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IN BRIEF

GENE REGULATION

Enhancer accessibility to FOXP3

Epigenetic events alter chromatin accessibility to transcriptional regulators, and the transition from a closed to an open chromatin state at gene enhancers directs early cell differentiation events. By contrast, Samstein *et al.* report that differentiation of regulatory T (T_{Reg}) cells does not involve changes in the accessibility of enhancers targeted by the transcriptional regulator FOXP3. Most FOXP3-binding enhancers pre-exist in an open state in T_{Reg} cell precursors. This open chromatin state is preserved by FOXO1 or other transcription factors in the absence of FOXP3. After T_{Reg} cell differentiation, FOXO1 is replaced by FOXP3, whereas other transcription factors are not displaced but participate in FOXP3 transcriptional complexes. Moreover, the few enhancers that exhibit an open chromatin state in T_{Reg} cells but not in T_{Reg} cell precursors are remodelled as a result of AP1 binding following T cell receptor stimulation.

ORIGINAL RESEARCH PAPER Samstein, R. M. *et al.* Foxp3 exploits a pre-existent enhancer landscape for regulatory T cell lineage specification. *Cell* **151**, 153–166 (2012)

T CELLS

MAIT cells specific for microbial metabolites

The T cell receptor (TCR) of the innate-like mucosal-associated invariant T (MAIT) cells consists of an invariant Vα chain combined with limited conserved Vβ chains, but the antigens recognized by MAIT cell TCRs were unknown. These TCRs are restricted to the monomorphic MHC class I-related protein (MR1), so Kjer-Nielsen *et al.* screened for antigens that can be presented by MR1. They observed that MR1 binds small organic compounds originating from vitamins (such as a pterin ring-containing derivative of folic acid) through conserved residues. Strikingly, folic acid derivatives presented by MR1 failed to activate MAIT cells, but this was not the case with MR1-binding metabolites of riboflavin, which are secreted by MAIT cell-activating microbes. So, the authors suggest that competition of pathogen-derived vitamin metabolites with other small organic compounds (possibly derived from diet or gut microbiota) for MR1 binding may shape MAIT cell responses.

ORIGINAL RESEARCH PAPER Kjer-Nielsen, L. *et al.* MR1 presents microbial vitamin B metabolites to MAIT cells. *Nature* 10 Oct 2012 (doi: 10.1038/nature11605)

DENDRITIC CELLS

Hoarding may keep old memories alive

Studies have shown that viral antigens persist in the host long after the infection itself is cleared. The mechanisms are unclear, but one suggestion is that low levels of viral transcripts linger in the host. To test this, Li *et al.* used a model that is independent of genetic information. They transferred naive ovalbumin (OVA)-specific $CD8^+$ T cells to OVA-immunized recipients and found that these cells proliferated *in vivo*, even 28 days after the initial OVA challenge. However, OVA protein could only be detected in draining lymph nodes for up to 3 days after challenge. Further work showed that dendritic cells (DCs) sequester immunostimulatory epitopes of OVA for as long as 21 days in culture. Treatment of DCs with agents that block heat shock protein 90 (HSP90) abolished their ability to retain immunostimulatory OVA epitopes. So, DCs may promote long-term protective immunity by sequestering pathogen-derived epitopes in an HSP90-dependent manner.

ORIGINAL RESEARCH PAPER Li, C. *et al.* Dendritic cells sequester antigenic epitopes for prolonged periods in the absence of antigen-encoding genetic information. *Proc. Natl Acad. Sci. USA* 8 Oct 2012 (doi:10.1073/pnas.1205867109)

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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)