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EDITORIAL

Metabolic Fire-Up T Cell Induction of Intestinal Inflammation

CD4 T-cell responses to gut microbiota are crucial in regulating intestinal inflammation. Whereas T helper (Th)1 and Th17 cells reactive to gut microbiota are central to the pathogenesis of inflammatory bowel disease (IBD), regulatory T cells (Treg) inhibit it. CD4 T-cell metabolism is highly dynamic. T-cell activation demands biosynthetic precursors and adequate energy for effector function.[1] Metabolic reprogramming of T effector cells and Treg cells leads to distinct metabolic programs. If activated T cells fail to induce appropriate metabolic pathways, effector function and the ability to induce or inhibit inflammatory disease are impaired.[2]

Pyruvate metabolism is one critical regulatory point in glucose metabolism that tips T cells' glycolytic or oxidative roles. The mitochondrial pyruvate dehydrogenase complex converts pyruvate to acetyl-CoA, which is further oxidized to the tricarboxylic acid cycle. In mitochondria, the tricarboxylic acid cycle uses various substrates to generate reducing equivalents, leading to ATP generation through OXPHOS. Pyruvate dehydrogenase complex activity is negatively regulated by pyruvate dehydrogenase kinases (PDK), which consist of 4 different isoforms of (PDK1–4).[3] A small molecule that inhibits PDKs 1-4 activity, dichloroacetate, has been approved by the Food and Drug Administration for the preclinical investigation of several types of cancers.[4] However, how PDK regulates CD4 T-cell induction of intestinal inflammation and IBD is still unclear.

A study by Lee et al[5] in this issue of *Cellular and Molecular Gastroenterology and Hepatology* demonstrated nicely that PDK4 in CD4 T cells promotes colitis development by metabolic and calcium signaling modulation. Previous works from the same group and others have shown that aberrant expression of PDKs has been positively associated with various diseases, including obesity, diabetes, and cancer. To determine whether PDK4 affects the pathogenesis of IBD, Lee et al[5] assessed PDK4 expression in inflamed intestinal tissues of the dextran sulfate sodium (DSS)-induced colitis model and patients with IBD. PDK4 expression was increased in lamina propria $CD4^+$ T cells but not in intestinal epithelial cells. To investigate whether the increased PDK4 in T cells plays a role in the pathogenesis of colitis, Lee et al[5] induced colitis in wild-type and germline PDK4 knockout (KO) mice using DSS and found that PDK4 KO mice developed less severe colitis with fewer Th1 and Th17 cells but more Treg cells in lamina propria than wild-type mice on DSS insults. Interestingly, CD4-specific PDK4 KO ($PDK4^{CD4}$) mice but not intestinal epithelial cell–specific PDK4 KO ($PDK4^{villin}$) recapitulated the phenotype of germline PDK4 KO mice on DSS insults, demonstrating that PDK4 in T cells, other than intestinal epithelial cells, promotes intestinal inflammation. Furthermore, Lee et al[5] transferred wild-type or PDK4 KO $CD4^+$ $CD45RB^{hi}$ T cells into *Rag1*$^{-/-}$ mice, a well-established T cell–induced chronic colitis model, and found that PDK4 KO T cells induced much less severe colitis in *Rag1*$^{-/-}$ recipient mice, confirming the role of PDK4 in the regulation of T-cell induction of colitis.

As Th1 and Th17 cells induce colitis and Treg cells inhibit it, Lee et al[5] found that PDK4 deficiency inhibited T-cell activation and Th17 cell differentiation but increased Treg cells. However, PDK4 deficiency did not affect Th1 cell development. Mechanistically, PDK4 deficiency resulted in impaired calcium homeostasis and metabolic reprogramming in CD4 T cells through the disrupted mitochondria-associated membrane, leading to altered CD4 T-cell expression of glycolytic genes and mTOR signaling pathways, which have been implicated in Th17 and Treg differentiation and function. Finally, Lee et al[5] demonstrated that GM-10395, a small molecule specifically inhibiting PDK4 they synthesized, prevented DSS colitis, providing a translational potential for targeting PDK4 in treating IBD.

The study by Lee et al[5] thus provides novel insights into the mechanism of PDK4-regulated T-cell metabolism in the pathogenesis of colitis. As with all exciting studies, it also raises many questions. The most intriguing question is how PDK4-mediated metabolism regulates Th17 and Treg differentiation and whether the decreased T-cell activation in PDK4-deficient CD4 T cells is associated with lower Th17 cell and higher Treg cell differentiation; and if so, how. Translationally, although Lee et al[5] showed nicely that PDK4 inhibitor GM-10395 prevents DSS colitis, more efforts are needed to demonstrate whether it can treat colitis, especially chronic colitis. Understanding those questions will provide novel insights into the understanding of metabolic regulation of intestinal homeostasis and the pathogenesis of IBD, thus offering novel therapeutic targets for the treatment of IBD.

WENJING YANG
YINGZI CONG, PhD
Department of Microbiology and Immunology
The University of Texas Medical Branch
Galveston, Texas
Sealy Center for Microbiome Research
The University of Texas Medical Branch
Galveston, Texas

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Correspondence
Address correspondence to: Yingzi Cong, PhD, Department of Microbiology and Immunology, The University of Texas Medical Branch, 301 University Boulevard, MRB 4.142C, Galveston, Texas 77555. e-mail: yicong@utmb.edu.

Conflicts of interest
The authors disclose no conflicts.

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