Minireview

Tumour necrosis factor, a key role in obesity?

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Abstract Tumour necrosis factor-α (TNF) is a pleiotropic cytokine involved in many metabolic responses in both normal and pathophysiological states. In spite of the fact that this cytokine (also known as "cachectin") has been related to many of the metabolic abnormalities associated with cachexia, recent studies suggest that TNF may also have a central role in obesity modulating energy expenditure, fat deposition and insulin resistance. This review deals with the role of TNF in the control of fat mass and obesity.

Key words: TNF; Insulin resistance; Adipose tissue; Obesity

1. Introduction

Obesity is a multifactorial syndrome representing one of the most important pathological states in Western countries. It therefore represents a highly expensive problem. This metabolic state is associated with hypertension, atherosclerosis, diabetes, cardiovascular problems and certain types of cancer.

Obesity is characterized by an increase in body fat stores linked to a lack of control on food intake and/or energy expenditure. Very recent experimental data have shown that fat tissue plays a pivotal role in the control of its own mass. Thus, adipose tissue is able to synthesize and release molecules which are able to regulate food intake and energy expenditure into the circulation, and therefore acts as an endocrine tissue. Among these compounds, leptin (the product of the *ob* gene) and tumour necrosis factor-α (TNF) might play a very important role. The aim of the present review is to summarize the experimental evidence involving TNF in human obesity.

2. TNF as a pleiotropic cytokine

Tumour necrosis factor-α (TNF) is a pleiotropic factor that exerts a variety of effects, such as growth promotion, growth inhibition, angiogenesis, cytotoxicity, inflammation, and immunomodulation [1]. This cytokine is synthesized mainly by macrophages in response to invasive stimuli, as an active 26 kDa membrane-bound precursor that is cleaved proteolytically to a mature 17 kDa form with the prosequence polypeptide remaining associated to the membrane [2]. The peptide is bioactive as a 51 kDa trimer, which can be recognized by two different receptors, TNFR1 or p55 (55 kDa) and TNFR2 or p75 (75 kDa). The human forms are known as p60 and p80 respectively, due to their slightly higher molecular weight. All these receptors are dimeric membrane-bound glycosylated proteins present in the majority of cellular types. In spite of this, the proportion of the two receptors varies between the different tissues. Interestingly, the affinity of the cytokine is higher for TNFR1 [3] in spite of the high homology that both receptors show in the extracellular domain. In addition to binding TNF, other cytokines can also bind to these receptors, thereby conferring a high pleiotropic potential. Although the exact biological functions of the two receptors are still not fully understood, it has been suggested that TNFR1 plays an important role in both the pro-inflammatory and cytotoxic responses [4], while the other receptor may act simply modulating the response generated by TNFR1 [5]. Due to its high affinity for its receptors, TNF can either act in an autocrine or paracrine way at low concentrations or in an endocrine fashion when it is released in high concentrations.

In addition to the membrane-bound receptors, soluble forms of the two receptors (corresponding to the extracellular domains and generated by proteolysis) are found in healthy individuals [6,7], and show a higher degree of affinity for the cytokine than the corresponding bound forms. When TNF is bound to these soluble receptors, it can no longer interact with the membrane forms and, therefore, it has been speculated that the presence of the soluble forms may constitute a way of regulating TNF actions [8]. Highly elevated concentrations of the soluble receptors are found in the course of AIDS [9], endotoxinemia [10] or cancer [11], which suggests a regulatory mechanism to counteract TNF production. Interestingly, Hotamisligil et al. [12] have shown that TNFR2 is overexpressed in adipose tissue of obese humans (with a strong correlation with BMI, hyperinsulinaemia and TNF mRNA levels in adipose tissue) and that the levels of the soluble receptor (sTNFR2) are elevated six-fold in the obese subjects as compared with the healthy controls. Conversely, the same authors report no change for the TNFR1 mRNA levels or circulating levels in the same group of patients. These results suggest that TNFR2 may play a role in obesity by modulating the actions of TNF. In addition, recent data show that TNF is also synthesized in non-immune cells such as muscle or adipose cells [13–15].

3. TNF induces important metabolic changes

In adipose tissue, TNF inhibits lipoprotein lipase synthesis [16] as well as the synthesis of acetyl-CoA carboxylase [17], fatty acid synthase [18], fatty acid-binding protein and glycerol phosphate dehydrogenase [19], all these enzymes being involved in fat synthesis. This cytokine also stimulates triacyl-

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glycerol degradation in the adipocyte by activating the hormone-sensitive lipase [18]. Partly as a result of these metabolic changes in adipose tissue and partly because it stimulates liver lipogenesis [20] and hepatic VLDL production [21], TNF causes a severe hypertriglyceridaemia. The high levels of the cytokine found in cancer [22] and chronic infection, AIDS in particular [23], could be related to the hypertriglyceridaemia present in these patients.

Concerning carbohydrate metabolism, the results obtained with experimental models are somewhat conflicting. It was first described that the cytokine increased glucose turnover and utilization in peripheral tissues in vivo [24]. However, TNF did not stimulate glucose utilization by rat epitrochlearis muscle in vitro [25]. Similarly, glucose utilization was not increased by TNF in isolated spleen cells or alveolar macrophages [25], suggesting that its action in vivo may not be direct. Later in vitro studies seem to indicate that TNF causes a decrease of insulin-induced glucose uptake in isolated cells due to a decrease in glucose (GLUT4) transporters [26]. However, no such evidence has been found in vivo.

4. TNF and insulin resistance

Pathological situations associated with a high TNF production show a state of peripheral insulin resistance. Among them, endotoxemia, cancer and trauma are normally associated with increases in circulating TNF and peripheral insulin resistance. Thus, the general clinical impression is that the insulin dose for diabetic patients must be increased if infection is present, thus suggesting an additional impairment to insulin resistance [27] (Fig. 1). Lang and Dobrescu [28], using an euglycemic clamp in septic rats (induced by injection of live *E. coli*), found that the septic state induced peripheral insulin resistance. It is well known that during infection there is a stimulation of macrophage TNF production by means of either LPS or other endotoxins released by the infecting agent. In addition, chronic administration of TNF to rats induces systemic insulin resistance [29]. Clinical administration of TNF to healthy humans has been reported as reducing insulin sensitivity by inducing hyperglycemia without lowering insulin levels [30].

Thus, since NIDDM is characterized by profound insulin resistance, TNF could also be responsible for this pathological state. Measurement of gene expression and protein levels for the cytokine in type II diabetic patients has confirmed this hypothesis [13,14]. In addition, an elevated expression of TNF was implicated in animal models of obesity and in the insulin-resistant diabetes mellitus which accompanies the disorder. In four models of obesity and insulin-resistant diabetes (the *fa/fa* obese Zucker rat, the *ob/ob* obese mice, the *tub/tub* obese mice and the *db/db* obese diabetic mice), expression of TNF mRNA in adipose tissue was induced, with corresponding elevation of TNF protein both locally and systemically [31]. Interestingly, in vitro studies using fully differentiated 3T3-L1 adipocytes have shown that when the cells are exposed to TNF they became insulin-resistant since insulin is not able to stimulate hexose transport [26]. This appears to be a consequence of a down-regulation in the expression of GLUT4, the insulin-stimulable glucose transporter. This observation may explain why in the same kind of cells, incorporation of glucose into lipids is diminished after incubation with supernatants of activated macrophages [18]. The same

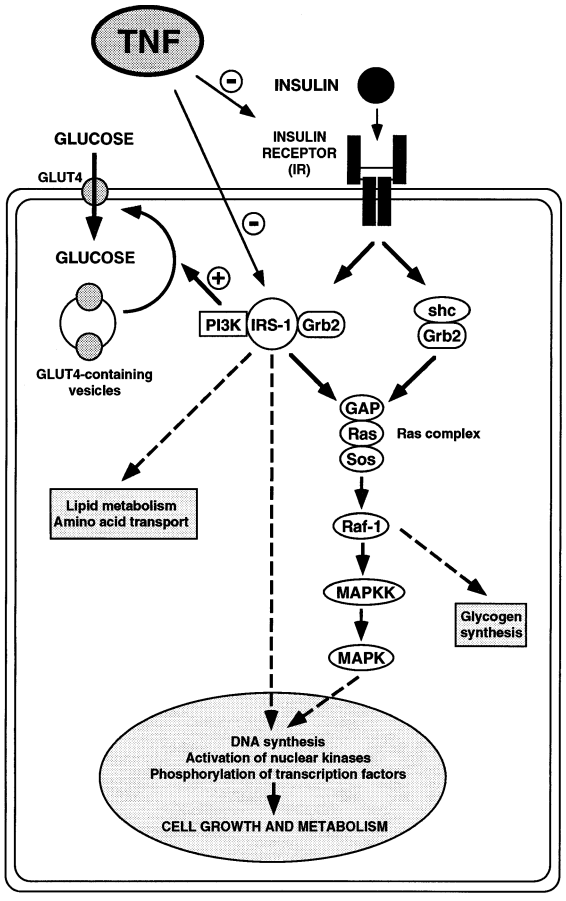

Fig. 1. Impairment of insulin action by TNF. TNF generates a state of multiple insulin resistance (liver, adipose, skeletal muscle) basically by decreasing insulin receptor (IR) and IRS phosphorylation and therefore the insulin signalling cascade. The results are changes in GLUT4 expression and the relevant metabolic alterations, such as an increase in lipolytic rate or a decrease in LPL in adipose tissue or a decrease in amino acid transport in skeletal muscle.

authors reported that long-term treatment of 3T3-F442A adipocytes with TNF led to down-regulation of the GLUT4 mRNA, and although no similar results have yet been reported in humans, their results suggest that the cytokine could be a key mediator of abnormal gene expression in obesity diabetes syndromes and could affect glucose homeostasis. In the same study, in vivo administration of the human TNF soluble receptor partially reversed the resistance to glucose-stimulated glucose uptake, thus suggesting that TNF could be one of the mediators of insulin resistance in several experimental obesity models [32]. Kern et al. [13] have reported an elevated expression of the TNF gene in the adipose tissue of obese subjects, with a high correlation existing between the levels of TNF mRNA, the body mass index and the circulating insulin levels. In the same study, however, there was no correlation found when the patients had a BMI above 45 kg/m^2. This discrepancy illustrates the complexity of the ethiology of the obesity syndrome in humans which can only be fully understood by integrating different modulatory mechanisms. Most interestingly, Saghizadeh et al. [15] have found that the TNF gene is also overexpressed in skeletal muscle in diabetic subjects, which further supports the role of the cytokine in the induction of a generalized state of insulin resistance.

Considerable attention is now being focused on the mechanism by which TNF induces resistance in the cascade of insulin signal transduction, the mechanism for tissue-specific overexpression in the obese adipocyte, and the possibility that interference with the pathway could be a new therapeutic approach to abrogate insulin resistance and thereby obesity-induced diabetes. Hofmann et al. [33] have shown an overexpression of TNF mRNA and TNF receptors mRNA in adipose tissue and muscle from a mouse model of non-insulin-dependent diabetes mellitus, the obese KKA^y mice. They also observed that the elevated expression of TNF mRNA can be partially reduced by oral administration of an insulin-sensitizing drug. Hotamisligil et al. [34] have shown that TNF has the ability to decrease the tyrosine kinase activity of the insulin receptor (IR). Treatment of cultured murine adipocytes with TNF was shown to induce serine phosphorylation of insulin receptor substrate-1 (IRS-1) and convert IRS-1 into an inhibitor of the insulin receptor tyrosine kinase in vitro, thus indicating that TNF induces insulin resistance through an unexpected action of IRS-1 attenuating insulin receptor signalling. Similar results were obtained with other cellular types such as hepatocytes [35,36], adipocytes [34,37], muscle cells [38] and fibroblasts [39,40]. It may thus be suggested that TNF expression is involved in a physiological loop, perhaps related to a limitation of obesity at the expense of promoting insulin resistance [41].

In spite of the experimental data, clinical observations based on blocking TNF action to counteract insulin resistance do not support the efficacy of this type of treatment. Thus Ofei et al. [42], after treating obese NIDDM patients with a monoclonal TNF antibody concluded that there was no reversal of insulin sensitivity or glycaemic control.

5. Has TNF a role in the control of adipose tissue mass?

In addition to the fact that both adipose and muscle tissue from either obese or diabetic subjects overexpress the TNF gene, the circulating levels of the cytokine are also correspondingly elevated, thus suggesting that the action of the cytokine is not just limited to the tissue where it is produced [43–46]. Indeed, TNF may act as a local signal regulating, in addition to insulin resistance, fat accumulation either directly by means of modulating the expression and synthesis of key enzymes in lipid accretion such as LPL [16] or hormone-sensitive lipase [18] or, indirectly, by controlling the rate of leptin secretion [47]. This molecule has been shown to have important effects on lipid metabolism in the adipocyte [48].

The etiology of human adiposity is complex and multifactorial and, on the basis of twin studies, is thought to have a strong genetic component. Genetic studies using sibling pair analysis have shown a linkage between a marker near the TNF locus and body fat content in Pima Indians [49].

But, what is the mechanism that activates adipocyte TNF mRNA synthesis during obesity? Bearing in mind that the TNF is in fact a counteracting molecule that will act to limit obesity, the adipocyte size could be involved. Other hormonal factors (elevated in the serum of obese patients) are the levels of insulin, IGF-1, glucocorticoids or other glucose-modified proteins [50] and could indeed have a role. Very recently, Morin et al. [51] have shown that diet fat content may influence the levels of TNF mRNA in adipocytes. Indeed, Wistar rats receiving isoenergetic diets but with a higher fat content (45% vs. 12% in controls) showed a higher TNF gene expression in adipose tissue. It is worth mentioning here that Westerterp [52] found a direct correlation between fat intake and obesity influence in human subjects, therefore reinforcing a possible role for ingested fat in modulating fat accumulation in adipose tissue.

A very elegant approach to elucidating the role of TNF in obesity consisted of generating obesity (either induced by diet or by crossing the mice with *ob*/*ob* animals) in TNF-deficient mice. Thus, Uysal et al. [53] generated obese mice with a targeted null mutation in the gene encoding TNF and also those encoding for the two TNF receptors. TNF-deficient mice show a lower body weight and fat accumulation than the wild-type. The absence of TNF resulted in significantly improved insulin sensitivity in both diet-induced obese mice and the ones related to the *ob*/*ob* model of obesity. These results clearly indicate that TNF is an important mediator of insulin resistance through its effects on several important sites of insulin action. Similarly Ventre et al. [54], also using mice lacking TNF, concluded that the cytokine was involved in the insulin sensitivity present in an hyperphagic model of rodent obesity.

To understand the implication of TNF in obesity in humans, studies with a longitudinal design become necessary where subjects with a low energy expenditure, a higher respiratory quotient (indicating a lower lipid oxidation) or a lower insulin sensitivity are followed for a long period of at least 10 years in a similar fashion to the studies carried out with the Pima Indians [55]. The fact that TNF may interfere in either of these three factors seems very attractive and therefore this type of study could serve to definitely conclude that TNF is involved in the control of body weight in human populations, both in health and disease, in this case, obesity.

6. Concluding remarks: TNF and leptin?

In conclusion, insulin resistance, associated with human obesity, is basically due to both a decrease in the levels of insulin-responsive glucose transporters and a decrease in the signal transduction associated with the binding of insulin to its receptors. It could be speculated that the generation of insulin resistance represents a mechanism to counteract the expansion of body fat [56] and therefore limits obesity. TNF seems to have a main role in activating this mechanism. However, TNF cannot be considered as the sole mediator or "adipostat" involved in the regulation of adipose mass (Fig. 2). The relatively ancient concept of the "adipostat" refers to the fact that the size of the body fat depot is sensed by the central nervous system through a product of fat metabolism circulating in the blood and affecting energy balance by interacting with the hypothalamus [57]. Many mediators have been proposed as carrying out this important function [58]. However, it has not been until recently that the discovery of leptin [59] caused a complete revolution in the field of body weight control. Indeed the product of the *ob* gene is a protein of 16 kDa synthesized in adipose tissue and secreted into the bloodstream. The molecule travels to the brain where it can act as a ponderostat or adipostat signal informing the brain of the adipose tissue mass, its main action resulting in the loss of appetite. Actually, the word leptin comes from the Greek "leptos" which means thin. The *ob*/*ob* mice have a defect in the production of this protein, resulting in hyperphagia and,

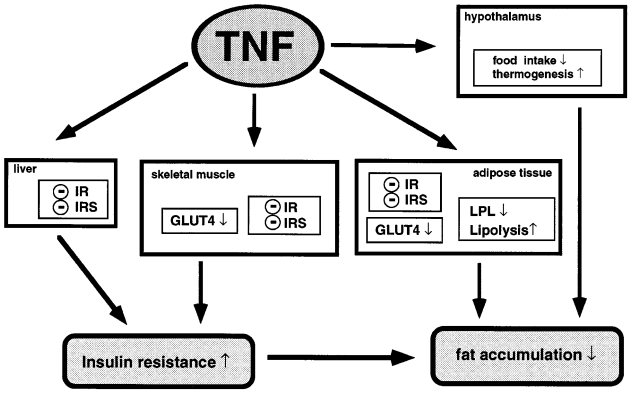

Fig. 2. Mechanisms involved in the regulation of body fat by TNF. TNF exerts multiple effects at different sites. It may influence food intake (either through leptin or IL-1) and thermogenesis both in BAT and skeletal muscle, therefore counteracting fat expansion. Similarly, it modulates LPL and hormone-sensitive lipase activities in adipose tissue, decreasing fat accumulation. On the other hand, it generates a state of multiple insulin resistance (liver, adipose, skeletal muscle) basically by decreasing the expression of GLUT4 transporters and by decreasing IRS phosphorylation and therefore the insulin signalling cascade. The insulin resistance status also contributes to the regulation of the adipose mass.

consequently, obesity. In other experimental models, such as the *fatty* rat, the production of the compound is normal but there seems to be a defect in the brain receptor [60], whose amino acid sequence indicates that it is similar to those found in class I cytokine receptor family [61]. In humans, leptin levels and production are correlated with fat mass and adipocyte size [62]; however, morbid obesity involves a certain degree of leptin resistance, and leptin levels do not correlate with BMI [63], as well as they do with other obese patients. Feeding a high-fat diet results in an increase in leptin production; conversely, weight decrease results in lower leptin levels [64]. In addition, leptin production is also under hormonal control, insulin having a key role in its production. It seems that hyperinsulinaemic-euglycaemic clamp in rats results in an increase in leptin mRNA in adipose tissue [65]. In addition, insulin causes an increase in leptin mRNA in cultured adipocytes, indicating a direct effect of the hormone on adipocyte leptin synthesis [66]. Similar actions on leptin expression are induced by glucocorticoids [67].

Taking TNF into consideration, we find very similar trends to those observed with leptin. First, it is expressed and secreted by adipose tissue and can influence thermogenesis and indirectly, possibly either via IL-1 or leptin [68], food intake. On the other hand, TNF has a direct (possibly paracrine) function in adipose tissue where it limits mass by stimulating lipolysis and decreasing LPL activity. We now know that leptin could have a similar function on lipid metabolism in adipose tissue [69]. TNF can also travel to the brain and influence hypothalamic function. One problem confronting such a hypothesis is the presence of the blood-brain barrier. However, a number of peripheral peptides, including angiotensin II, can rapidly affect the hypothalamus through nerve cells in the region of the circumventricular organs that lie outside the blood-brain barrier [70]. Alternatively, signals could be brought to the hypothalamus through nerve cells in the region of vagal afferent axons. Indeed, the intracraneal administration of cytokines results in a more effective stimulation of thermogenesis [71]. TNF thus exerts central actions which are complementary to the peripheral effects on tissues. In addition, TNF administration results in an increase in circulating leptin concentrations [68].

If TNF is a central adipostatic molecule involved in fat mass and body weight control, what happens during obesity? Firstly, there is an overexpression of the cytokine, which is aimed at stopping the hypertrophy of the tissue. The paracrine TNF action is thus aimed to decrease LPL activity and increase lipolysis at the same time as it generates insulin resistance (interfering with the entry of glucose into the cells) which further hampers the enlargement of the adipose tissue. Secondly, in obesity one should talk about a certain "TNF resistance" since the TNF which is released from adipose tissue does not seem to have a very important effect on the control of thermogenesis and food intake. Interestingly, Dascombe et al. [72] have demonstrated that genetically obese rats are not affected to the same extent (in terms of food intake decrease and increased BAT thermogenesis) as lean ones after intracraneal injections of the cytokine.

Finally, it has to be taken into consideration that it is not being suggested here that TNF is the sole adipostat; to the contrary, it is being postulated that the control of the fat mass is accomplished by different molecules (which signal to the brain fat mass). Among these molecules involved in the adipostatic function, TNF and leptin have fundamental roles, the former directly by influencing lipid metabolism and the later probably only by being a satiation factor and an insulin-counterregulatory hormone.

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