Inhibition of lung cancer growth: ATP citrate lyase knockdown and statin treatment leads to dual blockade of mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-kinase (PI3K)/AKT pathways.


Source

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Abstract

ATP citrate lyase (ACL) catalyzes the conversion of cytosolic citrate to acetyl-CoA and oxaloacetate. A definitive role for ACL in tumorigenesis has emerged from ACL RNAi and chemical inhibitor studies, showing that ACL inhibition limits tumor cell proliferation and survival and induces differentiation in vitro. In vivo, it reduces tumor growth leading to a cytostatic effect and induces differentiation. However, the underlying molecular mechanisms are poorly understood and agents that could enhance the efficacy of ACL inhibition have not been identified. Our studies focus on non-small cell lung cancer (NSCLC) lines, which show phosphatidylinositol 3-kinase (PI3K)/AKT activation secondary to a mutation in the K-Ras gene or the EGFR gene. Here we show that ACL knockdown promotes apoptosis and differentiation, leading to the inhibition of tumor growth in vivo. Moreover, in contrast to most studies, which elucidate how activation/suppression of signaling pathways can modify metabolism, we show that inhibition of a metabolic pathway "reverse signals" and attenuates PI3K/AKT signaling. Additionally, we find that statins, inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which act downstream of ACL in the cholesterol synthesis pathway, dramatically enhance the anti-tumor effects of ACL inhibition, even regressing established tumors. With statin treatment, both PI3K/AKT and the MAPK pathways are affected. Moreover, this combined treatment is able to reduce the growth of EGF receptor resistant tumor cell types. Given the essential role of lipid synthesis in numerous cancers, this work may impact therapy in a broad range of tumors.