Journal club

MOVE TO METABOLISM

In 2002, with the support of the Wellcome Trust, my laboratory moved to the University of Dundee, a leading centre for cell signalling research and the perfect environment in which to explore how serine/threonine kinases control T cell-mediated immune responses. What we had not appreciated was that many of our new colleagues worked on fundamental issues of how protein phosphorylation controls basic metabolic pathways. We found ourselves in a new community, one in which people asked questions about how cells sense changes in energy metabolism. We inevitably started to think about how T cells sense nutrients and modulate their metabolism to meet the energy demands of clonal expansion and effector function. One clear connection came from a paper published in 2005 by one of our colleagues, Grahame Hardie.

> “a biochemical link between Ca^{2+} signalling and a kinase that evolved to control the conservation and production of ATP”

Grahame had previously discovered the energy-sensing AMP-activated protein kinase (AMPK), which is activated by an increased intracellular AMP:ATP ratio and functions to restore energy balance by inhibiting ATP-consuming processes and stimulating ATP-generating pathways. The revelation that this might be important in T cells came when Grahame showed that Ca^{2+}–calmodulin-dependent protein kinase kinases (CaMKKs) could phosphorylate and activate AMPK. This established a biochemical link between Ca^{2+} signalling and a kinase that evolved to control the conservation and production of ATP. We immediately knew this would be relevant to T cells because it is well established that triggering of the T cell receptor induces a rapid increase in intracellular Ca^{2+} concentration and CaMKK activation. A collaboration with the Hardie group established that Ca^{2+} signalling in T cells activates AMPK (Tamás et al., 2006) and highlighted how antigen receptor signalling could control the activity of a key metabolic enzyme.

Metabolism is a relatively new focus for immunologists and is currently in the spotlight of research activities. My appreciation of its importance started with a move to Dundee, where a spirit of collaboration and the inspirational work of my colleagues opened my mind to the concept that immune cells can sense nutrients and that nutrient sensing is coupled to signal transduction pathways that determine cell fate.

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ORIGINAL ARTICLE Hawley, S. A. et al. Calmodulin-dependent protein kinase kinase-β is an alternative upstream kinase for AMP-activated protein kinase. *Cell Metab.* **2**, 9–19 (2005)
FURTHER READING Tamás, P. et al. Regulation of the energy sensor AMP-activated protein kinase by antigen receptor and Ca^{2+} in T lymphocytes. *J. Exp. Med.* **203**, 1665–1670 (2006)

IMMUNOMETABOLISM

Pro-tumour programming at the macrophage membrane

Toby Lawrence and colleagues have found that tumour cells can promote a pro-tumour phenotype in tumour-associated macrophages (TAMs) by inducing cholesterol efflux from the macrophage plasma membrane.

The authors used a mouse model of high-grade serous ovarian cancer — which is characterized by tumour cell colonization of the peritoneum — to explore how the tumour microenvironment affects TAM function. They injected cancer cells from the ID8 ovarian epithelial cell line into the peritoneum of mice and characterized gene expression profiles in peritoneal macrophages at different time points during tumour development. At 5 days post ID8 cell injection, TAMs showed an upregulation of genes associated with anti-tumour immunity; however, by the time the tumours had become more established at 21 days, there was a shift to a distinct set of immune genes in TAMs and upregulation of genes associated with cholesterol metabolism and efflux.

In keeping with this, TAMs isolated 21 days after ID8 cell injection showed a significant decrease in cholesterol-rich membrane microdomains. Bone marrow-derived macrophages that were co-cultured with ID8 cells also showed loss of membrane cholesterol, suggesting that ID8 cells actively induce cholesterol efflux in macrophages. Further analysis suggested that ID8 cells promote cholesterol efflux in macrophages by producing high molecular weight hyaluronic acid.

The depletion of membrane cholesterol was shown to increase macrophage expression of IL-4-associated genes while inhibiting IFNγ-induced genes, and further experiments indicated that this reprogramming of macrophages

IMMUNOMETABOLISM

Stromal support from IL-17

During inflammation, lymph node stromal cell populations expand and this supports the development of adaptive immunity. Mandy McGeachy and colleagues now show that IL-17 promotes the survival and proliferation of fibroblastic reticular cells (FRCs) in inflamed lymph nodes by enhancing their metabolic activity.

Using a model of experimental autoimmune encephalomyelitis in which mice were immunized with myelin oligodendrocyte glycoprotein (MOG) peptide in complete Freund's adjuvant (CFA), the authors found that T cell-derived IL-17 promoted the upregulation of extracellular matrix (ECM) components in inflamed lymph nodes. These ECM components are produced by FRCs, and, accordingly, IL-17 was shown to promote the expansion of lymph node FRC populations. Experiments in mice with an FRC-restricted IL-17 receptor deficiency (FRCΔ^{Il17ra} mice) indicated that this was due to a direct effect of IL-17 on FRCs. IL-17 also regulated FRC expansion in a colitis model, indicating that the effect was not a CFA-driven phenomenon.

Despite having fewer FRCs, immunized FRCΔ^{Il17ra} mice had similar numbers of lymph node $CD4^+$ T cells and B cells to control mice and did not show disrupted B cell and T cell zones. They also had comparable frequencies of naive, effector and IL-17-producing lymph node T cells. However, their numbers of germinal centre B cells and levels of total and MOG-specific antibody were markedly reduced.

Transcriptomic analyses indicated that *Il17ra*$^{-/-}$ FRCs had reduced expression of several IL-17 target genes — including genes encoding various inflammatory mediators, CEBPβ and the NF-κB coactivator IκBζ — and significant dysregulation of the cell cycle pathway. Many negative regulators of the cell cycle were increased in *Il17ra*$^{-/-}$ FRCs, and FRCs that could not respond to IL-17 were blocked from entering the S phase