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REVIEW ARTICLE

Regulation of inflammation in the adipose tissue in cancer cachexia: effect of exercise

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The paraneoplastic syndrome of cachexia is considered a degenerative chronic inflammatory disease, being deeply related to the increase of pro-inflammatory factors, especially tumour necrosis factor alpha (TNF-α). It is known that the adipose tissue is affected by cachexia and contributing with the secretion of pro-inflammatory factors which reach the adjacent tissues and the circulation. The effect of pro-inflammatory factors is balanced by the effect of anti-inflammatory factors, such as interleukin 10 (IL-10). The IL-10/TNF-α ratio has been recently postulated as a marker for the assessment of the degree of inflammation, which correlates with disease-associated morbidity and mortality. In order to counteract inflammation in chronic disease, our group has currently adopted chronic endurance exercise in models of cancer cachexia and chronic heart failure. Since it is clear that white adipose tissue is strongly implicated in the secretion of both pro- and anti-inflammatory factors in disease, we chose to address its contribution to cachexia-related inflammation and the effect of endurance training on the capacity of cytokine expression and secretion by this tissue. Our results show an enhancement of IL-10 adipose tissue content, and increased IL-10/TNF-α ratio induced by endurance training. The mechanisms are discussed.

KEY WORDS — cancer cachexia; adipose tissue; cytokines; physical exercise

INTRODUCTION

Cachexia is present in around 50–80% of patients with cancer in advanced stages, inducing marked depletion of lean and fat mass.[1–3] Amongst the tissues affected by the syndrome, the adipose tissue suffers important modifications. Previous studies by our group showed that Walker 256 tumour-bearing cachectic animals present modifications in the composition of fatty acids and an increase in the dimension of adipocytes of the mesenteric and retroperitoneal adipose tissue depots.[4] In addition to the changes in lipid composition and ultrastructure, cachexia also leads to an increase in the production of proteins related with inflammation, such as tumour necrosis factor alpha (TNF-α) and its membrane receptors (TNFR1 and TNFR2). This increase in the concentration of inflammatory mediators results in a worsening of local and systemic inflammation.[5]

The increasing recognition of the importance of adipose tissue as not simply an organ for energy storage in the form of triglycerides,[6] but as an endocrine organ, takes into account its capacity to produce high concentrations of inflammatory cytokines (e.g. TNF-α, interleukin 1β, monocyte chemiotactic protein 1), as well as of anti-inflammatory cytokines (interleukin 10, IL-10, antagonist receptor of IL-1). The balance between the secretion of pro- and anti-inflammatory factors essentially depends on the stimulus and on the location of the adipose tissue depot.[7–11]

Argilés *et al*.[1] proposed the adoption of the balance of pro- and anti-inflammatory cytokines as markers of the severity of cancer cachexia. Recently, the IL-10/TNF-α ratio has been adopted as a marker of the intensity of the inflammatory condition in obese individuals and animals.[12] A trend of this ratio towards pro-inflammatory status is closely related with decreased survival and morbidity.[13]

In the last few years, several studies have proposed that some degenerative chronic diseases, such as obesity, diabetes, osteoporosis, cancer cachexia, among other, are characterized by the presence of a mild chronic inflammatory condition, as a consequence of the increase in plasma concentration of pro-inflammatory cytokines, and of reactive C

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protein.[5,14–17] Bearing this in mind, several therapeutic interventions have been proposed, aimed at mitigating or even reversing the inflammatory condition present by lowering plasma inflammatory markers.[14,16,17] However, so far, no therapy has been able to completely restore the effects of cancer cachexia either in animals or patients.[18]

Among the various non-pharmacological strategies which have been investigated, chronic aerobic exercise is recommended both for the prevention and therapy of the chronic alterations in cachexia and several diseases.[19–22] Moreover, endurance training seems to induce an increase in the secretion of anti-inflammatory cytokines by the adipose tissue,[11] that is even more evident in disease (e.g. obesity, cancer cachexia), suggesting an important modulating role of this tissue.[1,13] Another highly relevant clinical aspect is the reduction of tumour weight and in the proliferation of tumour cells in animals subjected to a chronic aerobic training programme (8 weeks), of moderate intensity (60% VO_{2max}).[19,20,22,23] In spite of these effects, the detailed mechanisms through which such response occurs have not yet been elucidated.

Therefore, the aim of this review is to establish a better understanding regarding the role of the adipose tissue (which is markedly affected by cancer cachexia) in the local and systemic production of pro- and anti-inflammatory factors. A second aim is to address the mechanisms through which endurance training decreases adipose tissue contribution to cachexia inflammation.

CANCER CACHEXIA AND CYTOKINE PROFILE

Cachexia is the main paraneoplasic syndrome.[2] In a simple way, it is defined as a catabolic syndrome involving the loss of muscle mass and adipose tissue, whose etiology is unknown. In the 1980s wasting associated with cachexia was attributed to anorexia induced by factors produced by the tumour, and to the increase in energy expenditure. However, nutritional therapy fails to reverse these symptoms.[24] Therefore, since the late 1980s, cachexia has been viewed as a chronic inflammatory syndrome. Today, it is believed that factors produced by the tumour and by the host's tissues and cells induce the cachexia-associated metabolic changes and anorexia.[2,24] Thus, pro-inflammatory factors circulating in the blood are closely linked with the severity of cachexia.[1,14]

Cytokines are small polypeptides, which were originally described as having an immune regulatory role.[21] Cytokines facilitate the inflow of lymphocytes, neutrophiles, monocytes and other cells to focci of tissue and/or systemic inflammation.[25] Local inflammation is followed by a systemic response, known as acute phase response.[21] This response includes the production of countless acute phase proteins by the liver, such as C-reactive protein (CRP), which can be diminished by local injection of cytokines, e.g. TNF-α, IL-1β and IL-6, in laboratory animals or in humans.[25] TNF-α is markedly related to the worsening of cachexia, and several therapies have been adopted in attempt to block its action. However, so far, most of the studies have failed in restoring the damage caused by this cytokine.[1,14]

ACTIVATION OF THE INFLAMMATORY PATHWAY: ROLE OF TUMOUR NECROSIS FACTOR α

TNF-α was described in 1975 and was at first called cachexine, due to its powerful citotoxic effect on tumour cells.[1] It is a trimeric polypeptide (17 kDa), mainly produced by activated monocytes and macrophages, and other cells, such as lymphocytes, fibroblasts, neutrophiles, muscle and mastocytes. This cytokine can act on almost all types of nucleated cells, either through two types of membrane receptors', type I (TNFR-1, p55) and type II (TNFR-2, p75), or as a soluble molecule.[9]

The transmission of the signal mediated by TNF-α binding to its membrane receptors constitutes a highly complex and diverse phenomenon, mediated by reactions involving phosphorylation and ubiquitination of target proteins. After TNF-α binding to its receptor, the activation of TRAF (TNF receptor-associated factor, a ubiquitin ligase) 2- and/or 5-protein, seems to be essential for the activation of its intermediary signalling protein RIP (receptor interacting protein), through polyubiquitination of the protein. On the other hand, polyubiquitination of RIP constitutes a very important event in the interaction of pro-inflammatory kinase protein TAK 1 (transforming growth factor-β-activated kinase) and its substrate, the protein complex IKK (inhibitor κB kinase).[26] Thus, a fundamental step in the intracellular transmission mediated by the interaction between TNF-α and its receptor is the activation/phosphorylation of the kinase protein IKK, more specifically its β-subunit.

Nuclear factor κB (NF-κB) is a transcription factor associated with the expression of various pro-inflammatory factors.[26] When not stimulated, it is found in the cytoplasm connected to its inhibiting protein, inhibitor κB kinase (IκB). This complex prevents the translocation of NF-κB to the nucleus. Due to the complexity of the mechanism activating the inflammatory pathway, several strategies have been adopted in order to block and/or minimize NF-κB activation in several diseases.[1,20,27]

ACTIVATION OF THE ANTI-INFLAMMATORY PATHWAY: ROLE OF INTERLEUKIN 10

IL-10 is a 17 kDa homodymeric polypeptide which was first described as a factor produced by auxiliary lymphocyte T (type 2), with inhibiting properties upon clones of auxiliary lymphocyte T (type 1), notably on the proliferative response and production of cytokines.[28] This cytokine is produced by different types of cells, especially inflammatory cells such as macrophages and T lymphocytes, for which it is the main inhibitor of cytokine synthesis and functional activity.[29] Moreover, it also shows an important capacity to inhibit

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matrix metalloproteinases, which are considered important modulators in some diseases.[30] Its biological activity is mediated by its membrane receptor (IL-10R), which belongs to the subgroup of receptors similar to interferon (INF), known as class II cytokine receptors.[31]

Functionally, IL-10 binds to its receptor (IL-10R1) and transmits its activation signal via JAK-STAT (Janus Kinases–Signal Transducers and Activators of Transcription), specifically through JAK1 and STAT3; in macrophages this activation depends on SOCS3 (suppressor of cytokine signalling-3) modulating the expression of pro-inflammatory genes.[32,33]

Thus, IL-10 inhibits the production of several cytokines, such as TNF-α, IL-1β and IL-6, in a variety of cell types, besides stimulating IL-10 synthesis.[31,34] Corroborating the information previously cited, several studies have shown that the production of IL-10 is increased in inflammatory processes, playing a predominantly immune modulating role in these conditions.[12,13,35]

ANTI-INFLAMMATORY EFFECT OF PHYSICAL EXERCISE

Recently, several studies have characterized the relationship between chronic inflammation and the increase in inflammation markers, notably TNF-α, IL-1β, IL-6, while transversal studies have shown a positive correlation between physical inactivity and low grade systemic inflammation.[21,36,37] In the elderly,[38] as well as in patients with intermittent claudication,[39] diabetes type II[40] and atherosclerosis, the same correlation has been reported. In these conditions, the expression 'low grade systemic inflammation' has been used to describe a two–threefold increase in plasma concentrations of TNF-α, IL-1β, IL-6, IL-1ra, TNFR1 and 2 and CRP, inflammatory markers which have been shown to be important for the development and progression of diseases.[12,36–40] Yet, the origin of this systemic alteration has not been well characterized. Nevertheless, it has been proposed that the white adipose tissue and the mononuclear cells of peripheral blood (specially lymphocytes) represent the main sources of these cytokines.[37,41,42]

Longitudinal studies have shown that physical training is efficient in reducing plasma concentrations of CRP in female athletes practicing soccer and netball[43,44] and therefore have suggested that regular aerobic exercise (training) exerts a suppressing effect on low grade chronic systemic inflammation. To evaluate the anti-inflammatory effect of exercise, Starkie *et al.*[45] have shown that the experimental model of low grade systemic inflammation, as induced by venous administration of endotoxine (*Escherichia coli*) in healthy individuals, after a 3-h session of aerobic exercise in cycloergometer (75% do VO_{2max}), provoked a reduction in the concentration of TNF-α which was increased by endotoxine. The same suppressing effect induced by physical exercise was also shown in mice in which the receptors of TNF-α types 1 and 2 had been knocked out, diminishing the concentration of TNF-α.[46]

POSSIBLE MECHANISMS INVOLVED IN THE ANTI-INFLAMMATORY RESPONSE TO PHYSICAL EXERCISE

It is well characterized in the literature that after an acute session of physical exercise there is an increase in the concentration of IL-6 (above 100-fold), which depends on exercise variables such as intensity, duration, recruited muscle mass and individual aerobic capacity.[41,42] Moreover, this increase in the concentration of IL-6 is followed by increase in the concentrations of IL-ra and IL-10 in the plasma.[21]

Studies have shown that IL-6 leads to an anti-inflammatory *milieu*, not only by the induction of the production of anti-inflammatory cytokines, but also, in specific conditions, by inhibiting the production of TNF-α, as shown *in vitro*,[47] and in mice.[21] In humans, the infusion of recombinant IL-6, an experimental procedure which mimics the increase in concentration of IL-6 induced by physical exercise, inhibits the endotoxine induced increase in plasma TNF-α.[45] On the other hand, other studies have shown that IL-6-independent pathways are important.[46] Even if the increase in the concentration of circulating adrenaline induced by physical exercise, as well as its infusion in humans, has been shown to inhibit TNF-α in response to *in vivo* endotoxemia,[47] this induces only small alterations in plasma IL-6 concentration, suggesting that the inhibitory effect is caused by different pathways.[21,41]

The presence of altered plasma concentrations of IL-10 and IL-ra after physical exercise that contribute to the anti-inflammatory *milieu* may have an important role in mediating the anti-inflammatory effect of physical training. However, no study has evaluated the behaviour of this cytokine after training.

As previously described, IL-10 can affect different cell types and induce the suppression of the inflammatory response. Therefore, IL-10 is assumed to be the main molecule responsible for the 'orchestration' of anti-inflammatory reactions, in particular of those which involve the activation of monocytes/macrophages. In humans, when IL-10 is added to a culture of mononuclear and netrophile cells stimulated with LPS, the synthesis of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) is inhibited through post-transcriptional mechanisms, as a direct consequence of a higher rate of mRNA degradation of the corresponding genes.[48]

The anti-inflammatory effect induced by exercise comes first from the increase in IL-6, followed by the increase in IL-1ra and in IL-10. Reinforcing this idea, the administration of IL-6, in concentrations similar to those observed in the plasma of individuals after long duration and high intensity exercise, is able to reduce plasma TNF-α concentration.[45]

The chronic effect of exercise (training) on the production of pro-inflammatory cytokines has been recently studied.[49,50] Chen *et al.*[49] have shown that rats trained for 4 weeks under moderate intensity, when subjected to the infusion of LPS for 20 min, showed diminished production of TNF-α and IL-1β by blood cells (monocytes, neutrophiles) in relation to the sedentary group. Similar results were reported by Sloan

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et al.,[50] when sedentary subjects were submitted to a 12-week training programme, of two intensities (moderated—60% of the maximum heart rate and high—75 and 80% of the maximum heart rate). When blood cells (monocytes) were stimulated with LPS (before and after training) the capacity to produce TNF-α in the high intensity trained group was reduced in relation to pre-training. However, the group that trained under moderate intensity did not present any differences. The authors associate this lower production of TNF-α by blood cells with the anti-inflammatory effects of training.

Recently, our group has shown that the mesenteric adipose tissue of rats subjected to a chronic aerobic training protocol (8 weeks, five times a week, 60% do VO_{2max}) showed an increase in TNF-α concentration and a ever more exacerbated increase in that of IL-10, when compared with the sedentary group.[11] We speculate that the increase in TNF-α is related to modulation of lipid metabolism, by inducing increased lypolisis in adipose tissues (e.g. retro-peritoneal adipose tissue as suggested by Nara *et al*.[51] The increase in IL-10 concentration, blocks the possible effects of TNF-α, while the IL-10/TNF-α ratio is increased in the trained group in relation to the sedentary group. This regulation favours the anti-inflammatory environment in this specific tissue, and it can be one of the mechanisms through which chronic exercise increases anti-inflammatory response. Gomez-Merino *et al*.,[52] after subjecting animals to a high intensity training protocol for 7 weeks, reported an increase in the concentrations of IL-1ra, IL-1β and IL-12 in adipose tissue in relation to the sedentary group. The concentrations of TNF-α and IL-10 were not altered. We must stress that the intensity, volume and duration of the application of the training protocol are determining variables in the modulation of cytokines concentration,[21] which partially explains the discrepant results found in the study made by Gomez-Merino *et al* and our own.[52]

The beneficial effects of aerobic physical training in chronic diseases has led Costa Rosa[20] to suggest that 'exercise should be adopted as a complementary strategy in the treatment of chronic diseases', since several studies including experimental models of cancer cachexia,[19,20,22,23] heart failure[53,54] and caloric malnutrition[55] show encouraging results.

Furthermore, 8 weeks of endurance training decreases tumour weight (sedentary 17.2 g vs. trained 1.94 g) in rats.[22] The mechanism by which endurance training inhibits tumour growth is unknown, although it is clear that immune system function is enhanced by moderate intensity exercise training[20] leading to improved antitumour resistance.

FINAL CONSIDERATIONS

Taken together current studies suggest an extremely important role for IL-10 in chronic inflammatory diseases, mainly due to its modulating effect in the synthesis and secretion of TNF-α. Therefore, this cytokine is becoming a prominent therapeutic target. As the adoption of chronic aerobic training seems to be an important stimulus for the production of IL-10 by the adipose tissue it is suggested that physical activity has great potential for attenuating inflammation, and may in turn be of therapeutic potential in disease, especially in cancer associated cachexia.

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