ACC1 Inhibition Enhances Regulatory T-cell Suppressive Function by Controlling the Choice Between Fatty-Acid Synthesis and Oxidation

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Abstract
Regulatory T-cells (Treg) are critical for maintaining immune homeostasis. Pre-clinical studies show that Treg therapy can treat murine graft-vs-host disease (GVHD), and early phase clinical trials demonstrate reduced incidence of severe acute GVHD. However, high cell doses are required, and efficacy was incomplete in clinical trials. Therefore, methods to augment Treg function may further enhance the efficacy of Treg therapies.

One method to modulate Treg function is through metabolic manipulation. Acetyl-CoA carboxylase-1 (ACC1) controls the rate limiting step in fatty acid synthesis (FAS) and regulates fatty acid oxidation (FAO) by inhibiting the first step of mitochondrial FAO. ACC1 inhibition or genetic deletion enhances peripheral Treg generation, and is associated with increased FAO, with reduced FAS. Here, we show that ACC1 inhibition or deletion in murine Treg also enhances FAO-mediated oxidative phosphorylation, and enhances suppressive function in a FAO-dependent manner. Treg with genetic ACC1 deletion showed enhanced ability to treat established bronchiolitis obliterans in a murine model of chronic GVHD.

Pharmacological ACC1 inhibition with ND-630 (firsocostat), currently in clinical trials for non-alcoholic hepatic steatosis, resulted in enhanced expression of genes key for oxidative phosphorylation, and recapitulated the metabolic and functional phenotype of ACC1 knockout Treg. ND-630 treated Treg also demonstrated an increased ratio of fused mitochondria, a morphology which augments electron transport chain super-complex formation and supports increased FAO. Finally, treatment of *in vitro* expanded human Treg with ND-630 also enhanced oxidative phosphorylation and suppressive function, suggesting that ACC1 inhibition with ND-630 could be readily translatable for clinical trials.