Internal Medicine: Open Access

Camici et al., Intern Med 2014, 4:3
DOI: 10.4172/2165-8048.1000154

Review Article Open Access

Obesity and Increased Risk for Atherosclerosis and Cancer

Marcello Camici*, **Fabio Galetta and Angelo Carpi**

Department of Clinical and Experimental Medicine, Pisa University, Italy

***Corresponding author:** Marcello Camici, Department of Clinical and Experimental Medicine, Pisa University, Italy, Tel: 0039 056591781; E-mail: mcamici@tiscali.it

Received date: March 17, 2014, **Accepted date:** April 28, 2014, **Published date:** May 05, 2014

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 immunomudolatry cytokines/chemokines and adipokine dysregulation obesity-related. The aim of the study is to suggest a general hypothesis in pathogenetic 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 hetereogeneity reflects the specialization function that is adaptated by macrophages in different anatomical locations. This macrophage hetereogeneity 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).

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

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 1 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; Ifngamma-R: Interferon Gamma Receptor; ILR: Interleukin Receptor; Nfkb: Nuclear Factor Kappa B; ESRK: Extracellular Signal-Regulated Kinase; TNF: Tumor Tecrosis 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 triacylglycerols 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(MCPO-1) and macrophage inhibitor factor-1(MJF-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]. Macropahages 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/IKKI 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 ESKR/JNK signaling pathway with subsequent release of cytokines, chemokines and adipokines [26,27]. This activation could be also obtained by lypopolysaccharide (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).

	TNF- alpha	IL6	MCP-1	MIF	Adpn	Leptin	Resistin	Visfatin
Chemokine			Yes	Yes				
Cytokine	Yes	Yes						
Adipokine					Yes	Yes	Yes	Yes
Molecular structure	P	P	P	P	Pp	Pp	Pp	Pp
Membrane Receptor	TNFR	IL6-R	CCR2	(?)	R1/2	OB-R	(?)	RI
Transduction signaling	JNK NF-kB	JAK STAT	G-protein		p38MAPK AMPK PPAR-alpha	JAK STAT ERk	p38 ERK PI3K	ERK p38MAPK
Metabolic regulation	(+)	(+)	(+)	(+)	(-)	(+)	(+)(-)	(+)
Effects	+ IR	+ IR	+ IR	- MM	+IS	ME	+ IR	+IS
Associated diseases					D2 Ath CI CA IBD RA	EIH EIA EIC AS CA	D2 RA Ath NAFLD CKD HF	D2 ALI SE

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 pathway 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 cytokines which is not necessarily the case because of adipokines can in principle operate locally within the adipose tissue in an autocrine or paracrine manner and then more distally as endocrine factors to other organs target. The leptin receptor OBR is a member of the class I cytokine receptor family. The intracellular signaling pathways activated by leptin is not only JAK/STAT but also the mitogen-activated protein kinase (MAPK cascade), the PI3K (phosphoinositide 3-kinase)/PDE3B (phosphodiesterase 3B)/cAMP pathway, the 5'-AMP-activated protein kinase (AMPK cascade). Leptin shows multiple effects on immune function, suppresses appetite, promotes fatty acid oxidation. The Adiponectin receptor 1 and 2 serve as receptor for globular and full-length adiponectin and mediates increased AMPK, PPAR alfa ligands activities, p38MAPK and adiponectin-induced biological functions such as antinflammatory, insulin-sensitivity-induction, fatty acid stimulation. Resistin promotes insulin resistance, Visfatin is an insulin mimetic, Associated disease have been described with adipokines dysregulation.

(+): Increased in obesity; (-): Decreased in obesity; (+) (-): Variable in obesity; + IR: Promotes insulin resistance; + IS: Promotes insulin sensitivity; - MM: Inhibition Macrophage Migration; R1/2: Adiponectin Receptor 1 and 2; RI: Insulin Receptor; TNFR: Tumor Necrosis Factor Receptor; IL6-R: Interleukin 6 Receptor; CCR1: Cysteine-Cysteine Receptor 1; Pp: Polypeptide; P: Proteins; Adpn: Adiponectin; TNF-alpha: Tumor Necrosis Factor alpha; IL6: Interleukin 6; MCP-1: Monocyte Chemotactic Protein-1; MIF: Macrophage Inhibitory Factor; (?): Unknown; ME: Multiple Effects on immune function; ERK: Extracellular Signal-Regulated Kinase; PI3K: Phosphatidylinositol 3-Kinase; AMPK: Adenosinmonophosphate-activated Protein Kinase; MAPK: Mitogen-Activated Protein Kinase; STAT: Signal Transduction and Activator of Transcription; PPAR-alpha: Peroxisome-Proliferator-Activated Receptor alpha; D2: Type 2 Diabetes Mellitus; Ath: Atherosclerosis; CI: Cardiac Injury; CA: Cancer; IBD: Inflammatory Bowel Disease; RA: Rheumatoid Arthritis; EIH: Experimentally Induced Hepatitis; EIA: Experimentally Induced Arthritis; EIC: Experimentally Induced Colitis; AS: Asthma; ALI: Acute Lung Injury; SE: Sepsis; NAFLD: Non-Alcoholic Fatty Liver Disease; CKD: Chronic Kidney Disease; HF: Heart Failure

Adiponectin (Adpn) is a peptide hormone synthesized mainly by adipocytes, is present in the blood stream in three main forms and two Adpn receptors (Adipo R1-R2) have been identified [29-32].

In cell culture, in animals and human studies Adpn appears to have a protective effect on the cardiovascular system via its anti-atherogenic and anti-inflammatory effects [33]. Adpn 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].

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- beta 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-amonoacid 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-NFkB 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 dysregulation and atherosclerotic lesion formation [28]. Such studies have shown resistin stimulated 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 phosphorybolsyl transferase (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 7(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-kB), 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 serum 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] definied 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 cardia.

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 hyperrisestinemia, 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).

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 (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 (pre-menopausal women)
Progesterone	In premenopausal women only no observed effect or decreased levels with obesity in women with susceptibility to develop ovarian hyperandrogenism

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 betahydroxysteroid 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 actives hormones d4A and E1 into to 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 steroid 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.

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].

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 pathogenetic 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

inflammatory response with prevalence M1 macrophage phenotype and Th1 type response.

Not only, the observation that human adipose 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

1. Gordon S (1986) Biology of the macrophage. J Cell Sci Suppl 4: 267-286.
2. Gordon S (1998) The role of the macrophage in immune regulation. Res Immunol 149: 685-688.
3. Mosser DM (2003) The many faces of macrophage activation. J Leukoc Biol 73: 209-212.
4. Martinez FO, Sica A, Mantovani A, Locati M (2008) Macrophage activation and polarization. Front Biosci 13: 453-461.
5. Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, et al. (2004) The chemokine system in diverse forms of macrophage activation and polarization. Trends Immunol 25: 677-686.
6. Taylor PR, Martinez-Pomares L, Stacey M, Lin HH, Brown GD, et al. (2005) Macrophage receptors and immune recognition. Annu Rev Immunol 23: 901-944.
7. Mahoney JA, Gordon S (1998) Macrophage receptors and innate immunity. The Biochem 20: 12-16.
8. Cinti S (2001) The adipose organ: morphological perspectives of adipose tissues. Proc Nutr Soc 60: 319-328.
9. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, et al. (2003) Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 112: 1796-1808.
10. Nicholls DG, Locke RM (1984) Thermogenic mechanisms in brown fat. Physiol Rev 64: 1-64.
11. Gregoire FM, Smas CM, Sul HS (1998) Understanding adipocyte differentiation. Physiol Rev 78: 783-809.
12. Lin Y, Lee H, Berg AH, Lisanti MP, Shapiro L, et al. (2000) The lipopolysaccharide-activated toll-like receptor (TLR)-4 induces synthesis of the closely related receptor TLR-2 in adipocytes. J Biol Chem 275: 24255-24263.
13. Pelton PD, Zhou L, Demarest KT, Burris TP (1999) PPAR gamma activation induces the expression of the adipocyte fatty acid binding protein gene in human monocytes. Biochem Biophys Res Commun 261: 456-458.
14. Cousin B, Munoz O, Andre M, Fontanilles AM, Dani C, et al. (1999) A role for preadipocytes as macrophage-like cells. FASEB J 13: 305-312.
15. Lumeng CN, Bodzin JL, Saltiel AR (2007) Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest 117: 175-184.
16. Wood IS, Stezhka T, Trayhurn P (2011) Modulation of adipokine production, glucose uptake and lactate release in human adipocytes by small changes in oxygen tension. Pflugers Arch 462: 469-477.
17. Wood IS, de Heredia FP, Wang B, Trayhurn P (2009) Cellular hypoxia and adipose tissue dysfunction in obesity. Proc Nutr Soc 68: 370-377.
18. Oda T, Hirota K, Nishi K, Takabuchi S, Oda S, et al. (2006) Activation of hypoxia-inducible factor 1 during macrophage differentiation. Am J Physiol Cell Physiol 291: C104-113.
19. Ye J, Gao Z, Yin J, He Q (2007) Hypoxia is a potential risk factor for chronic inflammation and adiponectin reduction in adipose tissue of ob/ob and dietary obese mice. Am J Physiol Endocrinol Metab 293: E1118-1128.
20. Rausch ME, Weisberg S, Vardhana P, Tortoriello DV (2008) Obesity in C57BL/6J mice is characterized by adipose tissue hypoxia and cytotoxic T-cell infiltration. Int J Obes (Lond) 32: 451-463.
21. Trayhurn P, Wang B, Wood IS (2008) Hypoxia in adipose tissue: a basis for the dysregulation of tissue function in obesity? Br J Nutr 100: 227-235.
22. Duval C, Fruchart JC, Staels B (2004) PPAR alpha, fibrates, lipid metabolism and inflammation. Arch Mal Coeur Vaiss 97: 665-672.
23. Lee CH, Olson P, Evans RM (2003) Minireview: lipid metabolism, metabolic diseases, and peroxisome proliferator-activated receptors. Endocrinology 144: 2201-2207.
24. Wellen KE, Hotamisligil GS (2005) Inflammation, stress, and diabetes. J Clin Invest 115: 1111-1119.
25. Chawla A (2010) Control of macrophage activation and function by PPARs. Circ Res 106: 1559-1569.
26. Kopp A, Buechler C, Neumeier M, Weigert J, Aslanidis C, et al. (2009) Innate immunity and adipocyte function: ligand –specific activation of multiple toll-like receptors Modulates cytokine, adipokine and chemokine secretion in adipocytes. Obesity 17: 648-656.
27. Kopp A, Buechler C, Bala M, Neumeier M, Schölmerich J, et al. (2010) Toll-like receptor ligands cause proinflammatory and prodiabetic activation of adipocytes via phosphorylation of extracellular signal-regulated kinase and c-Jun N-terminal kinase but not interferon regulatory factor-3. Endocrinology 151: 1097-1108.
28. Frankel DS, Vasan RS, D'Agostino RB Sr, Benjamin EJ, Levy D, et al. (2009) Resistin, adiponectin, and risk of heart failure the Framingham offspring study. J Am Coll Cardiol 53: 754-762.
29. Libby P (2002) Inflammation in atherosclerosis. Nature 420: 868-874.
30. Piñeiro R, Iglesias MJ, Gallego R, Raghay K, Eiras S, et al. (2005) Adiponectin is synthesized and secreted by human and murine cardiomyocytes. FEBS Lett 579: 5163-5169.
31. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, et al. (2006) Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest 116: 1784-1792.
32. Berg AH, Combs TP, Scherer PE (2002) ACRP30/adiponectin: an adipokine regulating glucose and lipid metabolism. Trends Endocrinol Metab 13: 84-89.
33. Szmitko PE, Teoh H, Stewart DJ, Verma S (2007) Adiponectin and cardiovascular disease: state of the art? Am J Physiol Heart Circ Physiol 292: H1655-1663.

34. Matsuda M, Shimomura I, Sata M, Arita Y, Nishida M, et al. (2002) Role of adiponectin in preventing vascular stenosis. The missing link of adipo-vascular axis. J Biol Chem 277: 37487-37491.

35. Arita Y, Kihara S, Ouchi N, Maeda K, Kuriyama H (2002) Adipocyte-derived plasma protein adiponectin as a platelet derived growth factor – BB-binding protein And regulates growth factor induced common postreceptor signal in vascular smooth muscle cell. Circulation 106: 2893-2898

36. Ouchi N, Kihara S, Funahashi T, Nakamura T, Nishida M, et al. (2003) Reciprocal association of C-reactive protein with adiponectin in blood stream and adipose tissue. Circulation 107: 671-674.

37. Wolk R, Berger P, Lennon RJ, Brilakis ES, Davison DE, et al. (2007) Association between plasma adiponectin levels and unstable coronary syndromes. Eur Heart J 28: 292-298.

38. Otake H, Shite J, Shinke T, Watanabe S, Tanino Y, et al. (2008) Relation between plasma adiponectin, high-sensitivity C-reactive protein, and coronary plaque components in patients with acute coronary syndrome. Am J Cardiol 101: 1-7.

39. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, et al. (1994) Positional cloning of the mouse obese gene and its human homologue. Nature 372: 425-432.

40. Lago R, Gómez R, Lago F, Gómez-Reino J, Gualillo O (2008) Leptin beyond body weight regulation--current concepts concerning its role in immune function and inflammation. Cell Immunol 252: 139-145.

41. Koh KK, Park SM, Quon MJ (2008) Leptin and cardiovascular disease: response to therapeutic interventions. Circulation 117: 3238-3249.

42. Loffreda S, Yang SQ, Lin HZ, Karp CL, Brengman ML, et al. (1998) Leptin regulates proinflammatory immune responses. FASEB J 12: 57-65.

43. Yamagishi SI, Edelstein D, Du XL, Kaneda Y, Guzmán M, et al. (2001) Leptin induces mitochondrial superoxide production and monocyte chemoattractant protein-1 expression in aortic endothelial cells by increasing fatty acids oxidation via protein kinase A. J.Biolo.Chem 276: 25096-25100

44. Wolf G, Hamann A, Han DC, Helmchen U, Thaiss F, et al. (1999) Leptin stimulates proliferation and TGF-beta expression in renal glomerular endothelial cells: potential role in glomerulosclerosis [seecomments]. Kidney Int 56: 860-872.

45. Li L, Mamputu JC, Wiernsperger N, Renier G (2005) Signaling pathways involved in human vascular smooth muscle cell proliferation and matrix metalloproteinase-2 expression induced by leptin: inhibitory effect of metformin. Diabetes 54: 2227-2234.

46. Friedman JM, Halaas JL (1998) Leptin and the regulation of body weight in mammals. Nature 395: 763-770.

47. Wallace AM, McMahon AD, Packard CJ, Kelly A, Shepherd J, et al. (2001) Plasma leptin and the risk of cardiovascular disease in the west of Scotland coronary prevention study (WOSCOPS). Circulation 104: 3052-3056.

48. Patel SD, Rajala MW, Rossetti L, Scherer PE, Shapiro L (2004) Disulfide-dependent multimeric assembly of resistin family hormones. Science 304: 1154-1158.

49. Valsamakis G, McTernan PG, Chetty R, Al Daghri N, Field A, et al. (2004) Modest weight loss and reduction in waist circumference after medical treatment are associated with favorable changes in serum adipocytokines. Metabolism 53: 430-434.

50. Zhang J, Lei T, Chen X, Peng Y, Long H, et al. (2010) Resistin up-regulates COX-2 expression via TAK1-IKK-NF-kappaB signaling pathway. Inflammation 33: 25-33.

51. Reilly MP, Lehrke M, Wolfe ML, Rohatgi A, Lazar MA, et al. (2005) Resistin is an inflammatory marker of atherosclerosis in humans. Circulation 111: 932-939.

52. Cho Y, Lee SE, Lee HC, Hur J, Lee S, et al. (2011) Adipokine resistin is a key player to modulate monocytes, endothelial cells and smooth muscle cells, leading to progression of atherosclerosis in rabbit carotid artery. J.AmColl.Cardiol 57: 99-109

53. Jung HS, Park KH, Cho YM, Chung SS, Cho HJ, et al. (2006) Resistin is secreted from macrophages in atheromas and promotes atherosclerosis. Cardiovasc Res 69: 76-85.

54. Degawa-Yamauchi M, Bovenkerk JE, Juliar BE, Watson W, Kerr K, et al. (2003) Serum resistin (FIZZ3) protein is increased in obese humans. J Clin Endocrinol Metab 88: 5452-5455.

55. Samal B, Sun Y, Stearns G, Xie C, Suggs S, et al. (1994) Cloning and characterization of the cDNA encoding a novel human pre-B-cell colony-enhancing factor. Mol Cell Biol 14: 1431-1437.

56. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, et al. (2001) The hormone resistin links obesity to diabetes. Nature 409: 307-312.

57. Ognjanovic S, Bao S, Yamamoto SY, Garibay-Tupas J, Samal B, et al. (2001) Genomic organization of the gene coding for human pre-B-cell colony enhancing factor and expression in human fetal membranes. J Mol Endocrinol 26: 107-117.

58. Rongvaux A, Shea RJ, Mulks MH, Gigot D, Urbain J, et al. (2002) Pre-B-cell colony-enhancing factor, whose expression is up-regulated in activated lymphocytes, is a nicotinamide phosphoribosyltransferase, a cytosolic enzyme involved in NAD biosynthesis. Eur J Immunol 32: 3225-3234.

59. Wang P, Vanhoutte PM, Miao CY (2012) Visfatin and cardio-cerebro-vascular disease. J Cardiovasc Pharmacol 59: 1-9.

60. Romacho T, Azcutia V, Vazqueez-Bella M, Matesan z M (2009) Extracellular PBEF/NAMPT/vistati acitavates proi-inflammatory signalling in human vascular smooth muscle cells trough nicotinammide phosphoribosyl transferase activity. Diabetologia 52: 2455-2463.

61. Kim SR, Bae YH, Bae SK, Choi KS, Yoon KH, et al. (2008) Visfatin enhances ICAM-1 and VCAM-1 expression through ROS-dependent NF-kappaB activation in endothelial cells. Biochim Biophys Acta 1783: 886-895.

62. Adya R, Tan BK, Chen J, Randeva HS (2008) Nuclear factor-kappaB induction by visfatin in human vascular endothelial cells: its role in MMP-2/9 production and activation. Diabetes Care 31: 758-760.

63. Adya R, Tan BK, Punn A, Chen J, Randeva HS (2008) Visfatin induces human endothelial VEGF and MMP-2/9 production via MAPK and PI3K/Akt signalling pathways: novel insights into visfatin-induced angiogenesis. Cardiovasc Res 78: 356-365.

64. Salcedo R, Ponce ML, Young HA, Wasserman K, Ward JM, et al. (2000) Human endothelial cells express CCR2 and respond to MCP-1: direct role of MCP-1 in angiogenesis and tumor progression. Blood 96: 34-40.

65. Chen LF, Greene WC (2004) Shaping the nuclear action of NF-kappaB. Nat Rev Mol Cell Biol 5: 392-401.

66. Dahl TB, Yndestad A, Skjelland M, Oie E, Dahl A, et al. (2007) Increased expression of visfatin in macrophages of human unstable carotid and coronary atherosclerosis Possible role in inflammation and plaque destabilization. Circulation 115: 972-980.

67. Cheng KH, Chu CS, Lee KT, Lin TH, Hsieh CC, et al. (2008) Adipocytokines and proinflammatory mediators from abdominal and epicardial adipose tissue in patients with coronary artery disease. Int J Obes (Lond) 32: 268-274.

68. Zahorska-Markiewicz B, Olszanecka-Glinianowicz M, Janowska J, KoceÅ‚ak P, Semik-Grabarczyk E, et al. (2007) Serum concentration of visfatin in obese women. Metabolism 56: 1131-1134.

69. Zhong M, Tan HW, Gong HP, Wang SF, Zhang Y, et al. (2008) Increased serum visfatin in patients with metabolic syndrome and carotid atherosclerosis. Clin Endocrinol (Oxf) 69: 878-884.

70. Vainio H, Weiderpass E (2005) From hazard identification to weighing the benefits and drawbacks of prevention. Toxicol Appl Pharmacol 207: 28-33.

71. Calle EE, Kaaks R (2004) Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 4: 579-591.

72. Rockhill B, Newman B, Weinberg C (1998) Use and misuse of population attributable fractions. Am J Public Health 88: 15-19.

73. Cerhan JR, Janney CA, Vachon CM, Habermann TM, Kay NE, et al. (2002) Anthropometric characteristics, physical activity, and risk of non-Hodgkin's lymphoma subtypes and B-cell chronic lymphocytic leukemia: a prospective study. Am J Epidemiol 156: 527-535.
74. Mijovic T, How J, Payne RJ (2011) Obesity and thyroid cancer. Front Biosci (Schol Ed) 3: 555-564.
75. Cheng SP, Yin PH, Chang YC, Lee CH, Huang SY, et al. (2010) Differential roles of leptin in regulating cell migration in thyroid cancer cells. Oncol Rep 23: 1721-1727.
76. Cheng SP, Yin PH, Hsu YC, Chang YC, Huang SY, et al. (2011) Leptin enhances migration of human papillary thyroid cancer cells through the PI3K/AKT and MEK/ERK signaling pathways. Oncol Rep 26: 1265-1271.
77. Uddin S, Hussain AR, Siraj AK, Khan OS, Bavi PP, et al. (2011) Role of leptin and its receptors in the pathogenesis of thyroid cancer. Int J Clin Exp Pathol 4: 637-643.
78. Harari A, Endo B, Nishimoto S, Ituarte PH, Yeh MW (2012) Risk of advanced papillary thyroid cancer in obese patients. Arch Surg 147: 805-811.
79. Mantovani A, Allavena P, Sica A, Balkwill F (2008) Cancer-related inflammation. Nature 454: 436-444.
80. Hao NB, Lü MH, Fan YH, Cao YL, Zhang ZR, et al. (2012) Macrophages in tumor microenvironments and the progression of tumors. Clin Dev Immunol 2012: 948098.
81. Lumeng CN, Bodzin JL, Saltiel AR (2007) Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest 117: 175-184.
82. Mayi TH, Daoudi M, Derudas B, Gross B, Bories G, et al. (2012) Human adipose tissue macrophages display activation of cancer-related pathways. J Biol Chem 287: 21904-21913.
83. Okamoto Y, Kihara S, Ouchi N, Nishida M, Arita Y, et al. (2002) Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice. Circulation 106: 2767-2770.
84. Kawano T, Saito T, Yasu T, Saito T, Nakamura T, et al. (2005) Close association of hypoadiponectinemia with arteriosclerosis obliterans and ischemic heart disease. Metabolism 54: 653-656.
85. Dunajska K, Milewicz A, Jedrzejuk D, Szymczak J, Kuliczkowski W, et al. (2004) Plasma adiponectin concentration in relation to severity of coronary atherosclerosis and cardiovascular risk factors in middle-aged men. Endocrine 25: 215-221.
86. Teng-Hung Yu, Li-Fen Lu, Wei-Chin Ung (2011) Circulating vistati levels at admissionis associated with occlusion of the infarct-related artery in patients With acute ST-segment elevation myocardial infarction. Acta Cardiol 27: 77-85.
87. Li L, Han JL, Mao JM, Guo LJ, Gao W (2013) Association between serum resistin levels and cardiovascular events in postmenopausal women with Acute coronary syndrome undergoing percutaneous coronary intervention. Chinese Medical J 126: 1058-1062.
88. Hasty AH, Shimano H, Osuga J, Namatame I, Takahashi A, et al. (2001) Severe hypercholesterolemia, hypertriglyceridemia, and atherosclerosis in mice lacking both leptin and the low density lipoprotein receptor. J. Biol. Chem 276: 37402-37408.
89. Adams TD, Hunt SC (2009) Cancer and obesity: effect of bariatric surgery. World J Surg 33: 2028-2033.
90. IARC (2002) Handbook of Cancer Prevention: Weight Control and Physical Activity.