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IN BRIEF

MACROPHAGES

Lipid metabolism linked to anti-inflammatory functions

A recent study revealed homeostatic roles for foam cells (a type of macrophage present in atherosclerotic lesions) in lipid metabolism and inflammation. Spann *et al.* isolated foam cells from a mouse model of hypercholesterolaemia and analysed their transcriptomic and lipidomic profiles. High levels of exogenous cholesterol were shown to skew the cholesterol biosynthetic pathway to the production of desmosterol through downregulation of the enzyme DHCR24. Desmosterol is a liver X receptor (LXR) ligand, and intracellular desmosterol altered LXR- and SREBP (sterol regulatory element binding protein)-dependent fatty acid metabolism in foam cells. Moreover, high desmosterol levels inhibited pro-inflammatory gene expression through both LXR-dependent and LXR-independent mechanisms. These findings may foster the development of new therapies against cardiovascular disease.

ORIGINAL RESEARCH PAPER Spann, N. J. *et al.* Regulated accumulation of desmosterol integrates macrophage lipid metabolism and inflammatory responses. *Cell* **151**, 138–152 (2012)

SIGNALLING

Pellino3 — a self-control strategy for TLR3

Pellino family proteins are E3 ubiquitin ligases that can regulate members of the IL-1 receptor-associated kinase (IRAK) family. This study shows that Pellino3 negatively regulates type I interferon (IFN) expression following Toll-like receptor 3 (TLR3) activation. The authors generated Pellino3-deficient mice and found that macrophages from these animals produced increased levels of IFN following TLR3 stimulation but responded in a similar manner to wild-type macrophages when treated with other TLR agonists. Notably, the enhanced IFN response of Pellino3-deficient mice promoted protective immunity to encephalomyocarditis virus (ECMV). Pellino3 negatively regulated TLR3 signalling by associating with and ubiquitylating TNF receptor associated factor 6 (TRAF6) — this blocked IFN induction by preventing TRAF6-mediated ubiquitylation and activation of interferon regulatory factor 7 (IRF7). Activation of TLR3 upregulated Pellino3 expression, suggesting that this is an autoregulatory pathway that controls type I IFN induction.

ORIGINAL RESEARCH PAPER Siednienko, J. *et al.* Pellino3 targets the IRF7 pathway and facilitates autoregulation of TLR3- and viral-induced expression of type I interferons. *Nature Immunol.* 7 Oct 2012 (doi:10.1038/ni.2429)

TUMOUR IMMUNOLOGY

Inflammation blinds T cells to melanoma

Adoptive cell therapy (ACT) using melanoma-specific cytotoxic T cells can promote remission in patients with metastatic melanoma, but the tumours often return; this study offers an explanation why. The authors used both mouse and human systems to show that tumour necrosis factor (TNF) promotes the loss of melanoma-associated antigens, such as MART1 or gp100, from melanoma cells. This was a reversible phenomenon, as the melanoma cells reacquired expression of gp100 when transplanted into other hosts. Although the TNF-conditioned melanoma cells could no longer be recognized by T cells specific for melanocytic antigens, they could be targeted by T cells specific for other mutated proteins. Therefore, in future, the efficacy of ACT could be improved by targeting both melanocytic and non-melanocytic antigens.

ORIGINAL RESEARCH PAPER Landsberg, J. *et al.* Melanomas resist T-cell therapy through inflammation-induced reversible dedifferentiation. *Nature* 10 Oct 2012 (doi:10.1038/nature11538)