Targeting aldolase A in hepatocellular carcinoma leads to imbalanced glycolysis and energy stress due to uncontrolled FBP accumulation

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Abstract

Increased glycolytic flux is a hallmark of cancer; however, an increasing body of evidence indicates that glycolytic ATP production may be dispensable in cancer, as metabolic plasticity allows cancer cells to readily adapt to disruption of glycolysis by increasing ATP production via oxidative phosphorylation. Using functional genomic screening, we show here that liver cancer cells show a unique sensitivity toward aldolase A (ALDOA) depletion. Targeting glycolysis by disrupting the catalytic activity of ALDOA led to severe energy stress and cell cycle arrest in murine and human hepatocellular carcinoma cell lines. With a combination of metabolic flux analysis, metabolomics, stable-isotope tracing and mathematical modelling, we demonstrate that inhibiting ALDOA induced a state of imbalanced glycolysis in which the investment phase outpaced the payoff phase. Targeting ALDOA effectively converted glycolysis from an energy producing into an energy-consuming process. Moreover, we found that depletion of ALDOA extended survival and reduced cancer cell proliferation in an animal model of hepatocellular carcinoma. Thus, our findings indicate that induction of imbalanced glycolysis by targeting ALDOA presents a unique opportunity to overcome the inherent metabolic plasticity of cancer cells.