CD8⁺ T cells showed increased production of IFNγ and TNF when activated in vitro. Expression analysis confirmed that there was no difference in the levels of apoptosis markers in T cells from CYPD-deficient mice or wild-type mice. Thus, these results suggest that increased proliferation, and not reduced cell death, explained the higher number of CYPD-deficient T cells in the lungs of infected mice.

Given the localization of CYPD in mitochondria, the authors examined whether CYPD affected the metabolic activity of T cells. Bioenergetic flux analysis showed that both aerobic glycolysis and mitochondrial oxidative phosphorylation were elevated in CYPD-deficient T cells compared with wild-type T cells. The enhanced T cell activation and proliferation seemed to be regulated by mitochondrial reactive oxygen species (mROS), as mROS levels were higher in CYPD-deficient CD8⁺ T cells than in wild-type T cells, and quenching mROS blocked the increased proliferation and the aberrant metabolic activity of CYPD-deficient T cells.

Finally, the authors generated mixed bone marrow chimeric mice with T cells that were only CYPD-deficient or wild-type T cells. Five weeks after infection, there was significantly higher proliferation and IFNγ production by CYPD-deficient T cells than wild-type T cells in the lungs, suggesting that CYPD intrinsically regulates T cell responses to infection. Consistent with this observation, temporary depletion of T cells in CYPD-deficient mice prolonged their survival following infection. Furthermore, the survival of RAG1-deficient mice reconstituted with CYPD-deficient T cells was significantly reduced compared with those receiving wild-type T cells.

This study shows that although T cell responses are crucial for host defence against *M. tuberculosis* infection, T cell hyperproliferation and hyperactivation compromises TB disease tolerance.

Grant Otto

ORIGINAL ARTICLE Tzelepis, F. et al. Mitochondrial cyclophilin D regulates T cell metabolic responses and disease tolerance to tuberculosis. *Sci. Immunol.* **3**, eaar4135 (2018)

Next, the authors showed that a high-fibre diet did not affect neutrophil development but altered haematopoiesis by increasing macrophage precursors in the bone marrow. This led to an increase in the frequency of Ly6C⁻ patrolling monocytes relative to Ly6C⁺ inflammatory monocytes in the bone marrow and lungs after infection. Mice fed a high-fibre diet or given butyrate had more interstitial and alveolar macrophages following infection, and these macrophages had an alternative activation profile. The generation of alternatively activated macrophages (AAMs) was mediated by SCFAs acting on FFAR3 expressed by macrophage precursors, as only wild-type precursors and not *Ffar3*$^{-/-}$ precursors in chimeric mice led to an accumulation of lung AAMs in response to butyrate and infection. AAMs are less capable of producing the neutrophil chemoattractant CXCL1 than classically activated macrophages. Accordingly, airway CXCL1 levels in infected mice on a high-fibre diet were lower than those in infected animals on a control diet, thereby linking the altered macrophage phenotype to the diminished neutrophil response.

Finally, the authors assessed whether the antiviral T cell response was affected by dietary fibre. They noted that antiviral CD8⁺ T cells were more activated, had greater cytotoxic capacity and accumulated in higher numbers in the lungs of mice on a high-fibre diet than those of mice on a control diet. Indeed, these effects could be seen in vitro after culturing CD8⁺ T cells in the presence of butyrate, suggesting a direct effect of SCFAs on T cells, probably through FFAR3. The more activated phenotype of CD8⁺ T cells in mice on a high-fibre diet was associated with multiple alterations in T cell metabolism, including increased glycolytic rate, mitochondrial mass and capacity for oxidative phosphorylation.

So, a high-fibre diet protects against influenza virus by shaping monocyte development, to limit immunopathology, and CD8⁺ T cell metabolism, to enhance antiviral immunity.

Lucy Bird

ORIGINAL ARTICLE Trompette, A. et al. Dietary fibre confers protection against flu by shaping Ly6c⁻ patrolling monocyte hematopoiesis and CD8⁺ T cell metabolism. *Immunity* **48**, 992–1005 (2018)

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STARVATION SUPPRESSES T CELL APPETITE

The world is inhabited by more than 7.6 billion people, of whom one in nine suffer chronic undernourishment or starvation. How this 'nutrient-restricted' situation affects immune function had not, until recently, been investigated. Indeed, little thought had been given to how the biochemical changes that occur under conditions of nutrient stress translate to fundamental changes in immune cells and their capacity to generate antibodies or effector and memory cells for protection. A study published by Iyer et al. in 2012 changed all that.

Although it had already been recognized that malnutrition is associated with poor vaccine responses, Iyer et al. linked cellular nutrient levels in immune cells to the ability of cytotoxic T cells to mount a vigorous response to a challenge. The group discovered that chronic malnutrition limited the ability of the immune system to either replenish key cellular compartments through homeostatic proliferation or recruit antigen-specific memory T cells into a secondary response, two essential functions that are required for long-lived immune protection. Thus, the fate of immune cells — in this case, CD8⁺ T cells — is strongly determined by their metabolism, which directly influences immune health. The study also showed that immune cell metabolism depends on the protein and energy supplies in the diet and that this could be manipulated to improve immune outcomes.

The work of Iyer et al. provided a first clue to how different metabolic products in cells affect their development, maintenance and protective functions. In exciting developments extending from this landmark paper, it is now recognized that the metabolic and signalling requirements of T cells are interlinked. This affects both T cell fate and their capacity to reprogramme their functions to deal with particular types of infection. The metabolic programme of immune cells has also been found to influence the outcome of diseases such as obesity, diabetes and cancer. The oversupply of nutrients also affects immune cell function and can itself contribute to different types of disease. Collectively, these studies have led to an entirely new direction in immunological research. Emerging exciting questions will impact our understanding not only of immune cell function, but also of disease processes, and potentially uncover new therapeutic leads for treatment.

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ORIGINAL ARTICLE Iyer, S. S. et al. Protein energy malnutrition impairs homeostatic proliferation of memory CD8 T cells. *J. Immunol.* **188**, 77–84 (2012)