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Acetyl-CoA carboxylases are checkpoints in adipocyte differentiation

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Acetyl-CoA carboxylases (ACC) 1 and 2 depend on biotin as a coenzyme and catalyze the carboxylation of acetyl-CoA to malonyl-CoA. Malonyl-CoA produced by cytoplasmic ACC1 and mitochondrial ACC2 is a precursor in fatty acid (FA) synthesis and an inhibitor of mitochondrial FA oxidation, respectively. We hypothesized that ACCs are checkpoints in adipocyte differentiation, and used human mesenchymal stem cells (hMSC) and murine 3T3-L1 preadipocytes to test our hypothesis. The expression of ACC2 increased by 1500% in differentiating hMSC compared with non-differentiating hMSC, judged by qRT-PCR and western blot. This increase preceded the increase of adipocyte marker genes FABP4 and PPARy. Treatment of hMSCs with grape leaf extract (GLE) inhibited the differentiation into adipocytes judged by the abundance of PPARy/FABP4 mRNA and staining of lipid droplets with Oil Red-O. Likewise, treatment of 3T3-L1 cells with the microbial ACC inhibitor soraphen A inhibited differentiation, judged by decreased lipid accumulation. Treatment of transgenic fruit flies, predisposed to storing excess body lipids, with GLE decreased body lipids by ~50%. In future studies, we will use mutagenesis to determine which of the two ACCs is the critical checkpoint in differentiation. We conclude that ACCs are checkpoints in adipocyte differentiation and that manipulation of ACC activity decreases body fat.

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