cells towards a non-pathogenic gene signature.

In particular, there was a marked downregulation of genes controlling mitochondrial function in S1-S3C^{CD4} T_H17 cells, including subunits of the electron transport chain (ETC) complexes that mediate mitochondrial respiration and oxidative phosphorylation (OXPHOS). Mitochondrial respiration was significantly reduced in S1-S3C^{CD4} T_H17 cells compared with S3C^{CD4} T_H17 cells, although these cells had increased levels of mitochondrial reactive oxygen species (mROS).

Kaufmann, Kahlfuss et al. showed that S1-S3C^{CD4} T_H17 cells have an altered architecture of the inner mitochondrial membrane with loose cristae, which could increase electron leak from the ETC and hence generate mROS. In addition, SOCE in pathogenic T_H17 cells promotes the transcription of antioxidant genes. In the absence of SOCE, S1-S3C^{CD4} T_H17 cells had significantly increased levels of DNA damage and cell death compared with S3C^{CD4} T_H17 cells, which could be reduced by treatment with a ROS scavenger.

To demonstrate the in vivo relevance of these results, the authors treated T_H17 cells isolated from the lungs of S3C^{CD4} mice with oligomycin to block OXPHOS, which resulted in decreased expression of IL-17A and of other genes associated with the pathogenic T_H17 cell signature. The T cell-intrinsic role of SOCE was shown by the adoptive transfer of S3C^{CD4} T cells or S1-S3C^{CD4} T cells into *Rag1*$^{-/-}$ hosts, whereby the colitis observed in the former case was markedly attenuated in the latter case.

In summary, the data suggest that SOCE is essential for normal gene expression, function and structure of mitochondria in pathogenic T_H17 cells. The absence of SOCE impairs OXPHOS and results in increased mROS, which suppresses the pathogenic gene expression signature and decreases cell viability, respectively.

Kirsty Minton

ORIGINAL ARTICLE Kaufmann, U. et al. Calcium signaling controls pathogenic Th17 cell-mediated inflammation by regulating mitochondrial function. *Cell Metab.* https://doi.org/10.1016/j.cmet.2019.01.019 (2019)

tagged for degradation. However, after 30 mins of LPS stimulation, there was a shift to the presence of K63-linked polyubiquitylated ABCF1, coinciding with the late phase TRIF-dependent signalling. Analysis using small-molecule inhibitors revealed that the E3 ligases cIAP1 and cIAP2 target ABCF1 for K48-linked polyubiquitylation before TLR4 endocytosis. TRAF6 was likewise shown to associate with ABCF1 and be necessary for its K63-polyubiquitylation during late phase TLR4 signalling.

Next, the authors explored whether the E2 ligase activity of ABCF1 has a role in its positive regulation of TRIF-dependent signalling. Co-immunoprecipitation indicated an association between ABCF1 and SYK. A 30 min LPS stimulation of BMDMs overexpressing ABCF1, SYK and ubiquitin led to the formation of K63-polyubiquitylated SYK, which occurred only on transfection with wild-type *Abcf1* and not with the *Abcf1* C647S mutant, suggesting that the conserved cysteine is necessary for ubiquitin transfer and E2 activity of ABCF1. Further studies showed that ABCF1 also targets TRAF3 for K63-polyubiquitylation only after it also associates with TRIF.

Finally, a protective role for ABCF1 in septic shock was shown using mice heterozygous for *Abcf1*. Only 10% of *Abcf1*$^{+/-}$ mice survived 96 hours after high-dose LPS challenge, compared with 60% of wild-type mice. The *Abcf1*$^{+/-}$ mice were unable to switch from the hyperinflammatory phase to the endotoxin tolerance phase, and thus suffered exaggerated pro-inflammatory responses and ultimately renal circulatory failure and death.

So, ABCF1 acts as a molecular switch in macrophages that mediates the transition from cytokine storm to endotoxin tolerance during sepsis, and it may be a useful therapeutic target for dampening overactive immune responses in various inflammatory diseases.

Lucy Bird

ORIGINAL ARTICLE Arora, H. et al. The ATP-binding cassette gene ABCF1 functions as an E2 ubiquitin-conjugating enzyme controlling macrophage polarization to dampen lethal septic shock. *Immunity* **50**, 418–431 (2019)

Journal club

CD8$^+$ T CELLS CURE WITHOUT KILLING

In the mid-1990s, I was a clinical PhD student attending my first international immunology conference in San Francisco, where I heard a paper presented by Frank Chisari that revolutionized the existing dogma of cytotoxic T lymphocytes (CTLs). The findings published by Luca Guidotti et al. in 1996 provided definitive evidence in a transgenic mouse model of hepatitis B virus (HBV) infection that CD8$^+$ T cells could exert potent antiviral efficacy without lysing infected cells.

They showed that small numbers of HBV-specific CD8$^+$ T cells could clear the virus from infected hepatocytes throughout the liver in a perforin-independent manner. This non-cytolytic 'cure' was mediated by the production of IFNγ and tumour necrosis factor by CD8$^+$ T cells, which allowed for amplification of the effect over a longer range and for preservation of tissue integrity. Thus, small numbers of specific T cells had the potential to cure a widespread hepatotropic viral infection without destroying this vital organ.

This discovery provided a strong rational to support subsequent efforts to harness CD8$^+$ T cells for immunotherapy of infections such as HBV, with the aim of achieving immunological cure with minimal damage to the infected liver. The paradigm of CD8$^+$ T cells mediating their effector function through soluble mediators, in addition to lysis, turned out to be relevant in many settings beyond HBV. This realization that CTLs were not necessarily cytotoxic led to widespread use of the more generic term 'CD8$^+$ T cells' and to the adoption of functional assays based on their cytokine production.

Returning to the lab inspired by the conference, I scrutinized the literature and decided to direct my future research into HBV immunology, which linked well with my clinical specialization. Looking into what could be done in the human system, I came across work by Antonio Bertoletti and Carlo Ferrari defining HLA-A2-restricted HBV epitopes and showing that naturally occurring viral variants could antagonize cognate CD8$^+$ T cells. I was excited by the exquisite precision of virus-specific CD8$^+$ T cells but frustrated by the laborious techniques required to detect them at that time. However, peptide–MHC tetramers had just been described by John Altman et al. for the direct ex vivo analysis of antigen-specific CD8$^+$ T cells, so I contacted Andrew McMichael and persuaded his lab to construct one for an HBV epitope that Antonio Bertoletti had defined. Imagine my delight when I then discovered that Antonio was about to move to UCL, where I worked — it was the start of a great collaboration and I've focused on HBV immunology ever since.

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