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Combined inhibition of gluconeogenesis and glycolysis suppresses lung cancer spheroid growth.

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Background/Aims Due to the heterogeneous blood supply in solid tumors, cancer cells often face a shortage of important nutrients such as glucose. It is known that when the access of lung cancer cells to glucose is cut off, they can still bypass glucose metabolism and synthesize vital metabolites using some steps of gluconeogenesis by expression of phosphoenolpyruvate carboxykinase (PEPCK, PCK2). However, the effect of simultaneously suppressing gluconeogenesis and glycolysis in cancer cells has not been studied yet. We hypothesize, that combined inhibition of the former two pathways may lead to a synergistic effect in suppression of lung cancer spheroid growth.

Method/Results Glycolysis was inhibited by 2-Deoxyglucose, a widely studied glycolytic inhibitor, and gluconeogenesis was either inhibited using shRNA mediated silencing of PCK2 or pharmacologically with the PEPCK-inhibitor Axon1165. The effect of dual inhibition was assessed as growth of 3D lung cancer spheroids and proliferation rate of 2D cultured lung cancer cells. Combined inhibition of glycolysis and gluconeogenesis led to a synergistic effect in suppression of lung cancer spheroid growth and reduction of the proliferation rate in both inhibitor combinations.

Conclusion Inhibiting glycolysis and gluconeogenesis simultaneously seems to represent a promising approach to circumvent the metabolic flexibility of cancer cells. However, the underlying mechanisms behind the observed interaction need to be studied more extensively to understand the process leading to the synergy.