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CACHEXIA

Putting the brakes on lipid loss

Cancer-associated cachexia (CAC), a multifactorial wasting syndrome that is characterized by the loss of adipose tissue and muscle, occurs in many cancer patients, and about 15% of cancer-associated deaths can be attributed to CAC. Evidence suggests that fat breakdown in CAC is a result of the increased degradation of triglyceride lipids; so, Das, Zechner, Hoefler and colleagues examined the role of two enzymes that are crucial for triglyceride lipolysis in CAC.

Mice lacking either adipose triglyceride lipase (ATGL) or hormone-sensitive lipase (HSL) were subcutaneously injected with either Lewis lung carcinoma (LLC) cells or B16 melanoma cells. Wild-type mice with either LLC or B16 tumours had reduced total body weight (after subtracting tumour weight) and reduced white adipose tissue (WAT) weight compared with mice without tumours. By contrast, *Atgl*$^{-/-}$ mice had similar total body and WAT weights regardless of whether they carried tumours, and *Hsl*$^{-/-}$ mice had an intermediate phenotype in which loss of body weight or WAT occurred following tumour growth, but to a lesser degree than that observed in wild-type mice. These observations held true in both non-fasted and overnight-fasted animals and were not explained by variations in food intake. Overall, this suggests that loss of ATGL (and to some extent loss of HSL) can protect from tumour-associated loss of weight and WAT in mice.

> “loss of ATGL … can protect from tumour-associated loss of weight and WAT in mice.”

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What mechanisms underlie weight loss in tumour-bearing mice? WAT explants from wild-type mice carrying tumours had increased release of fatty acids and glycerol, indicating an increase in lipolysis, which was attributed to higher ATGL and HSL activity. This increase was not observed in explants from *Atgl*$^{-/-}$ mice and was partially reduced in those from *Hsl*$^{-/-}$ mice. In addition, plasma levels of circulating factors that are known to induce lipolysis, such as inflammatory cytokines, were increased following LLC or B16 cell injection in mice of all genotypes, suggesting that these factors operate upstream of ATGL and HSL induction.

Skeletal muscle is also depleted in CAC, and the authors observed a reduction in the weight of the gastrocnemius muscle (which forms part of the calf muscle in the leg) in wild-type mice bearing LLC or B16 tumours compared with mice without tumours. Mice lacking ATGL were protected from tumour-induced gastrocnemius muscle atrophy, and those lacking HSL were partially protected. Muscle loss in these mice seems to be a result of increased protein degradation by the proteasome, as well as increased apoptosis.

Analysis of WAT from autopsy samples of 27 patients, 12 of whom had malignancies, indicated higher ATGL and HSL activity in the patients with cancer compared with those without. Six of the 12 patients with malignancies had been defined as cachectic, and those patients had higher lipolytic enzyme activity than the patients without CAC. Furthermore, ATGL and HSL activity were significantly inversely correlated with body mass index in the cancer patients. These data imply that the mechanisms underlying CAC are similar in mice and humans, and that pharmacological inhibition of these lipases might prevent or reduce CAC.

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ORIGINAL RESEARCH PAPER Das, S. K. *et al.* Adipose triglyceride lipase contributes to cancer-associated cachexia. *Science* 16 Jun 2011 (doi:10.1126/science.1198973)