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IMMUNOMETABOLISM

ILC2s skew the fat

S.Bradbrook/NPG

Innate lymphoid cells (ILCs) are emerging as key regulators of the immune system, but they have also recently been linked to the regulation of host metabolism. Brestoff *et al.* now identify group 2 ILCs (ILC2s) in human adipose tissue and show that these cells protect against the development of obesity in mice by promoting the beiging of adipose tissue.

Recent work reported that ILC2s are present in the white adipose tissue (WAT) of mice. In agreement with this, Brestoff *et al.* identified lineage-negative cells with typical ILC2 characteristics — including the expression of the transcription factor GATA3 and the interleukin-33 (IL-33) receptor — in subcutaneous WAT from non-obese human donors. Furthermore, they found that obesity in both humans and mice is associated with decreased frequencies of ILC2s in WAT. They explored whether IL-33 regulates these ILC2s and, indeed, found that IL-33-deficient mice had fewer ILC2s in WAT than wild-type mice. Strikingly, when maintained on a normal diet, IL-33-deficient mice gained more weight, accumulated more WAT, and showed impaired glucose and insulin tolerance. By contrast, IL-33-treated wild-type mice showed greater accumulation of ILC2s in WAT and had decreased adiposity compared with controls. Treatment with IL-33 also prevented weight gain and improved glucose homeostasis in mice that were fed a high-fat diet. Thus, IL-33 supports ILC2 accumulation in WAT and this protects against obesity.

> “the IL-33–ILC2 axis could be targeted for the treatment of obesity and metabolic diseases”

The authors found that treatment with exogenous IL-33 increased caloric expenditure in mice, but this was not associated with altered food intake or greater physical activity. They examined whether IL-33 might instead regulate beige adipocytes. These adipocytes generate large amounts of heat and expend more calories than white adipocytes owing to the uncoupling of energy substrate oxidation from ATP synthesis, a process that depends on the expression of uncoupling protein 1 (UCP1). The authors showed that WAT from IL-33-deficient mice contained fewer beige adipocytes and lower levels of *Ucp1* transcripts than wild-type WAT. When ILC2s from the WAT of IL-33-treated mice were transferred to wild-type recipients they accumulated in recipient WAT, and this was associated with increased numbers of beige adipocytes and greater oxygen consumption in the WAT. Furthermore, IL-33 treatment was found to promote beiging in WAT, but only in the presence of ILC2s. Therefore, IL-33 seems to promote beiging in adipose tissue in an ILC2-dependent manner.

A further series of experiments showed that ILC2-mediated beiging does not require eosinophils or alternatively activated macrophages, which have previously been linked with beiging responses. However, transcriptional profiling of different mouse ILC populations identified proprotein convertase subtilisin/kexin type 1 (*Pcsk1*) as a gene that is enriched in ILC2s. PCSK1 cleaves certain prohormones into their active forms and loss-of-function mutations affecting this enzyme are associated with obesity in mice and humans. Proenkephalin A — which PCSK1 cleaves into various opioid-like peptides, including Met-enkephalin — was also enriched in ILC2s, and ILC2s upregulated the production of Met-enkephalin peptides in response to IL-33. Notably, the administration of Met-enkephalin peptides to wild-type mice led to increased numbers of $UCP1^+$ beige adipocytes and oxygen consumption in their WAT. Thus, ILC2s seem to induce beiging in WAT by producing Met-enkephalin peptides.

The authors suggest that the ability of ILC2s to simultaneously regulate immune and metabolic processes may have an evolutionary advantage in enabling the host to respond to diverse environmental challenges. In addition, they propose that the IL-33–ILC2 axis could be targeted for the treatment of obesity and metabolic diseases in humans.

Yvonne Bordon

ORIGINAL RESEARCH PAPER Brestoff, J. R. *et al.* Group 2 innate lymphoid cells promote beiging of white adipose tissue and limit obesity. *Nature* http://dx.doi.org/10.1038/nature14115 (2014)