# IN BRIEF

IMMUNOMETABOLISM

## The inflammasome-mediated caspase-1 activation controls adipocyte differentiation and insulin sensitivity

Stienstra, R. *et al. Cell Metab.* **12**, 593–605 (2010)

## The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance

Vandanmagsar, B. *et al. Nature Med.* 9 Jan 2011 (doi:10.1038/nm.2279)

Obesity is associated with chronic low-grade inflammation and is a known risk factor for a number of metabolic diseases, including type 2 diabetes. The link between obesity and inflammation has been unclear, but these studies show that obesity-induced activation of the NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome is crucial for caspase 1-mediated activation of inflammatory cytokines, such as interleukin-1β (IL-1β) and IL-18, which promote insulin resistance. Stienstra *et al.* found that caspase 1 expression was upregulated during differentiation of adipocytes, and mice fed a high-fat diet showed markedly increased levels of caspase 1, IL-1β and IL-18 expression in adipose tissue. Elevated IL-1β production was shown to contribute to insulin resistance in adipose tissue, and adipocytes from NLRP3-deficient or caspase 1-deficient mice showed increased insulin sensitivity and were more metabolically active. Furthermore, treatment of obese mice with a caspase 1 inhibitor improved insulin sensitivity in these animals.

In the second study, Vandanmagsar *et al.* showed a direct correlation between adiposity and the expression of NLRP3 and IL-1β in both humans and mice. Weight loss, resulting from calorie restriction or exercise, led to decreased NLRP3 expression and improved insulin sensitivity in adipose tissue. The authors found that ceramides (lipid molecules that are released into the circulation by adipocytes during progressive obesity) directly activate the NLRP3 inflammasome and induce caspase 1 activation in adipocytes and macrophages. NLRP3-deficient mice fed a high-fat diet showed increased insulin sensitivity and, interestingly, showed decreased expression of interferon-γ and reduced effector T cell numbers in adipose tissue. These results suggest that the NLRP3 inflammasome is also important for regulating adipose tissue T cell responses during obesity.

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## IL-17 regulates adipogenesis, glucose homeostasis, and obesity

Zúñiga, L. A. *et al. J. Immunol.* **185**, 6947–6959 (2010)

The pro-inflammatory cytokine interleukin-17 (IL-17) is upregulated in the blood of obese humans, but its role in metabolic disease remains unclear. This study shows that IL-17 is produced by γδ T cells in adipose tissue and acts as a negative regulator of adipogenesis and glucose metabolism. Comparison of mice fed a normal, low-fat or high-fat diet showed that increasing obesity promoted the accumulation of IL-17-producing γδ T cells in inguinal adipose tissue. Whereas most αβ T cells in adipose tissue produced interferon-γ (IFNγ) but little IL-17, adipose tissue γδ T cells produced high levels of IL-17 but low levels of IFNγ. Interestingly, IL-17 was shown to inhibit lipid uptake and insulin-induced glucose uptake by adipocytes, and to suppress adipogenesis. Young IL-17-deficient mice were more susceptible to diet-induced obesity than wild-type controls, but older IL-17-deficient mice were no longer protected from diet-induced obesity. The authors suggest that the positive metabolic effects of IL-17 may be overwhelmed by other mechanisms once obesity is established.