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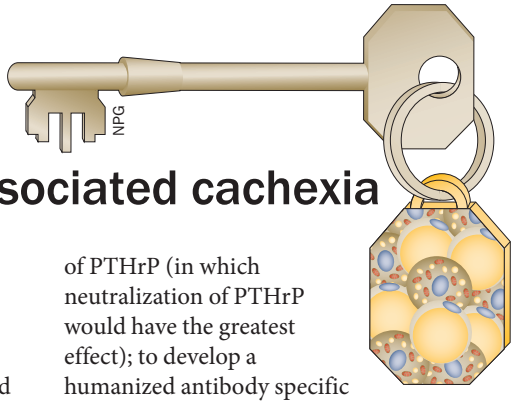

METABOLISM

WAT browning—key feature of cancer-associated cachexia

Two new studies highlight the important role of white adipose tissue (WAT) browning in the development and progression of cancer-associated cachexia (CAC)—a wasting disorder of adipose tissue and skeletal muscle.

In the first study, researchers led by Erwin Wagner observed a phenotypic switch from WAT to brown adipose tissue and increased energy expenditure, which preceded skeletal muscle atrophy, in many mouse models of CAC. "This is the first time that WAT browning has been recognized as being responsible for the pathogenesis of a disease," explains Wagner. "Until now, only the beneficial effects of WAT browning in the context of obesity and diabetes were known."

The researchers found increased levels of IL-6—a proinflammatory cytokine—in the blood of cachectic mice. Blocking IL-6 release in CAC mice rescued the cachectic phenotype. "Our data in animal models show that anti-inflammatory drugs are beneficial to ameliorate cachexia, but treatment should start as early as possible, before the full appearance of CAC," says Wagner.

In the second study, Bruce Spiegelman and colleagues identified tumour-induced factors that increased WAT browning. One of these factors, parathyroid-hormone-related protein (PTHrP), potently induced gene expression of markers of WAT browning and energy metabolism in adipocytes; injection of CAC mice with a PTHrP-neutralizing antibody prevented cachexia and skeletal muscle atrophy. The researchers next measured levels of PTHrP in patients diagnosed with lung or colorectal cancer. Patients with detectable levels of PTHrP had reduced lean body mass and increased energy expenditure compared with patients without detectable levels of PTHrP, confirming an association between elevated levels of PTHrP and tissue wasting and hypermetabolism.

Going forward, Spiegelman plans to screen human cancers to identify those that produce the greatest amounts of PTHrP (in which neutralization of PTHrP would have the greatest effect); to develop a humanized antibody specific for PTHrP that could be used in clinical trials; and to replicate the findings in mouse models of congestive heart failure and chronic kidney disease, as cachexia is also associated with these conditions.

Overall, these studies reveal the detrimental effects of WAT browning in the context of CAC. Inhibition of WAT browning might have therapeutic potential not only for treating patients with CAC, but also for patients with cachexia associated with other comorbidities.

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Original articles Petruzzelli, M. *et al*. A switch from white to brown fat increases energy expenditure in cancer-associated cachexia. *Cell Metab*. doi:10.1016/j.cmet.2014.06.011 | Kir, S. *et al*. Tumour-derived PTH-related protein triggers adipose tissue browning and cancer cachexia. *Nature* doi:10.1038/nature13528