**Transcription factors TEAD2 and E2A globally repress acetyl-CoA synthesis to promote tumorigenesis**

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Acetyl-coenzyme A (acetyl-CoA) plays an important role in metabolism, gene expression, signaling, and other cellular processes, via transfer of its acetyl group to proteins and metabolites. However, the synthesis and usage of acetyl-CoA in disease states such as cancer are poorly characterized. Here, we investigated global acetyl-CoA synthesis and protein acetylation in a mouse model and patient samples of hepatocellular carcinoma (HCC). Unexpectedly, we found that acetyl-CoA levels are decreased in HCC due to transcriptional down-regulation of all six acetyl-CoA biosynthesis pathways. This led to hypo-acetylation specifically of non-histone proteins, including many enzymes in metabolic pathways. Importantly, repression of acetyl-CoA synthesis promoted oncogenic dedifferentiation and proliferation. Mechanistically, acetyl-CoA synthesis was repressed by the transcription factors TEAD2 and E2A, previously unknown to control acetyl-CoA synthesis. Knockdown of TEAD2 and E2A restored acetyl-CoA levels and inhibited tumor growth. Our findings causally link transcriptional reprogramming of acetyl-CoA metabolism, dedifferentiation, and cancer.