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Review article

The impact of exercise training on adipose tissue remodelling in cancer cachexia

Rita Ferreira[a], Rita Nogueira-Ferreira[a,b], Rui Vitorino[b,c], Lúcio Lara Santos[d,e,f], Daniel Moreira-Gonçalves[a,g,*]

[a] QOPNA, Departamento de Química, Universidade de Aveiro, Aveiro, Portugal
[b] Departamento de Cirurgia e Fisiologia, Faculdade de Medicina, Universidade do Porto, Porto, Portugal
[c] iBiMED, Departamento de Ciências Médicas, Universidade de Aveiro, Aveiro, Portugal
[d] Experimental Pathology and Therapeutics Group – Research Center, IPO-Porto, Porto, Portugal
[e] Health School of University of Fernando Pessoa, Porto, Portugal
[f] Department of Surgical Oncology, IPO-Porto, Porto, Portugal
[g] CIAFEL, Faculdade de Desporto, Universidade do Porto, Porto, Portugal

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ABSTRACT

Cachexia affects the majority of patients with advanced cancer and no effective treatment is currently available to address this paraneoplastic syndrome. It is characterized by a reduction in body weight due to the loss of white adipose tissue (WAT) and skeletal muscle. The loss of WAT seems to occur at an earlier time point than skeletal muscle proteolysis, with recent evidence suggesting that the browning of WAT may be a major contributor to this process. Several factors seem to modulate WAT browning including pro-inflammatory cytokines; however, the underlying molecular pathways are poorly characterized.

Exercise training is currently recommended for the clinical management of low-grade inflammatory conditions as cancer cachexia. While it seems to counterbalance the impairment of skeletal muscle function and attenuate the loss of muscle mass, little is known regarding its effects in adipose tissue. The browning of WAT is one of the mechanisms through which exercise improves body composition in overweight/obese individuals. While this effect is obviously advantageous in this clinical setting, it remains to be clarified if exercise training could protect or exacerbate the cachexia-related catabolic phenotype occurring in adipose tissue of cancer patients. Herein, we overview the molecular players involved in adipose tissue remodelling in cancer cachexia and in exercise training and hypothesize on the mechanisms modulated by the synergetic effect of these conditions. A better understanding of how physical activity regulates body composition will certainly help in the development of successful multimodal therapeutic strategies for the clinical management of cancer cachexia.

Introduction

Cancer cachexia (CC) is a syndrome associated with poor prognosis, being responsible for about 20% of deaths in cancer patients.[1] This paraneoplastic syndrome is characterized by a hypermetabolic state that leads to the loss of adipose tissue and skeletal muscle.[2,3] Hormones, cytokines and other factors secreted by the tumour have been suggested to cause unbalanced energy expenditure, negative protein balance and increased lipolysis.[4–6] Deregulation of hypothalamic mechanisms controlling energy wasting, hunger and satiety have also been associated with CC, suggesting that neuroendocrine processes can regulate adipose tissue and skeletal muscle wasting.[1,4] Remodelling of adipose tissue seems to occur at an earlier time point than muscle proteolysis in CC. This is characterized by the browning of white adipose tissue (WAT) that leads to lipid mobilization/oxidation and heat production.[1,7,8] Whereas increased proteolysis seems to explain muscle wasting, elevated lipolysis has been reported to be the main cause of adipose tissue loss in cancer patients.[9] Nevertheless, the molecular pathways behind WAT adaptation to CC are poorly characterized.

Exercise training has been suggested as a preventive and therapeutic strategy for CC mostly because it prevents or counteracts muscle loss.[10,11] However, the impact of exercise training on CC-related WAT remodelling is poorly comprehended. In this review

* Corresponding author.
E-mail address: danielmgon@gmail.com (D. Moreira-Gonçalves).

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we overview the molecular pathways involved in CC-related WAT remodelling and the putative impact of exercise training on this process.

WAT remodelling in cancer and involved molecular players

The CC-related alterations in the metabolism of adipose tissue include changes in the expression of genes with regulatory roles in the browning of WAT, a process by which WAT is converted into brown adipose tissue (BAT).[12] Both WAT and BAT participate in the regulation of energy balance but while WAT is mainly involved in the maintenance of energy homeostasis by storing energy in the form of triglycerides, BAT is responsible for thermogenesis through lipid oxidation.[13]

Until recently, BAT was believed to be only present in neonatal and childhood periods whereas WAT is distributed all over the body.[14] Nowadays, depots of BAT are recognized to persist in adults which correlates with their leanness.[15] In CC, the presence of BAT was firstly noted when the use of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) scanning was introduced in the routine clinical practice for cancer staging.[16,17] This methodological approach works by monitoring glucose uptake and so it is not surprising that some non-tumour tissues utilizing glucose are also labelled. In fact, besides the labelling of brain, heart and bladder, some additional areas of glucose uptake were observed by PET, particularly in the neck and shoulder area. This was later attributed to BAT.[18] FDG uptake by BAT in adulthood implies the existence of thermogenically active adipose tissue, suggesting its involvement in energy wasting. So, FDG-PET seems an attractive non-invasive approach to determine BAT activity, supporting routinely employed clinical PET imaging to be extended to the diagnosis of patients at risk of CC.

WAT adipocytes are bigger than BAT adipocytes and have an unilocular morphology while BAT adipocytes present a multilocular morphology.[19,20] BAT has a large density of mitochondria and is among the most vascularized tissues of the body, which confer its characteristic brown colour.[19] Another type of adipocytes named brite (or beige) adipose cells were recently reported. These cells are located in WAT tissue in both subcutaneous and trunk compartments, and have the same thermogenic function of BAT cells. While brite adipocytes could be perceived as the result of 'transdifferentiation' of WAT to BAT in response to certain stimuli, there is also the suggestion that beige adipocytes are a new type of adipocytes derived from progenitors distinct from WAT and BAT.[21,22]

Browning of WAT in CC can be triggered by several factors, including sympathetic nervous system (SNS) signals that activate β3 adrenoceptors.[13,23,24] Consequently, there is an overexpression of zinc-α2-glycoprotein (ZAG), which activates a G-coupled receptor with the consequent activation of hormone sensitive lipase (HSL) and the release of glycerol and free fatty acids (FFAs) from adipocytes.[23] ZAG is one of the best described adipokines involved in CC-related WAT browning.[4,24] Other adipokines are secreted by BAT such as leptin, adiponectin and resistin.[25] The role of leptin in CC is not clear. In most studies the levels of this adipokine are positively correlated with body mass index (BMI), suggesting that low levels simply reflect diminished fat mass.[26] However, these low leptin levels did not seem to result in increased appetite and decreased energy expenditure as expected. Thus, hypothalamic insensitivity to the low circulating levels of leptin have been speculated to occur in CC.[27] Circulating adiponectin concentrations were inversely correlated with both free and total leptin concentrations in cancer patients suggesting that adiponectin antagonizes the effect of leptin after weight loss.[28] Indeed, adiponectin concentration was reported to be significantly higher in cachectic patients when compared with stable weight patients.[29] Higher production of adiponectin in CC seems to contribute to the wasting process, as adiponectin administration in experimental animal models was shown to increase energy expenditure.[30] However, some authors have suggested that catabolic reactions and uncontrolled energy consumption in CC may contribute to adipose tissue degradation and to the reduction of adiponectin expression.[31] Resistin is an adipose tissue derived hormone, also termed "adipocyte secreted factor" (ADSF) or "found in inflammatory zone" (FIZZ3).[32] Despite its association to a variety of inflammatory and autoimmune processes, and to increased cancer risk, the association of resistin with body weight, appetite and insulin resistance is not clear.[27] Indeed, the majority of the studies on CC did not report a correlation between resistin and fat mass.[33,34]

BAT also produces other substances as a result of its endocrine activity, such as vascular endothelial growth factor (VEGF).[25] By promoting a dense vascular network, VEGF, particularly VEGF-A, indirectly supports the high-energy consumption of BAT.[35,36] Fibroblast growth factor (FGF) 21, a protein originally known to be expressed by the liver in response to fasting, is secreted by BAT, especially during thermogenic activation.[25] Parathyroid-hormone related protein (PTHrP) was also involved in WAT browning.[37] Indeed, higher serum levels of this protein were associated with weight loss in cancer patients.[38] Fat-specific knockout of PTHrP was reported to prevent adipose browning and also to preserve muscle mass and improve muscle strength.[39]

WAT is a contributor to systemic inflammation, as adipocytes and infiltrating inflammatory cells, primarily macrophages, produce inflammatory mediators, initiating a negative set of effects in the adipose tissue function, including the death of adipocytes.[40] For instance, TNF-α inhibits lipoprotein lipase (LPL) activity, increases HSL mRNA expression and reduces GLUT4 expression, leading to reduced glucose transport and consequently to a decline in glucose availability for lipogenesis.[41] TNF-α also increases the expression of chemoattractant protein 1, attracting monocytes to the adipose tissue.[42] The resulting inflammatory response leads to the recruitment of macrophages that produce TNF-α, IL-6 and IL-1β, increasing macrophage recruitment, perpetuating this vicious cycle.[42] IL-6 might enhance thermogenesis acting directly on BAT or indirectly through the stimulation of the sympathetic nervous system.[2] The cytokine TNF-related weak inducer of apoptosis (TWEAK) secreted by the tumour was also associated to cachexia.[43,44] However, inconsistent results have been reported regarding the CC-related levels of pro-inflammatory cytokines, which might be justified by the transient nature of its secretion, cancer stage or distinct assays sensitivities. Besides cytokines, inflammatory-induced prostaglandins have also been proposed as key mediators of CC. Among prostaglandins, prostaglandin E2 (PGE2) seems to be involved in CC once inhibition of the inducible cyclooxygenase (COX-2) prevents body weight loss.[45]. Indeed, higher levels of PGE2 were reported in cancer patients with cachexia.[46]. Table 1 overviews the most described circulating mediators involved in CC-related WAT remodelling.

Cellular events underlying the browning of WAT

The main molecular sign of WAT browning is the overexpression of uncoupling protein 1 (UCP1). The brite cells formed in WAT are capable of performing thermogenesis because they contain pockets of UCP1-expressing multilocular cells.[25,37] UCP1 is a long chain fatty acid-activated protein, highly selective for brown and beige adipose cells, that sits in the inner membrane of mitochondria.[20] The thermogenic effect of this protein is due to the deviation of mitochondria from its function of ATP production by mediating proton leakage across the inner mitochondrial membrane[71], not allowing the protons to be used in the process of ATP synthesis.[20]

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