Stored fat fights against the body's attempts to lose weight

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The fatter we are, the more our body appears to produce a protein that inhibits our ability to burn fat, suggests new research published in the journal *Nature Communications*. The findings may have implications for the treatment of obesity and other metabolic diseases.

Most of the fat cells in the body act to store excess energy and release it when needed but some types of fat cells, known as brown adipocytes,

function primarily for a process known as thermogenesis, which generates heat to keep us warm. However, an international team of researchers from the Wellcome Trust-Medical Research Council Institute of Metabolic Sciences at the University of Cambridge, UK, and Toho University, Japan, have shown that a protein found in the body, known as sLR11, acts to suppress this process.

Researchers investigated why mice that lacked the gene for the production of this protein were far more resistant to weight gain. All mice – and, in fact, humans – increase their metabolic rate slightly when switched from a lower calorie diet to a higher calorie diet, but mice lacking the gene responded with a much greater increase, meaning that they were able to burn calories faster.

Further examinations revealed that in these mice, genes normally associated with brown adipose tissue were more active in white adipose tissue (which normally stores fat for energy release). In line with this observation, the mice themselves were indeed more thermogenic and had increased energy expenditure, particularly following high fat diet feeding.

The researchers were able to show that sLR11 binds to specific receptors on fat cells – in the same way that a key fits into a lock – to inhibit their ability to activate thermogenesis. In effect, sLR11 acts as a signal to increase the efficiency of fat to store energy and prevents excessive energy loss through unrestricted thermogenesis.

When the researchers examined levels of sLR11 in humans, they found that levels of the protein circulating in the blood correlated with total fat mass – in other words, the greater the levels of the protein, the higher the total fat mass. In addition, when obese patients underwent bariatric surgery, their degree of postoperative weight loss was directly proportional to the reduction in their sLR11 levels, suggesting that

sLR11 is produced by fat cells.

In their paper the authors suggest that sLR11 helps fat cells resist burning too much fat during 'spikes' in other metabolic signals following large meals or short term drops in temperature. This in turn makes adipose tissue more effective at storing energy over long periods of time.

There is growing interest in targeting thermogenesis with drugs in order to treat obesity, diabetes and other associated conditions such as heart disease. This is because it offers a mechanism for disposing of excess fat in a relatively safe manner. A number of molecules have already been identified that can increase thermogenesis and/or the number of fat cells capable of thermogenesis. However to date there have been very few molecules identified that can decrease thermogenesis.

These findings shed light on one of the mechanisms that the body employs to hold onto stored energy, where sLR11 levels increase in line with the amount of stored fat and act to prevent it being 'wasted' for thermogenesis.

Dr Andrew Whittle, joint first author, said: "Our discovery may help explain why overweight individuals find it incredibly hard to lose weight. Their stored fat is actively fighting against their efforts to burn it off at the molecular level."

Professor Toni Vidal-Puig, who led the team, added: "We have found an important mechanism that could be targeted not just to help increase people's ability to burn fat, but also help people with conditions where saving energy is important such as anorexia nervosa."

Jeremy Pearson, Associate Medical Director at the British Heart Foundation (BHF), which helped fund the research, said: "This research could stimulate the development of new drugs that either help reduce

obesity, by blocking the action of this protein, or control weight loss by mimicking its action. Based on this promising discovery, we look forward to the Cambridge team's future findings.

"But an effective medicine to treat obesity, which safely manages weight loss is still some way off. In the meantime people can find advice on healthy ways to lose weight and boost their heart healthy on the BHF website."

More information: Andrew J. Whittle et al. Soluble LR11/SorLA represses thermogenesis in adipose tissue and correlates with BMI in humans, *Nature Communications* (2015). DOI: 10.1038/ncomms9951

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