

## **T Cell Metabolism and Fate**

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Lymphocyte activation leads to rapid proliferation and differentiation and we have shown that CD4 T cell subsets are metabolically distinct. These specific metabolic programs may allow new understanding and approaches to manipulate immunity. Using metabolic network analysis of metabolomics and proteomics we defined several metabolic nodes differentially utilized by CD4 T cell subsets, including glutamine metabolism. By genetically deleting the glucose transporter Glut1 or the glutaminolysis enzyme, Glutaminase (GLS), we have shown that glycolysis and glutaminolysis are both used by activated T cells. All effector T cells require glycolysis, but we found that Th17 cells preferentially require GLS while Th1 cells are actively impaired by this enzyme. Thus, inhibition of GLS both reduces Th17 responses and promotes differentiation of Th1 cells and can lead to signs of T cell exhaustion. We show that GLS-deficiency can protect against Th17-mediated inflammatory models and also can augment effector function of Th1 CAR-T cells against B cell targets. Understanding mechanisms that regulate T cell metabolism may provide new tools to modulate immunity the balance of T cell effector populations to both suppress inflammation or promote effector function.