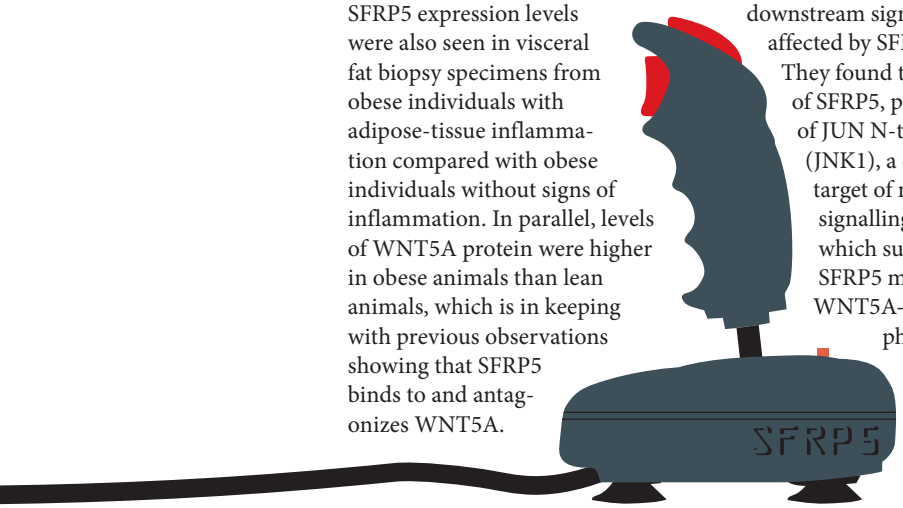
INFLAMMATION

The fat controller

Most adipokines — soluble mediators secreted mainly by fat cells — are pro-inflammatory and contribute to the state of low-grade inflammation that is often associated with obesity-linked metabolic disorders, such as type 2 diabetes. However, Ouchi *et al.* have identified a new adipokine with anti-inflammatory properties — secreted frizzled-related protein 5 (SFRP5). Expression of SFRP5 was found to be disturbed in mouse models of obesity and type 2 diabetes.

Gene expression analysis of adipose tissue in lean and obese mice revealed that SFRP5 expression is reduced in genetically obese mice (ob/ob mice) or wild-type mice placed on a high-calorie diet for prolonged periods. Lower SFRP5 expression levels were also seen in visceral fat biopsy specimens from obese individuals with adipose-tissue inflammation compared with obese individuals without signs of inflammation. In parallel, levels of WNT5A protein were higher in obese animals than lean animals, which is in keeping with previous observations showing that SFRP5 binds to and antagonizes WNT5A.



To investigate the role of SFRP5 in metabolism, the authors studied *Sfrp5*$^{-/-}$ mice. When these mice were placed on a high-calorie diet they developed raised glucose levels, impaired insulin sensitivity and higher liver fat content than wild-type mice on a high-calorie diet or *Sfrp5*$^{-/-}$ mice on a normal diet. Consistent with previous studies linking macrophages to insulin resistance, a large number of macrophages accumulated in the adipose tissue of *Sfrp5*$^{-/-}$ mice on a high-calorie diet. This was associated with increased secretion of pro-inflammatory cytokines, such as tumour necrosis factor and interleukin-6, by fat cells.

Next, the authors analysed the downstream signalling pathways affected by SFRP5 deficiency. They found that in the absence of SFRP5, phosphorylation of JUN N-terminal kinase 1 (JNK1), a downstream target of non-canonical Wnt signalling, was increased, which suggested that SFRP5 might antagonize WNT5A-induced JNK1 phosphorylation. Cell transfection studies proved this to be the case; forced expression of SFRP5 by adipocytes or macrophages blocked WNT5A-stimulated JNK1 phosphorylation and production of pro-inflammatory mediators. Accordingly, metabolic function was normal in mice lacking both SFRP5 and JNK1 when they received the high-calorie diet.

An exciting therapeutic potential for this pathway was shown by the finding that intravenous administration of an adenovirus encoding SFRP5 led to substantial improvements in glucose metabolism in *Sfrp5*$^{-/-}$ mice on a high-calorie diet. It also reversed the metabolic disturbances in ob/ob mice, leading to improved glucose and insulin sensitivity, reduced levels of pro-inflammatory mediators and attenuation of lipid accumulation in the liver.

So, SFRP5 secreted by adipocytes provides local control of fat tissue homeostasis under conditions of metabolic stress by inhibiting JNK1 activation downstream of Wnt signalling, and therefore is an encouraging new target for the control of obesity-linked metabolic disorders.

Lucy Bird,
Nature Reviews Immunology

ORIGINAL RESEARCH PAPER Ouchi, N. *et al.* Sfrp5 is an anti-inflammatory adipokine that modulates metabolic dysfunction in obesity. *Science* 17 Jun 2010 (doi:10.1126/science.1188280)