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A MODULAÇÃO DA LIPASE DE TRIACILGLICEROL DO ADIPÓCITO (ATGL) E DA PERILIPINA 1 CONTRIBUI PARA O AUMENTO DA LIPÓLISE EM PACIENTES CAQUÉTICOS

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RESUMO

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A caquexia associada ao câncer é uma síndrome inflamatória crônica que apresenta como uma das principais características uma profunda perda de massa gorda. O tecido adiposo é um importante órgão endócrino, capaz de secretar uma miríade de fatores, as adipocinas. A intensa redução da massa gorda observada na caquexia, cujas bases moleculares ainda não estão estabelecidas, poderia, portanto, implicar em alterações que vão além da simples redução das reservas energéticas. Postula-se que um aumento na lipólise decorrente do aumento na expressão e na atividade da lipase hormônio-sensível (LHS) seja o fator-chave por trás da atrofia do tecido adiposo nesta síndrome. Entretanto, a contribuição das novas proteínas relacionadas à lipólise [*adipose triglyceride lipase* (ATGL), *comparative gene identification – 58* (CGI-58) e perilipina 1] ainda é controversa. Foi objetivo deste estudo, caracterizar a expressão das proteínas relacionadas à lipólise (LHS, ATGL, CGI-58 e perilipina 1) e das adipocinas (adiponectina, leptina e visfatina) ao longo da progressão do estado caquético. Pacientes do Hospital Universitário foram divididos em três grupos: portadores de tumor com caquexia (TBC), portadores de tumor com peso estável (TB) e controles (CTR). Um modelo experimental de caquexia foi também estudado, representado pelos seguintes grupos: ratos portadores do carcinossarcoma de Walker 256 sacrificados no 7º dia (TB7) e no 14º dia (TB14) após a inoculação tumoral, e ratos controle. O tecido adiposo subcutâneo dos pacientes e o tecido adiposo epididimal dos animais foram investigados quanto aos aspectos morfológicos (HE) e morfométricos (área, diâmetro e perímetro dos adipócitos). Aspectos moleculares foram também examinados através da determinação do conteúdo protéico (ELISA e *Western blotting*) e expressão gênica (PCR tempo real) das seguintes proteínas: LHS, ATGL, CGI-58, perilipina 1, leptina, adiponectina, visfatina e fator de necrose tumoral-alfa (TNF-α). Verificamos um aumento da lipólise nos pacientes caquéticos, não apenas pelo aumento na expressão de LHS, mas também pela aumentada expressão da ATGL (quase 2 vezes em relação ao CTR) e redução no conteúdo de perilipina 1 (51 %). Nos animais em uma fase intermediária da síndrome, a qual se assemelha com o estágio observado em nosso modelo clínico, verificou-se ainda um desequilíbrio na secreção de fatores anti e pró-inflamatórios. No estágio final da caquexia as alterações são ainda mais profundas e houve redução na expressão de quase todas as proteínas analisadas nos

animais. Esta marcante redução na expressão de adipocinas e proteínas relacionadas à lipólise, associada à alteração na matriz extra-celular e formato dos adipócitos, sugere que no estágio final do estado caquético há um comprometimento da função celular como um todo. Verificamos que a caquexia induz importantes alterações morfológicas, moleculares e humorais no tecido adiposo branco, cuja intensidade relaciona-se diretamente com o estágio da progressão do estado caquético.

Palavras - chave: Caquexia associada ao câncer. Tecido adiposo. Lipólise. Adipocinas.

ABSTRACT

Silvério R. Modulation of adipose triglyceride lipase (ATGL) and perilipin 1 contributes to increased lipolysis in cachectic patients. [Ph.D. thesis (Cell and Tissue Biology)] São Paulo: Instituto de Ciências Biomédicas, Universidade de São Paulo; 2011.

Cancer cachexia, a chronic inflammatory syndrome, presents as a major feature marked loss of fat mass. The adipose tissue is an important endocrine organ, secreting a myriad of factors, the adipokines. Therefore, the fat mass depletion in cachexia, whose the molecular bases are not yet established, could result in more drastic changes than simple reduction of energy reserves. It is postulated that an increase in lipolysis due to increased expression and activity of hormone-sensitive lipase (HSL) is the key factor behind the atrophy of adipose tissue in this syndrome. However, the contribution of novel proteins related to lipolysis [adipose triglyceride lipase (ATGL), comparative gene identification - 58 (CGI-58) and perilipin 1] is still controversial. Our purpose was to characterize the expression of lipolysis-related proteins (HSL, ATGL, CGI-58 and perilipin 1) and adipokines (adiponectin, leptin and visfatin) along cachexia progression. Patients from University Hospital were divided into three groups: cachectic cancer patients (TBC), stable weight cancer patients (TB) and controls (CTR). Walker 256 carcinosarcoma, an experimental model of cachexia, was also studied. Animals were divided into: control (CTR), tumour-bearing studied on the seventh day (TB7) and tumour-bearing studied on the fourteenth day (TB14) after tumour inoculation. Subcutaneous adipose tissue of patients and epididymal adipose tissue of animals were investigated, regarding morphological (HE) and morphometric (area, perimeter and diameter of adipocytes) aspects. Molecular aspects were also examined by determining the protein content (Western blotting and ELISA) and gene expression (real-time PCR) of HSL, ATGL, CGI-58, perilipin 1, leptin, adiponectin, visfatin and tumor necrosis factor alpha (TNF-α). We found augmented lipolysis in cachectic patients associated with increased HSL expression, as well as upregulation of ATGL expression (almost 2.0 fold compared to CTR) and reduction in perilipin 1 content (by 51 %). In TB7 (intermediate stage of the syndrome, similar to the clinical study), there was an imbalance in the secretion of pro and anti-inflammatory factors. The alterations at the end stage of cachexia were even more profound and there was a reduction in the expression of almost all proteins analysed in the animals. The marked decrease in adipokine and lipolysis-related protein expression, associated with changes in the extracellular matrix and adipocytes shape, suggests impairment of cellular function in terminal cachexia. We conclude that cachexia induces important morphological,

molecular and humoral alterations in white adipose tissue, which are specific to the stage of the syndrome.

Keywords: Cancer cachexia. Adipose tissue. Lipolysis. Adipokines.

1 INTRODUÇÃO

A caquexia, cuja mais notável característica é a intensa e rápida perda de peso, é uma síndrome paraneoplásica que afeta cerca de dois terços dos pacientes com câncer avançado e é considerada a causa direta da morte em pelo menos 22% dos casos (Warren, 1932). Em cerca de 60 a 80% dos pacientes com câncer no trato digestório ou pulmão esta síndrome já está presente no momento do diagnóstico, reduzindo drasticamente a sobrevida e determinando prognóstico negativo (Bruera, 1997). A etiologia não completamente desvendada, associada à complexidade dos sintomas que a compõem, fazem com que a caquexia seja precariamente diagnosticada e, ainda com menor frequência, tratada (Springer et al., 2006; Evans et al., 2008).

Recentemente a caquexia foi concebida como uma síndrome multifatorial, com um quadro de inflamação sistêmica crônica, desencadeada tanto pelo tumor quanto pela reação do hospedeiro à sua presença (Fearon et al., 2011; Rydén et al., 2008). O papel do tumor da etiologia da síndrome inclui a secreção local de citocinas pró-inflamatórias que iniciam uma resposta inflamatória sistêmica e a produção de fatores pró-caquéticos que têm efeitos catabólicos diretos nos tecidos do hospedeiro (Skipworth et al., 2007). Os mecanismos do hospedeiro envolvem uma resposta exacerbada do organismo à presença do tumor, incluindo a ativação de uma resposta inflamatória sistêmica (Deans et al., 2006) e uma resposta de estresse neuro-endócrino (Barber et al., 2004; Costelli et al., 2006). Como resultado da interação tumor-hospedeiro há intensa depleção da musculatura esquelética e tecido adiposo, anorexia, alterações do gasto energético e do metabolismo de carboidratos, proteínas e lipídios (Argilés et al., 1997).

Se outrora imaginava-se que o tecido adiposo era um compartimento do qual o organismo podia prescindir, atualmente a sua importância fundamental como órgão endócrino está estabelecida.

Estudos prévios do nosso grupo mostraram que a caquexia afeta o tamanho, a morfologia e a composição de ácidos graxos em adipócitos (Bertevello e Seelaender, 2001). Posteriormente, demonstramos ainda a presença de macrófagos infiltrantes no tecido adiposo branco de animais caquéticos, concomitantemente à elevada produção de TNF-α e PGE2 por estas células, indicando a presença de inflamação local (Machado et al., 2004). É possível que este aumento na concentração de mediadores inflamatórios resulte em agravamento da inflamação sistêmica e, sendo assim, o tecido adiposo não seria apenas afetado por esta síndrome, como também possuiria papel fundamental no estabelecimento do quadro inflamatório característico da caquexia.

Na última década a importância do tecido adiposo como órgão endócrino, capaz de sintetizar e secretar uma ampla gama de fatores, denominados adipocinas, foi reconhecida (Ahima, 2006). As adipocinas atuam localmente, de modo autócrino, parácrino e/ou como sinais endócrinos para regular uma série de processos fisiológicos como sensibilidade à insulina e inflamação (Ahima, 2006). O balanço entre a secreção de fatores pró e anti-inflamatórios é dependente essencialmente do estímulo e do depósito do tecido adiposo (Coopack, 2001) e é adotado como marcador da severidade da caquexia associada ao câncer (Argilés et al., 1997). Neste contexto, Murphy et al. (2010) sugerem ainda que a perda de tecido adiposo na caquexia serve como um preditor de sobrevivência, podendo ser utilizada como ferramenta prognóstica.

Embora inúmeros estudos evidenciem o papel crucial do tecido adiposo na caquexia, as bases moleculares da sua depleção não são totalmente elucidadas. Estudos sugerem que um aumento na lipólise seja o fator-chave neste processo (Large et al., 1997; Skoog et al., 2001). Por muitos anos, a lipase hormônio sensível (LHS) foi considerada a enzima chave na regulação da lipólise (Langin, 2006a) e postula-se que a lipólise esteja aumentada na caquexia em decorrência do aumento na expressão e na atividade desta enzima (Agustsson et al, 2007). Todavia, é importante ressaltar que recentemente houve um considerável avanço em relação ao conhecimento da regulação do processo lipolítico e, atualmente, sabe-se que este é controlado por interações complexas entre proteínas que recobrem a gotícula lipídica e lipases, além de proteínas adicionais que atuam como cofatores enzimáticos.

Sendo assim, de acordo com o modelo lipolítico recentemente estabelecido, além da LHS outra lipase possui importante papel nesta via, a lipase de triacilglicerol do adipócito (ATGL). Esta enzima inicia a lipólise por remover especificamente o primeiro ácido graxo do triacilglicerol e o diacilclicerol resultante é então hidrolisado pela LHS (Jaworski et al., 2007). Outras proteínas estão também envolvidas na regulação do processo de lipólise, entre elas destacamos a perilipina 1, proteína mais abundante na superfície de gotículas lipídicas (Brasaemle, 2007), e a *comparative gene identification-58* (CGI-58), proteína coativadora da ATGL.

Apesar do número crescente de pesquisas visando elucidar os mecanismos através dos quais essas novas proteínas regulam o processo lipolítico, ainda não existem na literatura dados referentes à expressão destas durante a progressão do estado caquético.

1.1 Justificativa

Atualmente, o tecido adiposo é considerado um importante órgão endócrino tendo em vista o grande número de adipocinas que é capaz de secretar, estando estas envolvidas em uma ampla gama de respostas fisiológicas. Desta forma, a redução da massa do tecido adiposo, bem como as alterações morfofuncionais deste tecido observadas na caquexia, poderiam implicar em alterações que vão além da simples redução das reservas energéticas. Pela análise da literatura, verificamos que são poucos os estudos que avaliam as alterações fisiológicas no tecido adiposo durante a caquexia. Além disso, não encontramos, até o presente momento, estudos que verifiquem a expressão das recentemente descritas proteínas envolvidas no processo de lipólise (ATGL, perilipina e CGI-58) durante a progressão desta síndrome. Como buscamos a compreensão não apenas das alterações da via lipolítica *per se*, mas também a análise dessas modificações ao longo da progressão da caquexia, acreditamos que estes resultados poderão contribuir como base para o desenvolvimento futuro de possíveis intervenções terapêuticas.

2 CONCLUSÃO

No presente estudo verificamos que a caquexia induz importantes alterações morfológicas e moleculares no tecido adiposo branco. Em um estágio intermediário da síndrome, a modulação das duas principais lipases (ATGL e LHS) e da perilipina 1 contribui para o aumento da lipólise nos pacientes caquéticos. Concomitantemente, há um desequilíbrio na secreção tecidual de fatores pró e anti-inflamatórios, que pode agravar ainda mais o quadro inflamatório sistêmico característico desta condição. No estágio terminal da caquexia, as alterações teciduais são mais pronunciadas e ocorre uma redução na expressão de quase todas as proteínas estudadas, sugerindo um prejuízo na funcionalidade dos adipócitos. Desta forma, concluímos que as alterações no tecido adiposo podem ser utilizadas como marcadores indicativos de progressão da caquexia.

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