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Metabolic regulation of Th17/Treg balance

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The balance between pro-inflammatory and regulatory immune responses is essential for maintaining immune homeostasis. Among $CD4^+$ T-cell subsets, the interplay between Th17 cells and regulatory T cells (Tregs) represents a key checkpoint in controlling inflammation and preventing autoimmune pathology. Increasing evidence indicates that this balance is not determined solely by cytokine signaling but is also profoundly shaped by cellular metabolism [1, 2].

In this issue of the *Central European Journal of Immunology*, Jin and Tao provide new insights into the metabolic mechanisms governing Th17/Treg differentiation [3]. Through combined cellular and secretome proteomic analyses, the authors identify metabolic pathways as major determinants distinguishing these two $CD4^+$ T-cell subsets. In particular, they highlight glutamine metabolism and the activity of glutaminase (GLS) as critical regulators of T-cell fate. Their findings demonstrate that GLS promotes regulatory T-cell differentiation while suppressing the generation of Th17, and that downstream metabolites of glutamine metabolism, including glutamate, glutathione, and α-ketoglutarate, significantly influence this process [3]. These results suggest that glutaminase-mediated metabolic pathways may represent potential targets for modulating immune responses in autoimmune diseases.

The study is in line with the growing field of immunometabolism, which has become an increasingly important theme in recent publications among immunology-oriented journals, including the *Central European Journal of Immunology*. For example, Jin *et al*. recently demonstrated that $CD4^+$ T cells from patients with systemic lupus erythematosus display markedly enhanced glucose metabolism, characterized by increased glycolysis and oxidative phosphorylation that correlate with disease activity [4]. This metabolic reprogramming was associated with increased T-cell proliferation and cytokine production, highlighting the role of altered metabolic pathways in driving immune dysregulation in autoimmune disease [4]. Similarly, previous work published in the *Central European Journal of Immunology* showed that patients with type 2 diabetes mellitus exhibit alterations in the balance between Th17 and regulatory T cells, with a significant decrease in Treg populations, particularly in individuals with long-standing disease and poor metabolic control [5]. These findings suggest that metabolic disturbances associated with chronic disease progression may directly influence immune cell composition and contribute to systemic inflammation [5]. Importantly, the concept that metabolic pathways determine the functional fate of Th17 cells has also been supported by broader mechanistic studies. Karmaus *et al*. reported that Th17 cells are metabolically heterogeneous and that mTORC1-dependent anabolic metabolism promotes their differentiation toward inflammatory effector states, whereas reduced metabolic activity is associated with stem-like, long-lived Th17 populations with increased lineage stability [6]. Furthermore, Wagner *et al*. used single-cell metabolic modeling to show that pathogenic Th17 cells are characterized by a metabolic shift toward glycolysis and polyamine metabolism, pathways that directly regulate Th17 pathogenicity and the balance between Th17 and regulatory T-cell programs. Importantly, metabolic control of T-cell function is not limited to glucose utilization; it also involves sensing and metabolism of other nutrients, including amino acids. A recent study by Kulkarni *et al*. demonstrated that L-phenylalanine acts as a metabolic checkpoint regulating human Th2 cell function [7]. Through integrated metabolomics, transcriptomics, and functional analyses, the authors showed that intracellular phenylalanine promotes glycolysis while limiting oxidative phosphorylation. Additionally, through IL4I1-dependent mechanisms and inhibition of STAT6 and mTOR signaling pathways, phenylalanine restrains proliferation and differentiation of Th2 cells. Moreover, alterations in phenylalanine transport and metabolism were associated with the expansion of pathogenic Th2 cell populations in allergic disease, highlighting the importance of amino acid availability and transport in shaping T-cell responses [7].

Together, these studies emphasize that metabolic checkpoints are emerging as fundamental regulators of immune cell function. By linking glutaminase-dependent glutamine metabolism to the Th17/Treg balance, the *CEJI*-published manuscript highlighted in this Editors'

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Pick further strengthens the concept that metabolic pathways are integral components of immune regulation and promising targets for future immunomodulatory therapies.

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