Fatty acid synthesis tips the T_H17-T_{reg} cell balance

David O'Sullivan & Erika L Pearce

A recent study reports that *de novo* fatty acid synthesis is important for differentiation of T helper 17 (T_H17) cells. Suppression of this pathway through inhibition of acetyl-CoA carboxylase (ACC) with soraphen A prevents T_H17 cell differentiation and consequently enforces a regulatory T cell phenotype.

In response to different immune stimuli, naive T cells become activated, proliferate and differentiate into distinct functional subsets[1]. Cells in one such subset, T_H17 cells, secrete interleukin-17 (IL-17) and are important for antimicrobial immunity. However, during autoimmunity (when an immune response against the host's own tissues develops), cytokines such as IL-17 can be detrimental and lead to undesirable inflammation and pathology. Regulatory T (T_{reg}) cells, another T cell subset, act to constrain immune responses and therefore help prevent autoimmune disease. Eliciting the appropriate immune response requires suitable polarization of T cells toward the relevant lineage, which is regulated by multiple factors, including antigens, cytokines and metabolic pathway engagement[2]. Because most infections, cancers and autoimmune disease could potentially be controlled or attenuated by modifying T cell function, the identification of new approaches for therapeutically targeting these cells has clinical potential.

Activated T cells undergo changes in metabolism that are relevant to their function[3]. Glycolysis is a major metabolic pathway that yields energy and provides carbon for the biosynthesis of many molecules, including fatty acids. Mammalian target of rapamycin (mTOR) and hypoxia-inducible factor 1α (HIF-1α) promote glycolysis and polarize T cells toward a T_H17 phenotype[4]. Blocking mTOR or HIF-1α inhibits glycolysis and induces T_{reg} cell development[4,5]. Conversely, AMP-activated kinase (AMPK) is important for T_{reg} cells, as it promotes fatty acid oxidation, which is active in these cells, and opposes mTOR-dependent pathways needed for cell growth, including *de novo* fatty acid synthesis[2,6]. Thus, AMPK and mTOR influence the development of divergent T cell phenotypes by regulating metabolism (**Fig. 1**). In this issue of *Nature Medicine*, Sparwasser and colleagues[7] further investigate the role of the glycolytic-lipogenic pathway in the T_H17-T_{reg} cell balance. They demonstrate that under T_H17 polarizing conditions, activated mouse or human T cells gain a T_{reg} phenotype when this pathway is blocked through ACC inhibition.

ACCs catalyze the carboxylation of acetyl CoA to malonyl CoA, a key substrate for fatty acid synthesis (**Fig. 1**). The authors found that inhibition of ACCs by soraphen A (SorA), or T cell–specific genetic ablation of ACC1, but not ACC2, in cultures of naive mouse $CD4^+$ T cells activated in T_H17 polarizing conditions, blocked T_H17 cell development and strongly favored differentiation toward a functional T_{reg} phenotype. Through analysis of fatty acid uptake, the authors then demonstrated that SorA-treated cells acquired substantial amounts of exogenous fatty acid in comparison to T_H17 cells. In contrast, data from glucose tracing experiments revealed that T_H17 cells readily synthesized lipids from glucose; these cells also had increased expression of enzymes in the citrate-pyruvate shuttle system, which links carbohydrate and fat metabolism by transporting citrate across the mitochondrial membrane. Collectively, these results suggest that T_H17 cells depend on *de novo*–synthesized fatty acids rather than acquisition of extracellular fatty acids for development, highlighting the importance of the glycolytic-lipogenic pathway. The results by these authors also show impaired phospholipid production in T cells after SorA treatment, leading to decreased membrane synthesis. This effect might not only reduce T cell proliferation but also hinder the expansion of intracellular organelles. It was recently shown that the glycolytic-lipogenic pathway supports the endoplasmic reticulum and Golgi expansion required for dendritic cell activation[8]. It is possible that fatty acid synthesis inhibition leads to a similar membrane deficiency in T_H17 cells, leading to the T_{reg} phenotype.

SorA might also block T_H17 differentiation through feedback inhibition of glycolysis;

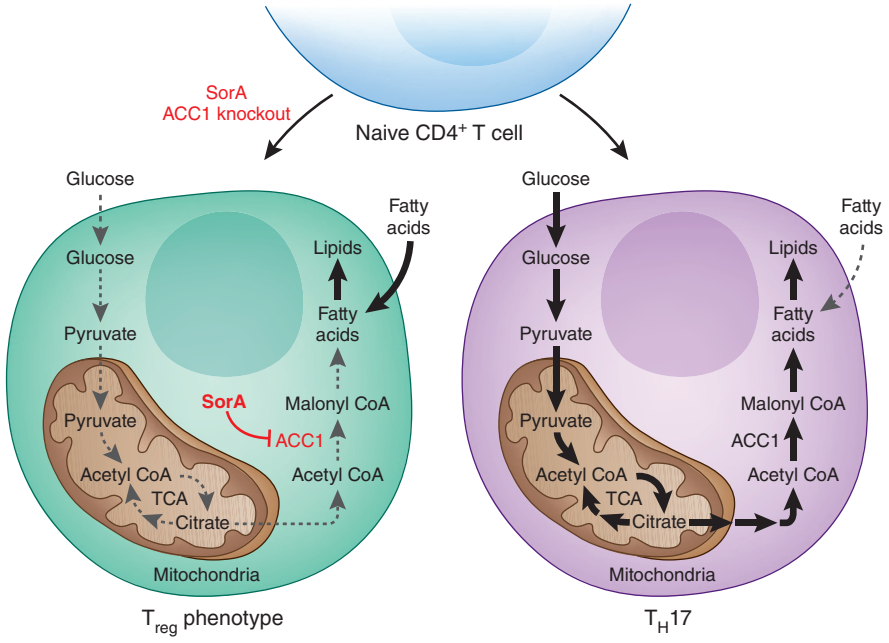

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Figure 1 Induction of the T_{reg} phenotype by inhibition of ACC1. Berod *et al.*[7] show that a T_{reg} phenotype is induced after activation of naive T cells under T_H17 polarizing conditions if ACC1 is inhibited—either by inhibition with the inhibitor SorA or by T cell specific knock out of ACC1—in mice (both indicated in red). T_H17 cells use the glycolytic-lipogenic pathway for lipid synthesis as indicated by the bold arrows. Inhibition of ACC1 results in a decreased flux through this pathway as represented by the grey dashed lines, with a concomitant increase in fatty acid uptake, enforcing a T_{reg} phenotype. TCA, tricarboxylic acid cycle.

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blocking ACC could result in the decreased utilization of glucose-derived citrate for fatty acid synthesis, causing the glycolysis pathway to 'back up'. The current data show a reduction in glucose-derived heavy labeled carbon in lipids and lower lactate levels in cells after SorA treatment, suggesting that glycolysis is impaired. However, when the authors added an excess of the fatty acid palmitate to SorA-treated cells, T_H17 cell development was restored, indicating that not only is glycolysis a critical process for T_H17 cell development but fatty acid synthesis is as well. This result also raises the possibility that SorA-inhibited T_H17 cells augment the uptake of extracellular fatty acids. In these conditions, where ACC is blocked and fatty acids are transported into the cells, it might have been expected that T_{reg} cells would develop. Perhaps intracellular synthesized fatty acids and acquired extracellular fatty acids are used for distinct purposes, and *de novo* fatty acid synthesis is not used simply for membranes but also to produce signaling molecules[9].

The current findings also raise the question of why T_H17 cells do not acquire fatty acids and instead rely on the ATP-costly process of *de novo* fatty acid synthesis, particularly when the need for lipids within this proliferating population would be substantial. In fact, $CD8^+$ effector T cells readily take up fatty acids[10], and *de novo* fatty acid synthesis is critical for optimal $CD8^+$ T cell expansion[11]. It is possible that differences in nutrient transport provide a mechanism to enforce polarization of one type of T helper cell subset over another.

To assess the relevance of these findings in disease, the authors carried out experiments in experimental autoimmune encephalitis (EAE), a mouse model of multiple sclerosis, which is a T_H17 cell–mediated autoimmune disease. T cell–specific deletion of ACC1 in this model significantly reduced $CD4^+$ T cell infiltration and the frequencies of T_H17 cells in the central nervous system. Strikingly, the mice also displayed no clinical signs of disease in the timeframe measured. Treating EAE mice with a SorA derivative also delayed disease onset. These data indicate the therapeutic potential of SorA in autoimmunity and of ACC-mediated fatty acid synthesis as a target to modulate the T_H17-T_{reg} cell balance *in vivo*. Furthermore, to show the relevance of the mouse findings to humans, the authors demonstrated that inhibition of ACC by SorA in human $CD4^+$ cord blood cells induced a T_{reg} phenotype.

T_H17 and T_{reg} cell differentiation is plastic[1], and hence to maintain a T_{reg} phenotype in SorA-treated cells, constant ACC blockade could be necessary. The authors show that treatment of EAE with a SorA derivative after disease onset did not reverse the disease, suggesting that ACC blockade may be effective only during T_H17 cell development. Whether SorA can induce a phenotypic change in fully differentiated T_H17 cells or whether long-term treatment in humans would be tolerable is unknown. Given its central role in fatty acid synthesis, there has been interest in inhibiting ACC to treat cancer and metabolic syndromes. These findings highlight the need to consider how targeting ACC would affect T cells in these settings, particularly in cancer, where the promotion of T_{reg} cells and the inhibition of T effector cells would be undesirable.

It was recently shown that butyrate from gut commensal bacteria promotes colonic T_{reg} cells[12]. Considering the results of Berod *et al.*[7], it is possible that this short-chain fatty acid is used for fatty acid oxidation in intestinal T cells, which could concomitantly decrease glycolysis and oppose fatty acid synthesis, shifting the T_h17-T_{reg} cell balance. It is also intriguing to speculate that gut bacteria produce metabolites similar to SorA to modulate host cell metabolism and influence the immune response, possibly regulating autoimmune susceptibility in humans. The work of Berod *et al.*[7] reveals ACC as a potential target for treating human T_H17 cell–mediated disease and further substantiates the role of metabolic pathways in cell-fate decisions.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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Asparagine endopeptidase cleaves tau and promotes neurodegeneration

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Truncation of tau contributes to the formation of neurofibrillary tangles in Alzheimer's disease. A new study finds a direct role for a lysosomal cysteine protease, asparagine endopeptidase, in cleaving tau into neurotoxic fragments.

Alzheimer's disease (AD) is the most common form of dementia, afflicting up to half of the population over the age of 85. AD has a complex etiology and is characterized by two neuropathological hallmarks: extracellular plaque deposits composed of amyloid-β and intracellular neurofibrillary tangles made of aggregated, truncated and hyperphosphorylated tau, a microtubule-associated protein. Mutations in amyloid-β–related genes underlie familial AD, and humans with these mutations and mouse models that mimic familial AD first show amyloid pathology followed by tau pathology. However, it is clear that tau can also contribute directly to neurodegeneration and is not simply a secondary effect of amyloid pathology. For instance, tau pathology (tauopathy) can cause toxicity when the brain is devoid of amyloid plaques, such as in frontotemporal dementia. Moreover, amyloid plaques are nontoxic in the absence of neurofibrillary tangles, and tangle pathology

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