Cytokine 57 (2012) 9–16

Contents lists available at SciVerse ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/issn/10434666

Adipose tissue inflammation and cancer cachexia: Possible role of nuclear transcription factors

M.L. Batista Jr. [a,c,*], S.B. Peres [b,e], M.E. McDonald [e], P.S.M. Alcantara [d], M. Olivan [c], J.P. Otoch [d], S.R. Farmer [e], M. Seelaender [c]

[a] Laboratory of Adipose Tissue Biology, Center for Integrated Biotechnology, University of Mogi das Cruzes, Mogi das Cruzes, Sao Paulo, Brazil
[b] Department of Physiology, State University of Maringa, Maringa, Parana, Brazil
[c] Cancer Metabolism Research Group, Institute of Biomedical Sciences, University of Sao Paulo, São Paulo, Brazil
[d] Department of Surgery Clinical, University Hospital, University of Sao Paulo, Sao Paulo, Brazil
[e] Department of Biochemistry, Boston University School of Medicine, Boston, USA

ARTICLE INFO

Article history:
Received 28 July 2011
Received in revised form 16 September 2011
Accepted 17 October 2011
Available online 17 November 2011

Keywords:
Cancer cachexia
Inflammation
White adipose tissue
NF-κB
PPARγ

ABSTRACT

Cancer cachexia is a multifaceted syndrome whose aetiology is extremely complex and is directly related to poor patient prognosis and survival. Changes in lipid metabolism in cancer cachexia result in marked reduction of total fat mass, increased lipolysis, total oxidation of fatty acids, hyperlipidaemia, hypertriglyceridaemia, and hypercholesterolaemia. These changes are believed to be induced by inflammatory mediators, such as tumour necrosis factor-α (TNF-α) and other factors.

Attention has recently been drawn to the current theory that cachexia is a chronic inflammatory state, mainly caused by the host's reaction to the tumour. Changes in expression of numerous inflammatory mediators, notably in white adipose tissue (WAT), may trigger several changes in WAT homeostasis. The inhibition of adipocyte differentiation by PPARγ is paralleled by the appearance of smaller adipocytes, which may partially account for the inhibitory effect of PPARγ on inflammatory gene expression. Furthermore, inflammatory modulation and/or inhibition seems to be dependent on the IKK/NF-κB pathway, suggesting that a possible interaction between NF-κB and PPARγ is required to modulate WAT inflammation induced by cancer cachexia.

In this article, current literature on the possible mechanisms of NF-κB and PPARγ regulation of WAT cells during cancer cachexia are discussed. This review aims to assess the role of a possible interaction between NF-κB and PPARγ in the setting of cancer cachexia as well as its significant role as a potential modulator of chronic inflammation that could be explored therapeutically.

1. Introduction

1.1. General comments (cachexia)

Cancer cachexia, whose most striking symptom is a marked and rapid decrease in body weight, characterised by a depletion of skeletal muscle and white adipose tissue (WAT) mass, affects around half of all patients with cancer and is present in most (more than two thirds) of those with advanced cancer [1,2]. Cachexia is thus extremely detrimental and is considered to be the direct cause of 20% of cancer deaths [3,4]. Cachectic patients also show higher morbidity related to radio- and chemotherapy treatment [5]. Although the syndrome has received growing attention in the last few decades, its cause remains unknown and no known therapy is available to reverse its detrimental effects [6].

Changes in lipid metabolism in cancer cachexia induce a marked reduction of total fat mass, increases in lipolysis, oxidation of fatty acids, and hyperlipidaemia. In addition, cachexia is associated with a reduction in the rate of lipogenesis, and diminished activity and expression of lipoprotein lipase (LPL) [2,7,8]. Enhanced levels of hormone sensitive lipase (HSL) mRNA and protein can be detected in tissues of cachectic patients (notably in the liver and WAT) [9]. Decreases in WAT content, a consequence of lipodystrophies and lipoatrophies, is also a characteristic of cancer cachexia;

Abbreviations: TFs, transcriptional factors; PPARs, peroxisome proliferator-activated receptors; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; IκBα, nuclear factor of κ light polypeptide gene enhancer in B-cells inhibitor, α; siRNA, small interfering RNA; PG, 15d-PGJ_2; p. MØ, peritoneal macrophages; TNF-α, tumour necrosis factors; CNS, central nervous system; LPS, lipopolysaccharide; NMDA/NO, *N*-methyl-D-aspartate/nitric oxide; IBD, inflammatory bowel disease; NR4A, nuclear hormone receptor 4A; NRs, nuclear receptors; HDAC3, histone deacetylase 3; GSK-3β, glycogen synthase kinase 3; TZD, thiazolidinedione; TR, troglitazone.

* Corresponding author. Address: Av. Dr. Cândido Xavier de Almeida Souza, 200, Vila Partenio, Mogi das Cruzes, SP, CEP: 08780-911, Brazil. Tel.: +55 11 3091 7225; fax: +55 11 3091 7402.
E-mail address: miguelj@umc.br (M.L. Batista Jr.).

1043-4666/$ - see front matter Crown Copyright © 2011 Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.cyto.2011.10.008

in fact, 85% decrease in body fat has been reported in lung cancer patients. This often leads to hyperlipidaemia and insulin resistance, as well as to complications in antitumour therapies [3]. The loss of fat depots cannot be fully explained by the reduction of appetite that leads to anorexia, and occurs frequently in association with the syndrome [10]. Recent studies [9,11–13] have proposed that the progress of cachexia is closely related with the imbalance of catabolic and anabolic processes in peripheral tissues, notably in the adipose tissue.

Until recently there has been no consensus on the factors that cause and maintain cachexia. Factors secreted by the growing tumour are apparently involved in the mobilisation of fatty acids and proteins [4,14]. Nevertheless, the conception of the syndrome as a chronic inflammatory state, in which the main causative factor is the host's reaction to the presence of the tumour, has become more common [15–17]. Thus, it has been claimed that the maintenance of this chronic inflammatory condition is a result of the production of chemical mediators associated with the depletion of WAT and skeletal muscle, which can be divided into two categories: (1) those whose source is the growing tumour and (2) humoral factors (mainly cytokines) [18], secreted by the host's cells and tissues [1,19,20] (Fig. 1).

Changes in the expression of numerous inflammatory mediators, including TNF-α and tumour-derived lipid-mobilising factors [18,21] from both the tumour and host tissue may trigger several disturbances in WAT homeostasis [13]. Loss of WAT is consistently present in patients and animal models of cancer and WAT seems to be consistently affected even before changes in body and free fat mass can be observed. Despite these facts, the importance of WAT physiology for the control of adiposity, as well as the role of adipocyte-secreted adipokines in the regulation of body composition in this setting has been only recently addressed [22–24].

It is well established that peroxisome proliferator activated receptor gamma (PPARγ) has a pivotal role in adipogenesis and adipocyte function, regulating WAT homeostasis [25]. In the recent years, a great deal of attention has been given to the possible role of PPARs, most notably PPARγ, in chronic inflammatory conditions, and to that this nuclear hormone receptor may contribute to the pathogenesis of many diseases in which disordered lipid metabolism is a common feature [26,27]. Furthermore, activation of PPARγ in WAT during these conditions seems to be dependent on the nuclear factor κB (NF-κB) pathway, suggesting that, possibly, an interaction between NF-κB and PPARγ is required to modulate WAT inflammation induced by cancer cachexia. In this article, we review the literature on the possible mechanisms of NF-κB and PPARγ regulation in the setting of cancer cachexia.

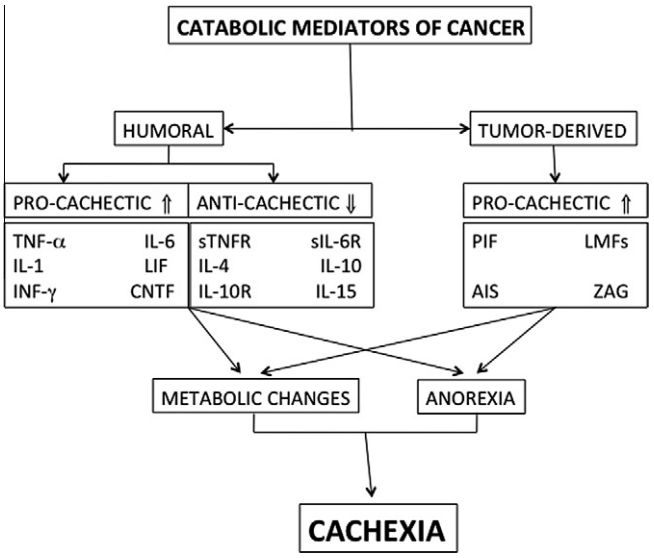

Fig. 1. Both tumor-derived and humoral (cytokines) factors are involved in mediating anorexia and metabolic changes, characteristic of the cachectic state. Combination of chemical mediators secreted by the host, including pro-cachectic factors (tumour necrosis factor-α (TNF-α); interleukin-6 (IL-6); interleukin-1β (IL-1β); interferon-γ (INF-γ); ciliary neurotrophic factor; and leukaemia inhibitor factor) and anti-cachectic factors (soluble receptor of TNF-α (sTNFR); soluble receptor of IL-6 (sIL-6R); antagonist receptor of IL-1 (IL-1ra); IL-4; IL-10; and IL-15), along those secreted by the tumour, such as proteolysis-inducing factor (PIF), lipid-mobilising factor (LMF; toxohormone-L and AIS; anaemia-inducing substance), and zinc-α 2-glycoprotein (ZAG; a protein belonging to the class I major histocompatibility complex family). Adapted with permission from [76].

1.2. WAT inflammation: infiltration of macrophages

Besides serving as an energy storage depot, WAT has numerous functions. It is well-accepted as the largest endocrine organ, secreting over 100 molecules described so far [12,28], which include cytokines (TNF-α, IL-6, IL-1β, IL-10, among many other) and adipokines (leptin, adiponectin, visfatin, to mention a few). Its secretory function is precisely controlled under physiological conditions; however, in pathophysiological conditions such as obesity, there is an increase in the production of cytokines and chemokines, followed by a pronounced macrophage (MØ) infiltration [29,30]. The interaction of soluble factors produced by the adipocytes and MØ regulates tissue functions in an autocrine and/or paracrine manner [31,32]. Among several inflammatory cytokines secreted by WAT,TNF-α has been the focus of most studies and has been shown to be a regulator of insulin resistance [33], inducer of apoptosis in pre-adipocytes and adipocytes [34], and a positive modulator of lipolysis [35,36]. Recently, alterations in leptin secretion have been shown to be modulated by TNF-α in cancer cachexia [37]. In addition, in cachectic rats, TNF-α, in combination with other cytokines, has also been associated to the reduction of LPL activity and lipogenesis and increases in HSL mRNA expression [7,38]. Therefore, TNF-α, along with other cytokines and hormones, may induce in WAT many of the metabolic alterations observed in cachectic patients [18].

In addition to highlighting the importance of WAT in the genesis and development of cancer cachexia, Machado et al. [37] have shown that rats afflicted with the Walker 256 carcinosarcoma show a significant increase in WAT macrophage infiltration (retro-peritoneal, epididymal, and mesenteric pads) already observed on the seventh day after the inoculation of the tumour (with induces death after 14 days), with the mesenteric deposit being the most affected (Fig. 2). Moreover, these cells secrete more TNF-α when cultivated either with homologue serum (from an animal subcutaneously inoculated with Walker 256 tumour) or when stimulated with phytohemagglutinin, demonstrating that such alteration is due to the presence of the tumour (Fig. 3). These results resemble those focused on obesity, metabolic syndrome, and type II diabetes, in which an increase in WATMØ infiltration is observed, suggesting that MØ seem to be the main local source of pro-inflammatory cytokines significantly contributing to systemic inflammation. Nonetheless, literature regarding the role of infiltrating MØ in WAT during the development of cancer cachexia lacks consistent data.

Immune system cells, such as activated MØ and lymphocytes, secrete cytokines that act at several different sites, including bone marrow, myocytes, hepatocytes, endothelial cells, neurons and adipocytes, and modulate a complex cascade of biological responses. These cascades lead to a series of alterations that ultimately result in body weight loss associated with cachexia. The main cytokines known to be involved in this condition are tumour necrosis factor-α (TNF-α), interleukin-1β and -6 (IL-1 β and IL-6), interferon-γ (IFN-γ), and leukotriene B4 (LTB4). Interestingly, these cytokines

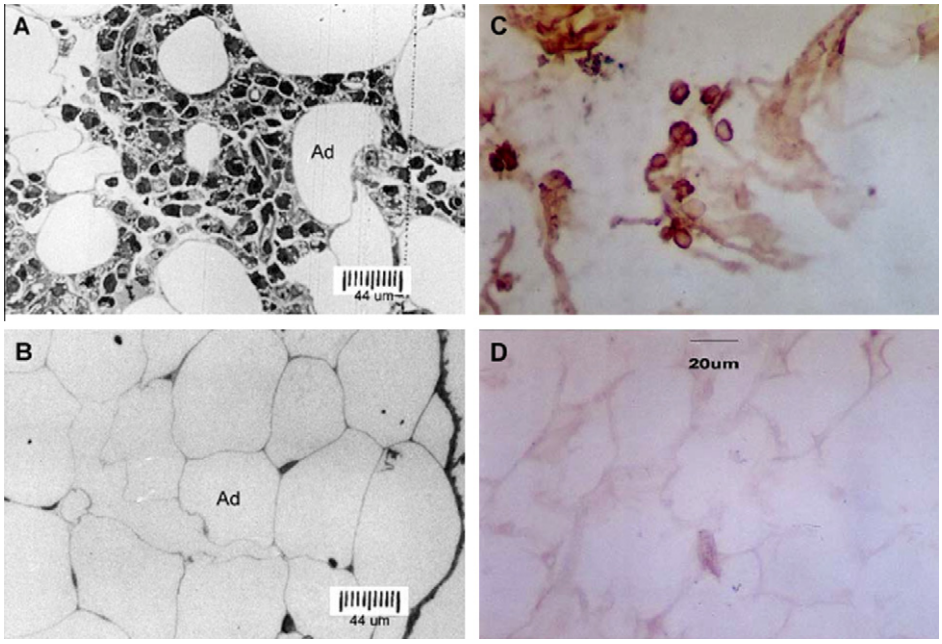

Fig. 2. Aspects of mesenteric adipose tissue of tumor bearing rats (A) at light microscopy, showing compicuous infiltration of leucocytes. Control rat tissue (B). *Ad* adipocyte. Immunocytochemistry with anti-rat mononuclear phagocyte in the mesenteric adipose tissue of tumor-bearing rats (C) and control reaction (D). Adapted with permission from [37].

Source	TB	TB + PHA	TB + TBserum
TNFα (pg/ml)			
EAT	1276.4±78.5	1763.2±145.9	1699.6±129.4
RPAT	1198.3±67.3	1604.3±114.9	1554.3±165.2
MES	1766.9±204.6*	2361.8±177.5*	2105.6±188.4*
PM	256.5±26.3$^{\#}$	1842.9±155.8^{a}	1699.5±112.8^{a}
PGE2 (pg/ml)			
EAT	278.5±18.9		348.4±27.3
RPAT	297.5±22.1		335.7±22.8
MES	310.6±27.0		356.2±31.9
PM	65.4±9.5$^{\#}$		304.7±23.6^{a}

Fig. 3. EAT epididimal adipose tissue, RPAT retroperitoneal adipose tissue, MES mesenteric adipose tissue, PM peritoneal macrophages, TB tumor-bearing, PHA after incubation with phytohemaglutinin (10 μg/mL), TB serum after incubation with autologous tumor-bearing rat serum (10%). Triplicates of samples obtained from 10 animals were used. Each mL contained 1.0×10^{-7} cells. $^{*}P < 0.05$ compared with EAT and RPAT; $^{a}P < 0.05$ compared with control PM. $^{\#}P < 0.05$ compared with adipose tissue-derivative cells. Adapted with permission from [37].

share similar metabolic effects, and their biological activities are interrelated, most notably in regard to the modulation of immune response (innate and adaptive) and inflammation. They also act synergistically in many situations [39].

The infiltrating MØ in cachectic rats can, in part, favour the establishment of an inflammatory milieu, similar to that observed in obesity. In this manner, infiltrating MØ may contribute to metabolic disturbances, thereby worsening cachexia and depleting fat deposits. The chemokine, monocyte chemotactic protein-1 (MCP-1), is believed to be responsible for the migration of monocytes to the adipose tissue in systemic chronic inflammation [40,41]. During the inflammatory process, MCP-1 plays an important role in promoting the attraction of monocytes, T lymphocytes, and natural killer to the site of inflammation [42].

TNF-α also induces the expression and production of MCP-1 by cultured adipocytes [43]. In contrast, IL-10, which is highly expressed by WAT [44], inhibits the production of MCP-1 by adipocytes and inhibits the production and expression of TNF-α, IL-6, and IL-1β by cultured monocytes. During cancer cachexia, TNF-α increases adipocyte and/or pre-adipocyte MCP-1 expression and production, leading to a higher recruitment of monocytes and aggravating inflammation. The infiltrating MØ also cause an increase in the release of other inflammatory cytokines (IL-6 and IL-1β) in addition to TNF-α and prostaglandin E_2 [37]. TNFα produced by macrophages within the WAT of cachectic subjects probably requires both the IKKβ (inhibitor of NF-κB kinase-β) and NF-κB. JNK-MAP4K4-AP1 (Jun N-terminal kinase–mitogen activated protein kinase kinase kinase kinase-4-Activator protein-1) signalling pathways. Macrophage-derived TNF-α enhances lipolysis and downregulates peroxisome proliferator-activated receptor γ (PPARγ)- mediated triglyceride (TG) biosynthesis and storage in adipocytes [45].

Adipocytes, in contrast, release anti-inflammatory cytokines (IL-10 and IL-1ra) in the attempt to minimise tissue inflammation by the following means: (1) through autocrine/paracrine action inhibiting MCP-1 production, (2) through inhibition of the production of inflammatory cytokines by MØ, and (3) through inhibition of monocyte infiltration. Moreover, MCP-1, and TNF-α receptors type I (TNFRI) and type II (TNFRII) [46] are modulated during cachexia. Despite the importance of MØ in the modulation of adipocyte function through a balance in the production of pro- and anti-inflammatory cytokines, and consequently, in the production of MCP-1 and other inflammatory mediators, the underlying mechanisms or, the details describing how this process takes place during the development of cancer-associated cachexia are not fully elucidated.

1.3. Alterations in adipose tissue and nuclear transcription factors related to the aetiology of cachexia

As described above, the molecular changes of WAT seem to be triggered before any detectable changes in body and free fat mass weight during cancer cachexia progression [4,23,37,47]. The importance of WAT in the control of adiposity and the role of

adipocyte-secreted adipokines in the regulation of body weight and local inflammation has spurred an interested in the potential roles of nuclear transcription factors in cachexia [11,44]. The role of PPARγ, which has a relevant action controlling adipogenesis and adipocyte function, as well as of the NF-κB pathway, which up-regulates the expression of genes involved in pro-inflammatory and immunological responses (cytokines, enzymes, immune receptors, and adhesion molecules) in this setting has been recently addressed [48]. On the other hand, alterations in the production and/or activity of adipokines that are involved in the pathogenesis of HIV-associated lipodystrophy [49]and the molecular mechanisms related with pathologic conditions such as lipodystrophy and cachexia are currently unknown.

Furthermore, a reduction in LPL activity and the capacity to incorporate long-chain fatty acids [50] is also accompanied by a major decrease in mRNA expression of specific adipogenic transcription factors, including CCAAT/enhancer binding protein alpha (C/EBP α), CCAAT/enhancer binding protein beta (C/EBP β), peroxisome proliferator activated receptor gamma (PPARγ), and sterol regulatory element binding protein-1c (SREBP-1c) and some of the target genes that encode lipogenic enzymes, such as acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), stearoyl-CoA desaturase-1 (SCD-1) and glycerol-3-phosphate acyltransferase (GPAT), proteins that are characteristically expressed in mature adipocytes [3].

The differentiation of adipocytes, also termed adipogenesis, is a process that is highly controlled by a set of transcription factors, which in turn regulate the gene expression of adipocytes [51]. Briefly, the CCAAT/enhancer binding proteins and PPARγ are key players in adipogenesis. *In vitro* studies have shown that the adipogenic program is triggered by the activation of C/EBP δ and β, the latter being responsible for activating the expression of PPARγ, which in turn induces the expression of C/EBPα. These factors cooperate with each other, inducing the expression of a series of proteins that confers the classical adipocyte phenotype upon the cell [51,52].

The maturation of the adipocyte is followed by the intracellular accumulation of triglyceride (TG), a process that is primarily mediated by SREBP-1C. Besides activating gene expression of PPARγ-2, SREBP-1C also activates lipogenesis via the expression of genes such as ACC, FAS, SCD-1, and GPAT [53]. In addition to TG synthesis, through PPARγ-mediated regulation of these proteins, it also regulates a subset of well-characterised proteins contributing to both lipid-droplet formation and lipid-droplet-regulated lipolysis [45], such as perilipin, CIDEA and FSP27 (CIDE family proteins). However, little is known about the possible effects of cachexia on adipogenesis.

1.4. Role PPARγ and inflammation

PPARγ is a member of a superfamily of nuclear receptors that plays an important role in the control of a multitude of physiological events. It is highly expressed in adipose tissue and stimulates the transcription of many adipocyte-specific genes and the initial steps of the adipogenesis, playing a critical role in the regulation of adipocyte differentiation [51]. There are two PPARγ isoforms, 1 and 2, which are generated by different promoters and alternative splicing mechanisms. PPARγ-1 is highly expressed in WAT and, to a lesser degree, in a variety of other cell types (MØ, pneumocytes, and colon epithelium, etc.) but PPARγ-2 is found exclusively in the adipose tissue. PPARγ can be pharmacologically activated by synthetic compounds called thiazolidinediones (TZD), which are clinically used as anti-diabetic agents [54]. However, the natural ligand for PPARγ has not been identified and remains the subject of intensive investigation. To be transcriptionally active, PPARγ has to partner with the RXR-α receptor, forming a heterodimer, which then binds to specific recognition sequences (PPREs) in the regulatory regions of target genes. Many genes involved in lipogenesis and insulin sensitivity contain binding sites to PPARγ such as aP2, LPL, adiponectin, phosphenolpyruvatecarboxykinase (PEPCK), and glucose transporter-4 (GLUT4) [52,55].

It is noteworthy that PPARγ is considered to be the master regulator of adipogenesis. A series of gain-of-function experiments conducted in non-adipogenic mouse fibroblasts ectopically expressing PPARγ, demonstrated that the expression of this nuclear factor alone is able to trigger the entire adipogenic program [51]. Gene knockout studies demonstrated conclusively that PPARγ is essential for adipocyte differentiation *in vivo*, clearly showing that PPARγ -/- mice were not able to develop either white or brown adipocytes *in vivo* [52]. Importantly, PPARγ is involved in ameliorating insulin sensitivity and, like PPAR α, in the attenuation of inflammation [27]. Finally, considering the importance of PPARγ in controlling adipogenesis and adipocyte function it would be interesting to address whether pharmacological manipulation of this nuclear receptor could revert cachexia associated with cancer.

Recently, a great deal of attention has been given to the possible role of the PPARs, notably PPARγ, in chronic inflammatory conditions. Inhibition of PPARγ function by inflammatory cytokines may contribute to the pathogenesis of many diseases, such as insulin resistance, atherosclerosis, inflammation, and cancer cachexia [56,57]. Disordered lipid metabolism is the common feature of these diseases.

Initial studies carried out with WAT from rats and 3T3-L1 fibroblasts have shown an antagonistic relationship between TNF-α and PPARγ, especially in regard to the control of adipocyte differentiation. In fact, TNF-α has been shown to be an inhibitor of LPL and mRNA expression in 3T3-L1 cells [58]. TNF-α also causes a marked dose-dependent reduction in LPL activity in adipocytes collected from human subcutaneous adipose tissue [59]. This alteration may also occur, at least partially, as a result of increased lipolysis in WAT associated with the subsequent increase in very low-density lipoprotein (VLDL) secretion by the liver [60]. Moreover, TNF-α is a powerful inhibitor of adipocyte differentiation through a mechanism that is characterised by the reduction of gene expression of adipogenic factors such as C/EBPα and PPARγ [61].

Another important function of PPARs is the inhibition of inflammatory gene expression [45,62]. The anti-inflammatory activity of PPARγ has been demonstrated in a study in which PMA-induced cytokine synthesis by macrophages was inhibited by prostanoids of the prostaglandin J2 family, which are also specific ligands for PPARγ [63]. In several model systems, PPARγ repressed target genes of the transcription factors nuclear factor-κB (NF-κB), nuclear factor of activated T cells (NFAT), activator protein 1 (AP1) and signal transducers and activators of transcription (STATs) in a signal-specific manner [45,64]. The inhibition of cytokine production by PPARγ is related to its function in the regulation of adipocyte differentiation. The inflammatory cytokine TNF-α antagonises the synthesis of PPARγ, blocks adipocyte differentiation, and contributes to insulin resistance. PPARγ ligands, in turn, promote insulin sensitivity and adipocyte differentiation, as well as blocking TNF-α production [45]. Bing et al.[3] have demonstrated that PPARγ mRNA is reduced in epididymal fat from tumour-bearing mice (MAC16), along with diminished expression of some lipogenic genes. However, how the inflammatory status induced by the presence of the tumour affects the biology of adipose tissue is still an issue to be experimentally explored.

On the other hand, regardless of that important role, little is known about the molecular mechanisms involved in these alterations. As recently reported, despite major reduction in mRNA levels of PPARγ in epididymal fat depots from tumour-bearing mice (MAC16), followed by reduction of the expression of genes related

Table 1
Selected articles regarding transcriptional factors in different inflammatory models and diseases conditions.

References	TFs	Type/model	General comments
Lehrke and Lazar (2005) [56]	PPAR γ	Review	Required for the accumulation of adipose tissue and hence contributes to obesity
Sharma and Staels (2007) [57]	PPAR γ	Review	Improves adipose tissue function and may have a role in preventing progression of insulin resistance
Ricote and Glass (2007) [62]	PPAR s	Review	Recent studies have highlighted molecular transrepression mechanism in macrophages
Azuma et al. (2001) [63]	PPAR γ	Original/p. Mϕ	PG may be a negative regulator of macrophage functions through PPAR γ
Straus and Glass (2007) [64]	PPARs	Review	Anti-inflammatory activity suggests their possible use for treating human inflammatory and autoimmune diseases
Zhande and Brownsey (1996) [87]	PPARs	Review	Necessary for the maintenance of the adipocyte phenotype and important component of the mechanism by which TNF-α exerts its antiadipogenic effects
Huang and Glass (2010) [88]	NF-κB	Review	Intersection of nuclear receptors and inflammation have revealed mechanisms of positive and negative transcriptional control
Baldwin et al. (1996) [66]	NF-κB	Review	Constitutively active in several cell types, potentially playing unexpected roles in regulation of gene expression and the implications for therapies of diseases
Yamamoto et al. (2004) [67]	NF-κB	Review	Kinases activate the NF-κB pathway through distinct steps demonstrating the potential for defining new therapeutic targets
Glezer et al. (2003) [68]	NF-κB	Original - CNS	Dexamethasone caused a stronger reduction in LPS induction of NF-kappaB in CNS
Celec et al. (2004) [69]	NF-κB	Review	*In vivo* studies have shown important facts regarding NF-κB participation in the pathogenesis of several diseases
De Bosscher et al. (2006) [72]	NF-κB	Review	Activated NRs, especially the glucorticoid receptor, the estrogen receptor and PPAR, can inhibit the activity of NF-κB
Rakonczay et al. (2008) [74]	NF-κB	Review/acute pacreatite	Recent advances in the investigation of pancreatic and extrapancreatic NF-κB activation have been related to acute pancreatitis
Sriwijitkamol et al. (2006) [65]	IκB/NFκB pathway	Original- Human skeletal muscle	Subjects with type 2 diabetes have reduced IκB protein abundance in muscle. Exercise training reverts this abnormality
Zamboni et al. (2007) [82]	NFκB pathway	Original/adipose tissue (subcutaneous)	Abdominal adiposity and leptin are independent predictors of adiponectin gene expression and ADP gene expression is strongly related to IκB-α mRNA
Ruan et al. (2002) [75]	NF-κB	Original/ 3T3-L1	Changes in adipocyte gene expression induced by TNF-alpha could lead to insulin resistance. NF-κB is an obligatory mediator of most of these responses
Gao et al. (2006) [79]	PPAR γ/NF-κB pathway	Original - sslkBα cell line and 3T3-L1 adipocytes	IκBα-dependent nuclear translocation of HDAC3 is responsible for PPAR γ inhibition by TNF-α
Su et al. (1999) [73]	PPAR γ/NF-κB	Original/colonic epithelial cells	TZD ligands for PPAR γ markedly reduce colonic inflammation in a mouse model of IBD, suggesting that colonic PPAR γ may be a therapeutic target
Ye (2008) [80]	PPAR γ/NF-κB	Review	PPAR γ activity is regulated by TNF-α at pre-translational and post-translational levels
Tamai et al. (2010) [78]	PPAR γ/C/EBP/ NF-κB	Original / 3T3-L1 adipocytes	Treatment with a PPAR γ agonist rendered the cells vulnerable to TNF-α-induced apoptosis in preadipocytes
Glass and Ogawa (2006) [89]	PPARs/LXLs/NF-κB/NR4A	Review	PPARs and LXRs function in a combinatorial manner with the glucocorticoid receptor to integrate local and systemic responses to inflammation
Ban et al. (2010) [48]	PPAR γ/NF-κB	Original - colon cancer cell	TR (PPARγ agonist) inhibits colon cancer cell growth via inactivation of NF-κB by suppressing GSK-3beta activity

with the lipid storing ability of adipose tissue through inhibiting fatty acid and triglyceride synthesis [3], little is known about the aetiology of cachexia or how these alterations and/or interactions take place over the development of this condition. For additional data on either this aspect or on the following section, please see Table 1.

1.5. NF-κB and inflammation

The transcription nuclear factor κB (NF-κB) was described in 1986 as a protein, which once activated by agents such as lipopolysaccharide (LPS), has the capacity to bind to a sequence of 10 base pairs on promoter region of the light κ chain genes of the antibody molecules of B cells (kB) [65,66]. The NF-κB "family" is comprised of five proteins, which include p65, p50, p52, RelB, and c-Rel. The dimerisation of these proteins is necessary to initiate the protein-DNA interaction. The predominant activated dimer is the p50–p65 heterodimer. In addition, p65 has a post-transcriptional C-terminal domain that is crucial for its capacity to activate inflammatory gene expression [67].

The activation of the NF-κB seems always to involve reactive oxygen species (oxidative stress) and the increase in intracellular calcium. When not stimulated, NF-κB is localised in the cytoplasm bound to an inhibitory protein, IκB. This complex prevents the translocation of the NF-κB to the nucleus. Therefore, the phosphorylation and the degradation of IκB are necessary for the activation and translocation of this nuclear factor [68].

NF-κB up-regulates the expression of genes involved in pro-inflammatory and immunological responses (cytokines, enzymes, immune receptors, and adhesion molecules), in addition to regulating the synthesis of C-reactive protein and initiating the transcription of cytokines such as TNF-α, IL-1β, IL-2, and IL-6 [69]. In patients with sepsis, the expression of NF-κB is high, and when persistent, is associated with higher death rates [70].

NF-κB and AP1 regulate most of the immune response associated genes and the majority of immune suppressive reagents

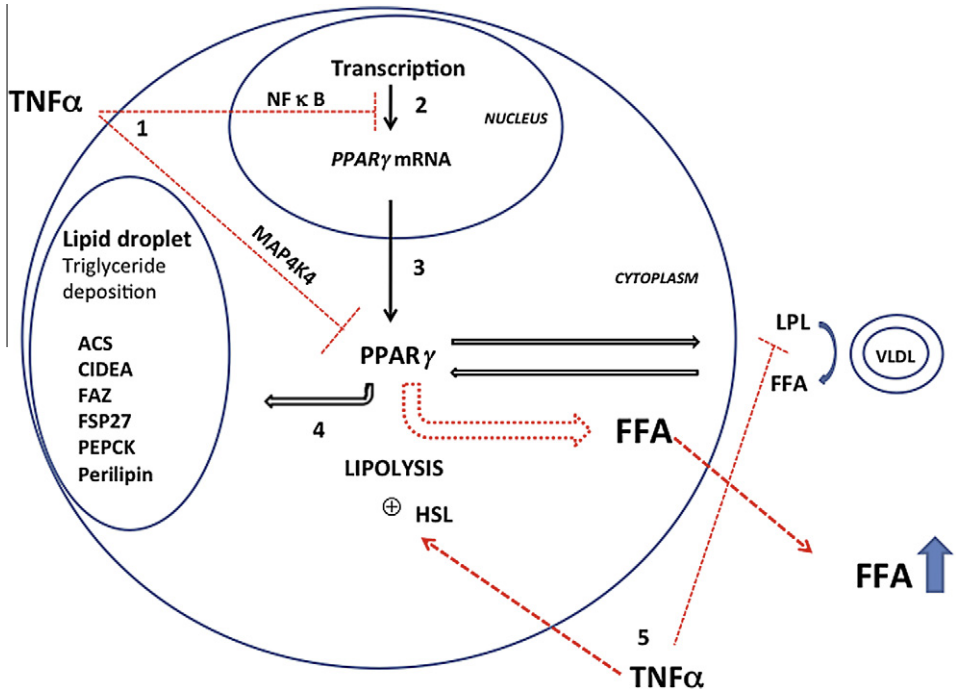

Fig. 4. PPARγ downregulation by TNF-α (from both tumor-derived and infiltrated macrophages) impairs triglyceride storage in adipose tissue cells. Peroxisome proliferator-activated receptorγ (PPARγ) expression may be regulated at the transcriptional level by tumor-necrosis factor-α (TNF-α) (arrow 1) through the activation of nuclear factor-κB (NF-κB), which negatively regulate PPARγ mRNA (arrow 2) and protein (arrow 3) expression. Up-regulation of MAP4K4 (mitogen-activated protein kinase kinase kinase kinase-4) induced by TNF-α may also transcriptionally control PPARγ (arrow 4) that can contribute to the control of triglyceride biosynthesis, hydrolysis and deposition in the lipid droplet – the lipid storage organelle of adipocytes (arrow 5); phosphoenolpyruvate carboxykinase (PEPCK), fatty acid synthase (FAS), Acyl-CoA synthetase (ACS), lipoprotein lipase (LPL) and lipid-droplet proteins including CIDEA, FSP27 and perilipin. Adapted from [45].

inhibit the activation of these transcription factors [71]. A strong inhibition of NF-κB and AP1 activation by PPARγ ligands has been observed in macrophage and epithelial cells [72]. Although the activation of NF-κ B andAP1 upon cell stimulation is well-described, the mechanisms by which PPARγ inhibits both AP1 and NF-κB activation could result indirectly from the PPARγ-induced genes in the macrophage and the T cells. Recently, Su et al. [73] demonstrated a role of the PPARγ ligand 15-deoxyprostaglandin J2 (15d-PGJ2) in inhibiting epithelial inflammation and in the inhibition of NF-κB activation, which is mediated by an IkB-α-dependent mechanism, indicating the function of PPARγ in regulation of NF-κB activation to be indirect. More recently, however, direct binding of 15d-PGJ2 with IκB has been identified, an effect that inhibits the activation of IκB and results in inhibition of NF-κB activation [74].

Ruan et al. [75] have shown that 3T3-L1 cells cultivated at the presence of TNF-α demonstrate a wide range of alterations in gene expression, which are critical for insulin sensitivity and adipogenesis. Moreover, TNF-α is also able to induce the expression of several transcription factors and genes related to the activation of NF-κB, as well as genes involved in cell growth, proliferation, and inflammation. TNF-α suppresses the gene expression of several nuclear transcription factors that are essential for adipocyte differentiation and function, including PPARγ, RXRα, and C/EBPα. Thus, along with the important role of TNF-α in the aetiology and progress of the cachexia [1,19,76,77], TNF-α also inhibits PPARγ activity at two different levels [78]. Recently, [79] reported a reduced expression of PPARγ in adipocytes after chronic (>16 h) treatment with TNF-α. On the other hand, acute TNF-α treatment inhibits the PPARγ ligand-dependent activity without decreasing its expression or its DNA-binding activity. Thus, both chronic and acute inhibition is dependent on the IKK/NF-κB pathway [79,80]. In regard to the acute effect of TNF-α, NF-κB was reported to reduce the DNA-binding activity of PPARγ [78]. However, the most important result of this study, corroborated by others [81,82] was the fact that the activation of the NF-κB is essential for the alterations induced by TNF-α in the expression of genes related with insulin resistance and metabolism of lipids in the 3T3-L1 cells (Fig. 4).

Previous reports suggest the possibility of selective deletion of TNF-α in the adipocytes in the adipose tissue, and in the decrease of WAT mass through multiple mechanisms including inhibition of lipogenesis, facilitation of lipolysis, suppression of adipogenesis and selective induction of adipocyte apoptosis [78,83]. However, in preadipocytes (*in vitro*), following exposure to TNF-α, there is a rapid activation of NF-κB, a phenomenon that does not occur in native adipocytes. Inhibition of NF-κB renders preadipocytes susceptible to TNF-α -induced apoptosis, suggesting that distinct NF-κB activities are the determinants for the separate apoptotic responses [83].

As previously mentioned, during adipocyte differentiation, the expression and activity of PPARγ are upregulated. Treatment of preadipocytes with a PPARγ agonist attenuated NF-κB activation and rendered the cells vulnerable to TNF-α -induced apoptosis. Conversely, treatment of adipocytes with a PPARγ antagonist enhanced NF-κB activation and conferred resistance to TNF-α -induced apoptosis, suggesting the involvement of PPARγ in the suppression of NF-κB in adipocytes [84,85]. Following differentiation of preadipocytes, expression and activity of C/EBP, especially C/EBPα and C/EBPβ, are upregulated in adipocytes, indicating that overexpression of individual C/EBPs significantly inhibited activation of NF-κB in preadipocytes [78,86]. Furthermore, in the same study, transfection with siRNA for C/EBPα and C/EBPβ enhanced the activity of the NF-κB pathways in adipocytes, suggesting that C/EBP is also involved in the repression of NF-κB in these cells.

Taking together, these results suggest novel mechanisms by which TNF-α selectively inhibits adipogenesis in the adipose tissue. The C/EBP and PPARγ-mediated suppression of NF-κB may contribute to TNF-α -related loss of adipose tissue mass under certain pathological situations, such as cachexia [83].

Nevertheless, as far as we know, no study has evaluated the activation and/or suppression of the NF-κB pathway in adipocytes in a cachectic state or how these alterations take place throughout the development of this condition in animal models or in patients with various neoplasms.

2. Concluding remarks

Studies over the last 10 year shave demonstrated that chronic inflammation underlies cancer cachexia. Based on extensive experimental evidence, the role of adipose tissue as a dominant regulator of whole-body lipid and glucose homoeostases is now well established; dysfunctions in adipose tissue metabolism have a direct impact on lipid and glucose homoeostases. Adipose tissue inflammation in cancer cachexia includes abnormal secretion of cytokines, impairment in triglyceride storage and increased lipolysis. As consequence, adipocytes from cancer cachectic subjects may secrete large amounts of MCP-1, possibly contributing to macrophage infiltration into adipose tissue. Interestingly, recent studies have highlighted the negative regulation by cytokines, including TNFα, of gene products that are crucial for lipid storage, such as the transcriptional factor PPARγ and its downstream target genes that control fatty acid synthesis, esterification and sequestration as triglyceride in lipid droplets.

In addition, a possible interaction between NF-κB and PPARγ in the modulation of several functions in white adipose tissue has been proposed to play an important role in this setting and may also have a significant role as a potential modulator of the process that could be explored therapeutically. However, additional studies are required before an optimum treatment is identified.

References

[1] Bing C, Trayhurn P. Regulation of adipose tissue metabolism in cancer cachexia. Curr Opin Clin Nutr Metab Care 2008;11:201–7.
[2] Fearon KCH, Moses AGW. Cancer cachexia. Int J Cardiol 2002;85:73–81.
[3] Bing C, Russell S, Becket E, Pope M, Tisdale MJ, Trayhurn P, et al. Adipose atrophy in cancer cachexia: morphologic and molecular analysis of adipose tissue in tumour-bearing mice. Br J Cancer 2006;95:1028–37.
[4] Tisdale M. Cachexia in cancer patients. Nat Rev Cancer 2002;2:862–71.
[5] Walz DA. Cancer-related anorexia-cachexia syndrome. Clin J Oncol Nurs 2010;14:283–7.
[6] von Haehling S, Genth-Zotz S, Anker SD, Volk HD. Cachexia: a therapeutic approach beyond cytokine antagonism. Int J Cardiol 2002;85:173–83.
[7] Argilés JM, Alvarez B, López-Soriano FJ. The metabolic basis of cancer cachexia. Med Res Rev 1997;17:477–98.
[8] Inui A. Cancer anorexia–cachexia syndrome: current issues in research and management. CA Cancer J Clin 2002;52:72–91.
[9] Agustsson T, Ryden M, Hoffstedt J, van Harmelen V, Dicker A, Laurencikiene J, et al. Mechanism of increased lipolysis in cancer cachexia. Cancer Res 2007;67:5531–7.
[10] Bing C, Brown M, King P, Collins P, Tisdale MJ, Williams G. Increased gene expression of brown fat uncoupling protein (UCP)1 and skeletal muscle UCP2 and UCP3 in MAC16-induced cancer cachexia. Cancer Res 2000;60:2405–10.
[11] Trayhurn P, Bing C. Appetite and energy balance signals from adipocytes. Philos Trans R Soc Lond B Biol Sci 2006;361:1237–49.
[12] Bing C, Trayhurn P. New insights into adipose tissue atrophy in cancer cachexia. Proc Nutr Soc 2009;68:385–92.
[13] Ryden M, Agustsson T, Laurencikiene J, Britton T, Sjolin E, Isaksson B, et al. Lipolysis–not inflammation, cell death, or lipogenesis–is involved in adipose tissue loss in cancer cachexia. Cancer 2008;113:1695–704.
[14] Argiles JM, Busquets S, Lopez-Soriano FJ. Cytokines as mediators and targets for cancer cachexia. Cancer Treat Res 2006;130:199–217.
[15] Fearon KC, Moses AG. Cancer cachexia. Int J Cardiol 2002;85:73–81.
[16] Deans C, Wigmore SJ. Systemic inflammation, cachexia and prognosis in patients with cancer. Curr Opin Clin Nutr Metab Care 2005;8:265–9.
[17] Delano MJ, Moldawer LL. The origins of cachexia in acute and chronic inflammatory diseases. Nutr Clin Pract 2006;21:68–81.
[18] Argiles JM, Busquets S, Toledo M, Lopez-Soriano FJ. The role of cytokines in cancer cachexia. Curr Opin Support Palliat Care 2009;3:263–8.
[19] Argiles JM, Moore-Carrasco R, Busquets S, Lopez-Soriano FJ. Catabolic mediators as targets for cancer cachexia. Drug Discov Today 2003;8:838–44.
[20] Argiles JM, Moore-Carrasco R, Fuster G, Busquets S, Lopez-Soriano FJ. Cancer cachexia: the molecular mechanisms. Int J Biochem Cell Biol 2003;35:405–9.
[21] Tisdale MJ. Cachexia in cancer patients. Nat Rev Cancer 2002;2:862–71.
[22] Trayhurn P, Bing C, Wood IS. Adipose tissue and adipokines–energy regulation from the human perspective. J Nutr 2006;136:1935S–9S.
[23] Fouladiun M, Korner U, Bosaeus I, Daneryd P, Hyltander A, Lundholm KG. Body composition and time course changes in regional distribution of fat and lean tissue in unselected cancer patients on palliative care–correlations with food intake, metabolism, exercise capacity, and hormones. Cancer 2005;103:2189–98.
[24] Hauner H. Adipose tissue inflammation: are small or large fat cells to blame? Diabetologia 2010;53:223–5.
[25] Okuno A, Tamemoto H, Tobe K, Ueki K, Mori Y, Iwamoto K, et al. Troglitazone increases the number of small adipocytes without the change of white adipose tissue mass in obese Zucker rats. J Clin Invest 1998;101:1354–61.
[26] Jernas M, Palming J, Sjoholm K, Jennische E, Svensson PA, Gabrielsson BG, et al. Separation of human adipocytes by size: hypertrophic fat cells display distinct gene expression. FASEB J 2006;20:1540–2.
[27] Stienstra R, Duval C, Keshtkar S, van der Laak J, Kersten S, Muller M. Peroxisome proliferator-activated receptor gamma activation promotes infiltration of alternatively activated macrophages into adipose tissue. J Biol Chem 2008;283:22620–7.
[28] Hauner H. The new concept of adipose tissue function. Physiol Behav 2004;83:653–8.
[29] Takahashi A, Kono K, Ichihara F, Sugai H, Amemiya H, Iizuka H, et al. Macrophages in tumor-draining lymph node with different characteristics induce T-cell apoptosis in patients with advanced stage-gastric cancer. Int J Cancer 2003;104:393–9.
[30] Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante Jr AW. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003;112:1796–808.
[31] Bouloumie A, Curat CA, Sengenes C, Lolmede K, Miranville A, Busse R. Role of macrophage tissue infiltration in metabolic diseases. Curr Opin Clin Nutr Metab Care 2005;8:347–54.
[32] Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 2006;6:772–83.
[33] Capel F, Klimcakova E, Viguerie N, Roussel B, Vitkova M, Kovacikova M, et al. Macrophages and adipocytes in human obesity: adipose tissue gene expression and insulin sensitivity during calorie restriction and weight stabilization. Diabetes 2009;58:1558–67.
[34] Ro HS, Zhang L, Majdalawieh A, Kim SW, Wu X, Lyons PJ, et al. Adipocyte enhancer-binding protein 1 modulates adiposity and energy homeostasis. Obesity (Silver Spring) 2007;15:288–302.
[35] Doerrler W, Feingold KR, Grunfeld C. Cytokines induce catabolic effects in cultured adipocytes by multiple mechanisms. Cytokine 1994;6:478–84.
[36] Carmen GY, Victor SM. Signalling mechanisms regulating lipolysis. Cell Signal 2006;18:401–8.
[37] Machado AP, Costa Rosa LFPB, Seelaender MCL. Adipose tissue in Walker 256 tumour-induced cachexia: possible association between decreased leptin concentration and mononuclear cell infiltration. Cell Tissue Res 2004;318:503–14.
[38] Tisdale MJ. Cancer cachexia. Langenbecks Arch Surg 2004;389:299–305.
[39] Pond CM. Adipose tissue and the immune system. Prostaglandins, Leukot Essent Fatty Acids 2005;73:17–30.
[40] Brake DK, Smith EO, Mersmann H, Smith CW, Robker RL. ICAM-1 expression in adipose tissue: effects of diet-induced obesity in mice. Am J Physiol Cell Physiol 2006;291:C1232–9.
[41] Yu R, Kim CS, Kwon BS, Kawada T. Mesenteric adipose tissue-derived monocyte chemoattractant protein-1 plays a crucial role in adipose tissue macrophage migration and activation in obese mice. Obesity (Silver Spring) 2006;14:1353–62.
[42] Biswas SK, Sodhi A. In vitro activation of murine peritoneal macrophages by monocyte chemoattractant protein-1: upregulation of CD11b, production of proinflammatory cytokines, and the signal transduction pathway. J Interferon Cytokine Res 2002;22:527–38.
[43] Wang B, Trayhurn P. Acute and prolonged effects of TNF-alpha on the expression and secretion of inflammation-related adipokines by human adipocytes differentiated in culture. Pflugers Arch 2006;452:418–27.
[44] Juge-Aubry CE, Somm E, Pernin A, Alizadeh N, Giusti V, Dayer JM, et al. Adipose tissue is a regulated source of interleukin-10. Cytokine 2005;29:270–4.
[45] Guilherme A, Virbasius JV, Puri V, Czech MP. Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. Nat Rev Mol Cell Biol 2008;9:367–77.
[46] Figueras M, Busquets S, Carbo N, Almendro V, Argiles JM, Lopez-Soriano FJ. Cancer cachexia results in an increase in TNF-alpha receptor gene expression in both skeletal muscle and adipose tissue. Int J Oncol 2005;27:855–60.
[47] Byerley LO, Lee SH, Redmann S, Culberson C, Clemens M, Lively MO. Evidence for a novel serum factor distinct from zinc alpha-2 glycoprotein that promotes body fat loss early in the development of cachexia. Nutr Cancer 2010;62:484–94.

[48] Ban JO, Kwak DH, Oh JH, Park EJ, Cho MC, Song HS, et al. Suppression of NF-kappaB and GSK-3beta is involved in colon cancer cell growth inhibition by the PPAR agonist troglitazone. Chem Biol Interact 2010;188:75–85.
[49] Bastard JP, Caron M, Vidal H, Jan V, Auclair M, Vigouroux C, et al. Association between altered expression of adipogenic factor SREBP1 in lipoatrophic adipose tissue from HIV-1-infected patients and abnormal adipocyte differentiation and insulin resistance. Lancet 2002;359:1026–31.
[50] Seelaender MC, Costa-Rosa LF, Curi R. Fatty acid oxidation in lymphocytes from Walker 256 tumor-bearing rats. Braz J Med Biol Res 1996;29:445–51.
[51] Farmer SR. Regulation of PPAR gamma activity during adipogenesis. Int J Obes (Lond) 2005;29(Suppl 1):S13–6.
[52] Rosen ED. The transcriptional basis of adipocyte development. Prostaglandins Leukot Essent Fatty Acids 2005;73:31–4.
[53] Shimano H, Yahagi N, Amemiya-Kudo M, Hasty AH, Osuga J, Tamura Y, et al. Sterol regulatory element-binding protein-1 as a key transcription factor for nutritional induction of lipogenic enzyme genes. J Biol Chem 1999;274:35832–9.
[54] Fonseca-Alaniz MH, Takada J, Alonso-Vale MI, Lima FB. The adipose tissue as a regulatory center of the metabolism. Arq Bras Endocrinol Metabol 2006;50:216–29.
[55] Rosen ED, Spiegelman BM. Adipocytes as regulators of energy balance and glucose homeostasis. Nature. 2006;444:847–53.
[56] Lehrke M, Lazar MA. The many faces of PPARgamma. Cell 2005;123:993–9.
[57] Sharma AM, Staels B. Review: Peroxisome proliferator-activated receptor gamma and adipose tissue–understanding obesity-related changes in regulation of lipid and glucose metabolism. J Clin Endocrinol Metab 2007;92:386–95.
[58] Morin CL, Schlaepfer IR, Eckel RH. Tumor necrosis factor-alpha eliminates binding of NF-Y and an octamer-binding protein to the lipoprotein lipase promoter in 3T3–L1 adipocytes. J Clin Invest 1995;95:1684–9.
[59] Montague CT, Prins JB, Sanders L, Zhang J, Sewter CP, Digby J, et al. Depot-related gene expression in human subcutaneous and omental adipocytes. Diabetes 1998;47:1384–91.
[60] Marshall MK, Doerrler W, Feingold KR, Grunfeld C. Leukemia inhibitory factor induces changes in lipid metabolism in cultured adipocytes. Endocrinology 1994;135:141–7.
[61] McTernan PG, Harte AL, Anderson LA, Green A, Smith SA, Holder JC, et al. Insulin and rosiglitazone regulation of lipolysis and lipogenesis in human adipose tissue in vitro. Diabetes 2002;51:1493–8.
[62] Ricote M, Glass CK. PPARs and molecular mechanisms of transrepression. Biochim Biophys Acta 2007;1771:926–35.
[63] Azuma Y, Shinohara M, Wang PL, Ohura K. 15-Deoxy-delta(12, 14)-prostaglandin J2 is a negative regulator of macrophage functions. Int Immunopharmacol 2001;1:2101–8.
[64] Straus DS, Glass CK. Anti-inflammatory actions of PPAR ligands: new insights on cellular and molecular mechanisms. Trends Immunol 2007;28:551–8.
[65] Sriwijitkamol A, Christ-Roberts C, Berria R, Eagan P, Pratipanawatr T, DeFronzo RA, et al. Reduced skeletal muscle inhibitor of kappa}b{beta content is associated with insulin resistance in subjects with type 2 diabetes: Reversal by exercise training. Diabetes 2006;55:760–7.
[66] Baldwin Jr AS. The NF-kappa B and I kappa B proteins: new discoveries and insights. Annu Rev Immunol 1996;14:649–83.
[67] Yamamoto Y, Gaynor R. IkappaB kinases: key regulators of the NFkappaB pathway. Trends Biochem Sci 2004;29:72–9.
[68] Glezer I, Munhoz CD, Kawamoto EM, Marcourakis T, Avellar MCW, Scavone C. MK-801 and 7-Ni attenuate the activation of brain NF-[kappa]B induced by LPS. Neuropharmacology 2003;45:1120–9.
[69] Celec P. Nuclear factor kappa B in molecular biomedicine: the next generation. Biomed Pharmacother 2004;58:365–71.
[70] Abraham E. Tissue factor inhibition and clinical trial results of tissue factor pathway inhibitor in sepsis. Crit Care Med 2000;28:S31–3.
[71] Zhang B, Berger J, Hu E, Szalkowski D, White-Carrington S, Spiegelman BM, et al. Negative regulation of peroxisome proliferator-activated receptor-gamma gene expression contributes to the antiadipogenic effects of tumor necrosis factor-alpha. Mol Endocrinol 1996;10:1457–66.
[72] De Bosscher K, Vanden Berghe W, Haegeman G. Cross-talk between nuclear receptors and nuclear factor kappaB. Oncogene 2006;25:6868–86.
[73] Su CG, Wen X, Bailey ST, Jiang W, Rangwala SM, Keilbaugh SA, et al. A novel therapy for colitis utilizing PPAR-gamma ligands to inhibit the epithelial inflammatory response. J Clin Invest 1999;104:383–9.
[74] Rakonczay Jr Z, Hegyi P, Takacs T, McCarroll J, Saluja AK. The role of NF-kappaB activation in the pathogenesis of acute pancreatitis. Gut 2008;57:259–67.
[75] Ruan H, Hacohen N, Golub TR, Van Parijs L, Lodish HF. Tumor necrosis factor-alpha suppresses adipocyte-specific genes and activates expression of preadipocyte genes in 3T3–L1 adipocytes: nuclear factor-kappaB activation by TNF-alpha is obligatory. Diabetes 2002;51:1319–36.
[76] Argiles JM, Busquets S, Lopez-Soriano FJ. Cytokines in the pathogenesis of cancer cachexia. Curr Opin Clin Nutr Metab Care 2003;6:401–6.
[77] Argiles JM, Busquets S, Felipe A, Lopez-Soriano FJ. Molecular mechanisms involved in muscle wasting in cancer and ageing: cachexia versus sarcopenia. Int J Biochem Cell Biol 2005;37:1084–104.
[78] Tamai M, Shimada T, Hiramatsu N, Hayakawa K, Okamura M, Tagawa Y, et al. Selective deletion of adipocytes, but not preadipocytes, by TNF-alpha through C/EBP- and PPARgamma-mediated suppression of NF-kappaB. Lab Invest 2010;90:1385–95.
[79] Gao Z, He Q, Peng B, Chiao PJ, Ye J. Regulation of nuclear translocation of HDAC3 by IkappaBalpha is required for tumor necrosis factor inhibition of peroxisome proliferator-activated receptor gamma function. J Biol Chem 2006;281:4540–7.
[80] Ye J. Regulation of PPARgamma function by TNF-alpha. Biochem Biophys Res Commun 2008;374:405–8.
[81] Ruan H, Zarnowski MJ, Cushman SW, Lodish HF. Standard isolation of primary adipose cells from mouse epididymal fat pads induces inflammatory mediators and down-regulates adipocyte genes. J Biol Chem 2003;278:47585–93.
[82] Zamboni M, Di Francesco V, Garbin U, Fratta Pasini A, Mazzali G, Stranieri C, et al. Adiponectin gene expression and adipocyte NF-kappaB transcriptional activity in elderly overweight and obese women: inter-relationships with fat distribution, hs-CRP, leptin and insulin resistance. Int J Obes (Lond) 2007;31:1104–9.
[83] Tamai M, Shimada T, Hiramatsu N, Hayakawa K, Okamura M, Tagawa Y, et al. Selective deletion of adipocytes, but not preadipocytes, by TNF-alpha through C/EBP- and PPARgamma-mediated suppression of NF-kappaB. Lab Invest 90:1385-95.
[84] Prins JB, Niesler CU, Winterford CM, Bright NA, Siddle K, O'Rahilly S, et al. Tumor necrosis factor-alpha induces apoptosis of human adipose cells. Diabetes 1997;46:1939–44.
[85] Qian H, Hausman DB, Compton MM, Martin RJ, Della-Fera MA, Hartzell DL, et al. TNFalpha induces and insulin inhibits caspase 3-dependent adipocyte apoptosis. Biochem Biophys Res Commun 2001;284:1176–83.
[86] Farmer SR, Spiegelman BM. Cell Differentiation. Curr Opin Cell Biol 2007;19:603–4.
[87] Zhande R, Brownsey RW. Cell volume and the metabolic actions of insulin. Biochem Cell Biol 1996;74:513–22.
[88] Huang W, Glass CK. Nuclear receptors and inflammation control: molecular mechanisms and pathophysiological relevance. Arterioscl Throm Vas 2010;30:1542–9.
[89] Glass CK, Ogawa S. Combinatorial roles of nuclear receptors in inflammation and immunity. Nat Rev Immunol 2006;6:44–55.