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news

Another piece in the molecular puzzle of obesity

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Researchers at the University of Michigan Medical School (UMMS) have found that the molecule SH2-B, which interacts with JAK2, a cell signalling protein activated by leptin, is required for maintaining normal energy metabolism and body weight. 'SH2-B seems to be an endogenous enhancer of leptin sensitivity: disruption of the *SH2-B* gene results in severe leptin resistance, hyperphagia, obesity and obesity-associated metabolic syndrome,' explains senior author Liangyou Rui from the Department of Molecular and Integrative Physiology, UMMS, Ann Arbor, MI, USA.

SH2-B helps regulate leptin sensitivity

Leptin is known to regulate energy balance and body weight by activating its receptor LEPRb and multiple downstream signalling pathways in the hypothalamus. Leptin stimulates activation of LEPRb-associated JAK2, which initiates cell signalling. 'SH2-B is a key regulator of leptin sensitivity, energy balance and body weight, due to its association with JAK2,' adds Rui. His group studied the effects of knocking out the *SH2-B* gene in mice and observed that *SH2-B* homozygous null mice were severely hyperphagic and obese and developed hyperleptinaemia, hyperinsulineamia, hyperlipidaemia, hepatic steatosis and hyperglycaemia. 'On the other side of the coin, overexpression of *SH2-B* counteracted chemical inhibition of leptin signalling in cultured cells,' says Rui.

> '...SH2-B as a very promising marker of obesity in animal models.'

SH2-B as a drug candidate?

Emanuela Taioli (Fondazione Policlinico IRCCS, Unit of Molecular and Genetic Epidemiology, Milan, Italy) regards SH2-B as a very promising marker of obesity in animal models. 'SH2-B could be used together with leptin to increase the body sensitivity to leptin. However, this mechanism has been shown in animal models only. Leptin itself is less associated with obesity in humans than it is in animal models and it would be necessary to transfer the work in the current study into human subjects before tackling drug development,' she says. 'The elegant study by Rui's group showing the development of obesity in SH2-B knockout mice clearly suggests a critical role of SH2-B in leptin signaling and energy homeostasis,' agrees Abhiram Sahu (Department of Cell Biology and Physiology, University of Pittsburgh School of Medicine, PA, USA). However, he agrees with Taioli that the major task now is to demonstrate that SH2-B signaling is altered in the hypothalamus during the development of diet-induced obesity, the common form of obesity in humans.

> 'Developing breakthrough treatments in obesity could still take some time'

Is a pill for obesity likely anway?

Sahu warns that 'unless one can demonstrate that increasing SH2-B activity prevents or attenuates the development of diet-induced obesity, it is difficult to suggest whether SH2-B can be used to develop drugs to treat the obese.' Gene therapy or investigating the genetic component of obesity specifically related to SH2-B might be a more worthwhile approach, he suggests. He also thinks that, because obesity is a complex mechanism involving multiple players, it might be extremely difficult to develop any 'magic pill' to curb fatness. 'It may require to use combination of pills along with a sincere effort to balance energy intake and energy expenditure. Developing breakthrough treatments in obesity could still take some time,' he says. Among the hot prospects, endocannabinoids, Ghrelin, PYY3-36, melanocortin receptors, adiponectin, peroxisome proliferator-activated receptors and SOCS3 are notable targets for drug development, says Sahu.

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