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Glutaminolysis as a metabolic checkpoint of protective Th1/Th17 immunity against *Mycobacterium tuberculosis*

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Dear Readers,

In this issue of the *Central European Journal of Immunology* (CEJI), Cai *et al*. report their investigation into how metabolic reprogramming of immune cells influences the outcome of *Mycobacterium tuberculosis* infection, focusing on glutaminase 1 (GLS1), the rate-limiting enzyme of glutaminolysis in $CD4^+$ T cells from patients with active tuberculosis (TB) [1]. GLS1 was markedly upregulated in peripheral blood mononuclear cells (PBMCs) and increased further after stimulation with *M. tuberculosis* H37Rv lysate. Blocking the enzyme reduced T helper 1 (Th1) and T helper 17 (Th17) differentiation, lowered ATP production, oxygen consumption, and extracellular acidification in stimulated PBMCs, and, notably, enhanced intracellular survival of *M. tuberculosis* within infected macrophages. The authors attribute this last effect to histone acetylation: GLS1-derived acetyl coenzyme A (acetyl-CoA) maintains acetylation of histone H3 at lysine 9 (H3K9ac) and lysine 27 (H3K27ac) at the interferon γ (IFN-γ) and interleukin 17 (IL-17) promoters, and both the histone marks and cytokine production were restored by supplementation with glutamate or acetate.

These findings extend an established body of work identifying glutaminase as a checkpoint in $CD4^+$ T-cell fate. Johnson *et al*. showed that GLS-dependent metabolism regulates Th17 and Th1 differentiation in opposite ways [2], and subsequent studies in psoriasis and Sjögren's syndrome demonstrated that pharmacologic GLS1 blockade can dampen pathogenic Th17/Th1 responses in autoimmune disease [3]. Notably, Cai *et al*. described the same checkpoint working in the opposite clinical direction [1]. In TB, glutaminolysis does not drive a pathogenic autoimmune response but instead sustains a protective one. Consequently, GLS1 inhibition impairs rather than enhances host defense. Any attempt to develop GLS1 inhibitors as immunomodulatory drugs will need to take this context dependence into account.

The data also correspond with two findings specific to *M. tuberculosis* biology. Koeken *et al*. reported that glutamine metabolism is required for effective host defense against the pathogen [4], and Yu *et al*. showed that *M. tuberculosis* hijacks GLS1-mediated glutaminolysis to survive inside macrophages [5]. Cai *et al*. add a mechanistic layer to both observations by showing how this metabolic pathway feeds into transcription, through histone acetylation at the IFN-γ and IL-17 loci [1].

The paper offers mechanistic insights into how a druggable metabolic enzyme contributes to the epigenetic control of antimycobacterial immunity, and it will be of interest to researchers working at the interface of immunometabolism, epigenetics, and infectious disease. In fact, metabolic control of immune cell activities, including $CD4^+$ T-cell function, has been a recurring topic in CEJI. Recently, Jin *et al*. reported enhanced glycolysis and oxidative phosphorylation in $CD4^+$ T cells from patients with systemic lupus erythematosus, which correlated with disease activity [6], and Wang *et al*. used transcriptomics to analyze how anaerobic glycolysis shapes proliferation in Jurkat T cells [7]. Taken together with the present paper, these studies point to an important direction in the study of metabolic control of immune cells, which should be recognized not as a passive consequence of activation but as an active determinant of function that can be modulated either to restrain pathogenic responses, as in lupus, or, as demonstrated here, to reinforce protective ones.

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