IN BRIEF

INFLAMMATION

The protein kinase IKKε regulates energy balance in obese mice

Chiang, S.-H. *et al. Cell* **1387**, 961–975 (2009)

Obesity is associated with chronic low-level inflammation and increased levels of pro-inflammatory cytokines, which block insulin action and contribute to the development of type 2 diabetes, but the molecular mechanisms of the inflammatory link between obesity and diabetes are unclear. In this study, feeding mice a high-fat diet led to low-level nuclear factor-κB (NF-κB) activation and increased expression of the NF-κB target inhibitor of NF-κB kinase-ε (IKKε) in adipocytes and M1-polarized macrophages of white adipose tissue and liver. IKKε-deficient mice on a high-fat diet had a smaller increase in fat mass and liver weight than wild-type control mice, and they also maintained normal insulin signalling. A high-fat diet increased the secretion of pro-inflammatory cytokines in the adipose tissue and livers of wild-type but not IKKε-deficient mice, which correlated with markedly less infiltration of adipose tissue by M1 macrophages in the IKKε-deficient mice. These results indicate that IKKε is a crucial factor in the crosstalk between liver cells, adipocytes and macrophages that regulates both inflammatory and metabolic processes, which makes it an appealing new therapeutic target.

NATURAL KILLER CELLS

The basic leucine zipper transcription factor E4BP4 is essential for natural killer cell development

Gascoyne, D. M. *et al. Nature Immunol.* 13 Sep 2009 (doi:10.1038/ni.1787)

This study identifies E4BP4 (also known as NFIL3) as the first factor to specifically regulate commitment to the natural killer (NK) cell lineage. NK cells were almost entirely absent from the periphery of *E4bp4*$^{-/-}$ mice, whereas NKT, B and T cell populations were unaffected, and these mice had minimal NK cell cytotoxic activity against MHC class I-deficient target cells. Cell-intrinsic E4BP4 expression was shown to be required during NK cell development for the transition of NK cell precursors to immature and mature NK cells. The effect of E4BP4 on NK cell lineage commitment, in the absence of effects on survival or proliferation, was mediated downstream of the interleukin-15 receptor and upstream of the transcription factor ID2. Other interleukin-15-dependent cell types, such as NKT cells and CD8^{+} memory T cells, were not affected by deficiency of E4BP4, showing that the requirement for E4BP4 is specific to the NK cell lineage.

IMMUNE REGULATION

Suppression of cell-mediated immunity following recognition of phagosome-confined bacteria

Bahjat, K. S. *et al. PLoS Pathog.* **5**, e1000568 (2009)

After being engulfed by a host cell, *Listeria monocytogenes* is recognized by innate immune receptors in the phagosome, but this does not result in protective adaptive immunity until the bacterium enters the host cell cytosol. This study compared the immune response to bacterial strains that were restricted to the phagosome or cytosol. The generation of a protective T cell response to cytosolic bacteria was inhibited by the presence of phagosomal bacteria during the initial infection. Phagosome-confined bacteria inhibited inflammatory cytokine production and resulted in increased levels of interleukin-10. Blockade of the interleukin-10 receptor prevented the inhibitory effect of phagosomal bacteria on protective immunity to cytosolic bacteria. These results show that the entry of bacteria to the cytosol is required not only for efficient antigen presentation but also to avoid an active immunosuppressive pathway.