of smooth muscle cells from media [28]. During obesity among the top contributors of inflammatory stimuli of vessel wall are some immunomodulatory cytokines/chemokines and adipokines (Table 2).

<table>
<thead>
<tr>
<th>Chemokine</th>
<th>TNF-alpha</th>
<th>IL6</th>
<th>MCP-1</th>
<th>MIF</th>
<th>Adpn</th>
<th>Leptin</th>
<th>Resistin</th>
<th>Visfatin</th>
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<tr>
<td>Cytokine</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
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<td>CCR2</td>
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<td>R1/2</td>
<td>OB-R</td>
<td>(?)</td>
<td>RI</td>
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<td>Transduction signaling</td>
<td>JNK</td>
<td>JAK</td>
<td>STAT</td>
<td>G-protein</td>
<td>p38MAPK</td>
<td>AMPK</td>
<td>PPAR-alpha</td>
<td>JAK</td>
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<tr>
<td>Metabolic regulation</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>(+)</td>
<td>(+)(-)</td>
<td>(+)(-)</td>
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<tr>
<td>Effects</td>
<td>+ IR</td>
<td>+ IR</td>
<td>+ IR</td>
<td>- MM</td>
<td>+IS</td>
<td>ME</td>
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<td>Associated diseases</td>
<td>D2</td>
<td>Ah</td>
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<td>CA</td>
<td>IBD</td>
<td>RA</td>
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Table 2: Immunomodulatory cytokines, chemokines, adipokines during obesity. Cytokines have an autocrine or paracrine action but not endocrine and chemokines are cytokines with action on chemotaxis. Cytokines are expressed in a wide range of cell types and tissues; they are proteins with receptor based mechanism of action. Cytokines induce cell migration and activation by binding to specific G-protein-coupled cell-surface receptors on target cells thus activating multiple intracellular signaling pathways that regulate the intracellular machinery necessary to propel the cell in its chosen direction. Adipokines are proteins first named adipocytokines and subsequently the term adipokines has been introduced: the name adipokine is to be preferred since the expression adipocytokines carries the interference that the secreted proteins are adipocytes, is present in the blood stream in three main forms and two adipokine receptors (Adipo R1-R2) have been identified [29-32]. In cell culture, in animals and human studies Adnp appears to have a protective effect on the cardiovascular system via its anti-atherogenic and anti-inflammatory effects [33]. Adnp inhibits in macrophages TNF-α induced activation of NF-KB dependent proinflammatory pathway, lipid accumulation to form foam cells by blocking macrophage scavenger receptor class A, in endothelial cell reduces...
expression of endothelial adhesion molecules and oxidative stress, reduces smooth muscle cells proliferation, migration and attenuates fibrous cap formation [34,35].

Adiponectin (Adpn) plasma concentration is decreased in obesity [36]. Hypoadiponectinemia has been associated with coronary lesions and acute coronary syndromes and its involvement in the development of atherosclerosis appears to be more related to the stability of the atherosclerotic plaque than the atherosclerotic burden [37,38].

Leptin is a peptide hormone synthesized and secreted specifically by adipocytes encoded by the obese gene (ob) [39]. Leptin receptor (OB-R) has been identified with ubiquitous distribution in the central nervous system and the periphery [40]. In cell culture, in animals and human studies leptin appears to have a dangerous effect on the cardiovascular system via its atherogenic and proinflammatory effects [41]. Leptin potentiates secretion of tumor necrosis factor alpha (TNF-α) and interleukin 2 and 6, increases generation and accumulation of reactive oxygen species and enhances expression of monocyte chemoattractant protein-1 [42,43]. Leptin stimulates production of proinflammatory cytokines and enhances production of Th1-type cytokines. In endothelial cells leptin stimulates transforming growth factor-β synthesis whereas in smooth muscle cells stimulates migration and proliferation of vascular smooth cells and expression of matrix metalloproteinase-2 [44,45].

Leptin is increased in obesity [46] but leptin resistance more than hyperleptinemia seems contribute to the atherosclerosis development during obesity because of several clinical studies shows that hyperleptinemia predicts acute cardiovascular events independent of traditional risk factors [47].

Resistin, also known as FIZZ3 belongs to a family of cysteine-rich proteins termed resistin-like molecules (RELMs) is a 114-aminoacid polypeptide encoded by the Rein gene [48]. Resistin was shown to circulate in two distinct assembly states detected in rodents and humans [49] and up-regulates COX-2 expression via TAK-1-IKK-NFκB signaling pathway so appears to have a proinflammatory activity but the receptor for resistin is unknown [50]. Several studies have examined resistin as a cardiovascular risk factor and a potential contributor to endothelial dysfunction and atherosclerosis lesion formation [28]. Such studies have shown resistin stimulates factors including endothelin-1, vascular cell adhesion molecule-1, monocyte chemoattractant protein-1, thus contributing to cardiovascular disease [51]. Hyperresistinemia in animals such as rabbit seems to be a key player to modulate monocytes, endothelial cells and smooth muscle cells leading to progression of atherosclerosis in carotid artery and in humans during obesity seems to promote atherosclerosis in atheromas where is secreted from macrophages [52,53]. Serum resistin is increased in obese humans [54].

Human Visfatin also termed nicotinamide phosphorylase (Nampt), identified as a protein involved in immune B-cell maturation (pre-beta colony enhancing factor, PBEF) is ubiquitously expressed in all tissues [55,56]. The visfatin gene spans a length of 34.7 kb on the long arm of chromosome 7q22 and may differentially expressed in different tissues [57]. Receptor for visfatin is unknown. Visfatin exerts a mainly intracellular role where has Nampt activity and catalyzes the rate-limiting step in nicotinamide adenine dinucleotide (NAD) biosynthesis (i.e. the conversion of nicotinamide to nicotinamide mononucleotide (NMN) [58]. In cell culture, in animals and human studies visfatin appears to be an adipocytokine with proinflammatory and immunomodulating properties in cardio-cerebro-vascular disease [59] because of activates proinflammatory signaling in human vascular smooth muscle [60], increases leukocyte adhesion to endothelial cells by induction of cell adhesion molecules such as VCAM-1, increases nuclear factor-kappaB(NF-κB), vascular endothelial growth factor (VEGF), metalloproteinases 2/9 (MMP 2/9), monocyte actrant protein-1(MCP-1) [61-65]. Visfatin has been implicated in the pathogenesis of unstable atheroma because of visfatin gene expression is markedly enhanced in carotid plaques from symptomatic compared with plaques from asymptomatic individuals [66] and visfatin tissue levels of epicardial fat tissue from patients with coronary heart disease (CHD) are higher than non-CHD control subjects [67]. There are controversies regarding the circulating levels of visfatin in obesity and possibly explanations for the variability has been proposed [68]. In patients with metabolic syndrome circulating levels of visfatin have been observed significantly higher in those with carotid plaque than in those without carotid plaques and visfatin independently correlated with maximum carotid intima media thickness [69].

**Obesity and Cancer**

The International Agency for Research on Cancer (IARC) has determined that, based on results from epidemiological studies, people who are overweight or obese are at increased risk of developing several cancer types, including adenocarcinoma of the oesophagus, colon cancer, breast cancer (in postmenopausal women), endometrial cancer and kidney (renal-cell) cancer [70,71]. Epidemiological evidence, such as the Population Attributable Fraction [72] defined as the proportion or percentage of disease in a population that is attributable to a given risk factor, indicate that the above mentioned cancers are obesity-related in United State population and European population while other cancers are likely obesity-related (cancers of pancreas, liver, gold bladder, gastric, cardio).

For other cancers (lung, cervical cancer, and ovarian cancer) epidemiological studies of the association between overweight/obesity and cancer are inconclusive and limited but suggestive for a link.

Few studies have examined the relationship between hematopoietic cancers and overweight/obesity [73].

At present, the strongest empirical support for mechanisms to link obesity and cancer risk involves the metabolic and endocrine effects of obesity and the alterations that they induce in the production of peptide and steroid hormones.

In obesity the increased release from adipose tissue of free fatty acids, tumor necrosis factor alpha, switch polarization in M1 state of macrophages and the hyperresistinemia, hyperleptinemia, hypoadiponectinemia lead to development of insulin resistance and compensatory hyperinsulinaemia (chronic hyperinsulinaemia). Increased insulin levels in turn, lead to reduced liver synthesis and blood levels of insulin-like growth factor binding protein 1 (IGFB1) and probably also reduce IGFB1 synthesis locally in other tissues.

Increased fasting levels of insulin in the plasma are generally also associated with reduced levels of IGFB2 in the blood. This results in increased levels of bioavailable insulin growth factor 1 (IGF1). In the target cells the insulin and IGF1 signal through the insulin receptor and IGF1 receptor, respectively, promotes cellular proliferation and inhibits apoptosis: the effects of these peptides might contribute to tumorigenesis (Table 3).
forms. the PI3K/AKT and MEK/ERK signalling pathways [76]. Leptin roles in regulating cell migration in thyroid cancer cells [75] because of contribute to tumorigenesis [73].

delta4-androstemedione (d4A) and testosterone (T) into the active hormones T and E2, respectively. Is ATMs isolated and compared with monocyte-derived macrophages from the same obese patients shows that ATMs only modulate cancer cell function and the concentrations of ATMs-secreted factors related to cancer are elevated in serum of obese patients [82].

So the human adipose tissue macrophages display activation of cancer-related pathways.

Discussion

Nowadays the link between obesity-related inflammation and risk for atherosclerosis development is established in adipokine dysfunction as inflammatory pathogenic mechanism for arterial vessel wall.

In apoliporotein E deficient mice adiponectin reduces atherosclerosis [83]. It has been observed a close association of hypoadiponectinemia with atherosclerosis obliterans and ischemic heart disease [84] and plasma adiponectin concentration in relation to severity of coronary atherosclerosis and cardiovascular risk factors in middle-aged men [85]. Circulating visfatin level at admission is associated with occlusion of the infarct-related artery in patients with acute ST-segment elevation myocardial infarction [86]. Resistin is secreted from macrophages in atheromas and promotes atherosclerosis [87] and there is association between serum resistin level and cardiovascular events in postmenopausal women with acute coronary syndromes undergoing percutaneous coronary intervention [88]. Leptin may protect against atherosclerosis in specific animals models. For example low density lipoprotein receptor knockout mice lacking leptin (LDLR/-/-; ob/ob) develop more atherosclerotic lesions than LDLR/-/- control mice [89].

So the future research in this field may be how counteracting the adipokine dysfunction.

At present the molecular biological mechanisms linking overweight and obesity to cancer development are poorly understood in regard to the adipokine dysfunction: further research to define the causal role of adipokine dysfunction in various types of cancer obesity-related is needed.

In fact, nothing could be more true because of recent longitudinal studies on metabolic surgery revealed that weight loss results in lower cancer rates [90].

In addition to changes in hormone metabolism(insulin, IGF1, sex steroids) as carcinogenetic mechanism obesity-related, the overweight and obesity also contribute to the regulation of immune and

Macrophages play a prominent role in the malignancy microenvironment and distinct subsets in cancer have been described [79]. Tumor associated macrophages (TAMs) are termed macrophages in human microenvironments cancer and they can be classified into classical activated M1-like or alternatively activated M2-like macrophages: in the tumor microenvironment TAMs play a role in tumor progression influencing angiogenesis, lymphoangiogenesis, growth, metastasis and immunosuppression [80].

Adipose tissue macrophages (ATMs) are termed macrophages that infiltrate adipose tissue during obesity where there is a phenotypic switch in M1 type polarization [81].

Comparison with gene expression profiles of human TAMs shows that ATMs resemble TAMs and not monocyte-derived macrophages. In fact ATMs isolated and compared with monocyte-derived macrophages from the same obese patients shows that ATMs only modulate cancer cell function and the concentrations of ATMs-secreted factors related to cancer are elevated in serum of obese patients [82].

Table 3: Effects of overweight/obesity on growth factor and hormone production

POS: Polycystic Ovary Syndrome; IGF-1: Insulin Growth Factor 1; IGFBP: Insulin Growth Factor-Binding Protein; SHBG: Sex Hormone Binding Globulin

Furthermore, adipose tissue produces the enzymes aromatases and 17 beta-hydroxysteroid dehydrogenase (17b-HSD). So in obese subjects, there is typically an increased conversion of androgens, delta4-androstemedione (d4A) and testosterone (T) into the oestrogens oestrone (E1) and oestradiol (E2), respectively, by aromatase. 17b-HSD converts the less biologically active hormones d4A and E1 into the active hormones T and E2, respectively.

In parallel, obesity leads to hyperinsulinaemia, which in turn causes a reduction in the hepatic synthesis and circulating levels of sex hormone-binding globulin (SHBG). The combined effect of increased formation of oestrone and testosterone, along with induced levels of SHBG, leads to an increase in the bioavailable fractions of E2 and T that can diffuse to target cells where they bind to oestrogen and androgen receptors.

The effects of sex steroids binding their receptors can vary, depending on the tissue types, but in some tissues, such as breast epithelium and endometrium, they promote cellular proliferation and inhibit apoptosis: the effects of these sex steroids hormones might also contribute to tumorigenesis [73].

Recent epidemiological studies show that there is sufficient evidence that obesity can predispose to an increased risk of thyroid cancer in both man and women [74]. Leptin seems to have differential roles in regulating cell migration in thyroid cancer cells [75] because of enhances migration of human papillary thyroid cancer cells through the PI3K/AKT and MEK/ERK signalling pathways [76]. Leptin receptor is overexpressed in papillary thyroid cancer and is associated with tumor aggressiveness [77]. The study of Harari et al [78] by a retrospective review shows that obese patients the papillary thyroid cancer is present with more advanced stage and more aggressive forms.

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Hormone and growth factor | Overweight/obesity versus normal weight
---|---
Insulin | Increased levels (chronic hyperinsulinemia) in obesity
Free IGF-1 | Increased levels in obesity
IGFBP1 | Decreased levels in obesity
SHBG | Decreased levels in obesity
Total Testosterone | Decreased levels in obesity (men). No observed effects in women. Increased levels in obesity (premenopausal women with POS)
Free Testosterone | Not observed effects in obesity (men). Increased levels in obesity (premenopausal women)
Total oestradiol | Not observed effects (postmenopausal women). Increased levels in obesity (postmenopausal women and men)
Free oestradiol | Increased levels in obesity. No observed effects (premenopausal women)
Progesterone | In premenopausal women only no observed effect or decreased levels with obesity in women with susceptibility to develop ovarian hyperandrogenism
inflammatory response with prevalence M1 macrophage phenotype and Th1 type response.

Not only, the observation that human adipose tissue macrophages display activation of cancer-related pathway and that tumor associated macrophages may play a role in tumor progression, indicate that targeting macrophages in the tumor microenvironment may provide more efficacious novel therapies for future tumor management regarding i.e. chemotherapy resistance, repolarization of TAM or their therapeutic depletion.

Finally local cross-talk between foam cells and macrophages in artery vessel wall or adipocytes and tumor associated macrophages in cancer microenvironment may suggest a common pathogenetic mechanism of atherogenesis and cancerogenesis elicited by same stimulus such as the hypoxia.

Additional studies of these factors may increase our understanding of adipose tissue as an endocrine and regulatory organ.

Above all in the Western Countries such as United States and European Union where the overweight and obesity are increasing and the amount of physical activity is decreasing in most populations, it will also be important to develop successful intervention strategies both at the individual and community levels for weight loss and maintenance. This fact has been focused in the volume 6 of the IARC (International Agency for Research on Cancer) that summarizes the evidence of mechanisms (e.g. as related to hormonal metabolism and immune function) involved in the development of the consequences of epidemic overweight and obesity. Limiting weight gain reduces the risk of postmenopausal breast cancer and cancer of the colon, endometrium, kidney (renal-cell) and adenocarcinoma of oesophagus. Regular physical activity reduces the risk of breast and colon cancer and possibly that of endometrial and prostate cancer.

References


