Anti-inflammatory adipokine to combat metabolic dysfunction

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Diet-induced obesity triggers the infiltration of immune cells into adipose tissue, leading to inflammation and promoting the development of type 2 diabetes. Adipose tissue is an active endocrine organ that secretes hormones and cytokines (known as adipokines when derived from adipose tissue), which mainly have pro-inflammatory functions. However, Ouchi et al. now report that secreted frizzled-related protein 5 (Sfrp5) is a newly identified anti-inflammatory adipokine. Sfrp5 expression and secretion were reduced in rodent models of obesity and type 2 diabetes, and Sfrp5-deficient mice exhibited classical markers of metabolic dysfunction, such as elevated fasting glucose and insulin levels, increased liver triglycerides, reduced glucose clearance, and increased insulin resistance and adipose tissue macrophage infiltration. Conversely, Sfrp5 treatment reversed metabolic dysfunction in several mouse models of obesity. The researchers propose that Sfrp5 neutralises Wnt5a-mediated noncanonical JNK1 activation, a key pathway that regulates adipose tissue inflammation and glucose metabolism, in both adipocytes and macrophages. These findings identify Sfrp5 as an anti-inflammatory adipokine that could be targeted in therapies for obesity-induced type 2 diabetes. *M.R.*

Ouchi, N., Higuchi, A., Ohashi, K., Oshima, Y., Gokce, N., Shibata, R., Akasaki, Y., Shimono, A. and Walsh, K. (2010). Sfrp5 is an anti-inflammatory adipokine that modulates metabolic dysfunction in obesity. *Science* **329**, 454-457.

Boning up on energy metabolism

Recently, it emerged that bone is an important endocrine organ that regulates energy metabolism through osteocalcin, a hormone that favours insulin secretion and sensitivity, and energy expenditure. According to the general rules of endocrinology, these observations suggested that insulin might in turn affect the endocrine function of bones. To address this issue, Ferron et al. engineered an osteoblast-specific insulin-receptor-deficient mouse model and demonstrated that maintenance of whole-body glucose homeostasis requires insulin signalling in osteoblasts. Insulin signalling in osteoblasts essentially hijacks the functional interaction that exists in bone between osteoblasts and osteoclasts. In osteoblasts, insulin signalling inhibits the expression of an inhibitor of bone resorption, thereby upregulating this function. Osteoclasts resorb bone under highly acidic conditions, providing a favourable environment for the activation of osteocalcin, which, in turn, stimulates insulin secretion. This mechanism occurs in mice and in humans. These results further underscore the tight relationship that has emerged recently between bone physiology and glucose homeostasis; they also have important implications for the treatment of diseases such as type 2 diabetes and osteoporosis. *M.R.*

Ferron, M., Wei, J., Yoshizawa, T., Del Fattore, A., DePinho, R. A., Teti, A., Ducy, P. and Karsenty, G. (2010). Insulin signaling in osteoblasts integrates bone remodeling and energy metabolism. *Cell* **142**, 296-308.

The first mouse model of ependymoma

Although ependymomas – a group of CNS tumours – have a similar appearance in affected patients, who are mostly children, the underlying genetic alterations and clinical outcomes vary depending on the location of the tumour, hindering the development of useful animal models. Using cross-species genomics, Johnson et al. have now broken through this barrier. They compared the transcriptomes of subgroups of human ependymoma with those of spatially and developmentally distinct groups of mouse neural stem cells (NSCs), and found a close match between a subset of human supratentorial ependymomas and embryonic cerebral NSCs from mice with deletion of the tumour suppressor gene *Ink4a/Arf*. The human tumours were also found to have amplification and/or overexpression of *EphB2*, the product of which is involved in numerous developmental processes. When the matched mouse NSCs were transduced with *EphB2* and transplanted into the mouse forebrain, tumours that were histologically and molecularly identical to the human ependymomas resulted, with high penetrance. This approach could be used to develop models for other ependymoma subgroups, potentially helping to attain a cure for this often-incurable set of diseases. *J.H.*

Johnson, R. A., Wright, K. D., Poppleton, H., Mohankumar, K. M., Finkelstein, D., Pounds, S. B., Rand, V., Leary, S. E., White, E., Eden, C. et al. (2010). Cross-species genomics matches driver mutations and cell compartments to model ependymoma. *Nature* **466**, 632-636.

A lysosomal sulfatase influences neurodegeneration

Kufs' disease is a rare, adult-onset form of a group of neurodegenerative disorders known as neuronal ceroid lipofuscinoses (NCLs). Although some of the genetic and cellular defects underlying early-onset, inherited NCLs have been identified, the causes of Kufs' disease are less clear. Through genetic analyses of American Staffordshire terriers that suffer from a late-onset form of NCL, Abitbol et al. uncovered a role for a lysosomal sulfatase, *arylsulfatase G* (*ARSG*), in disease pathology. The researchers found that an NCL-associated mutation near the region of *ARSG* encoding the enzyme's catalytic domain caused a 75% reduction in its sulfatase activity, supporting previous findings that lysosomal defects underlie NCLs. These findings reveal a role for *ARSG* in regulating neuronal homeostasis and open up the possibility that sulfatase deficiency might cause or modify the pathology of NCLs in humans. *S.A.*

Abitbol, M., Thibaud, J. L., Olby, N. J., Hitte, C., Puech, J. P., Maurer, M., Pilot-Storck, F., Hédan, B., Dréano, S., Brahimi S. et al. (2010). A canine Arylsulfatase G (ARSG) mutation leading to a sulfatase deficiency is associated with neuronal ceroid lipofuscinosis. *Proc. Natl. Acad. Sci. USA* Aug 2 [Epub ahead of print] [doi: 10.1073/pnas.0914206107]