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Introduction

Glycolysis is defined as the sequence of 10 enzymatic reactions converting glucose to pyruvate, which is accompanied by release of energy in the form of ATP. In normal cells, pyruvate then enters the mitochondrial carboxylic acid cycle in the presence of oxygen, or is converted to lactic acid in its absence. Glycolysis is critical for providing rapidly dividing normal and cancer cells with energy and metabolic intermediates to synthesize cellular biomass. Malignant transformation greatly increases aerobic glycolysis (Warburg effect), which favors production of additional ATP and metabolites for biomass synthesis, and enables uncontrolled proliferation. Solid tumors also have an abnormal vasculature that leads to poor blood perfusion and hypoxia. A cancer cell's response to hypoxia is mediated by the hypoxia-inducible transcription factors HIF-1 and 2, which increase the expression of numerous survival factors, including genes that encode VEGF. HIF-1 also upregulates the expression of several glycolytic enzymes. Both glycolysis and HIF activity are critical for cancer cell survival, and have been proposed as therapeutic targets for agents that inhibit tumor growth.

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Definition of a Novel Feed-Forward Mechanism for Glycolysis-HIF1α Signaling in Hypoxic Tumors Highlights Aldolase A as a Therapeutic Target

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Abstract

The hypoxia-inducible transcription factor HIF1α drives expression of many glycolytic enzymes. Here, we show that hypoxic glycolysis, in turn, increases HIF1α transcriptional activity and stimulates tumor growth, revealing a novel feed-forward mechanism of glycolysis-HIF1α signaling. Negative regulation of HIF1α by AMPK1 is bypassed in hypoxic cells, due to ATP elevation by increased glycolysis, thereby preventing phosphorylation and inactivation of the HIF1α transcriptional coactivator p300. Notably, of the HIF1α-activated glycolytic enzymes we evaluated by gene silencing, aldolase A (ALDOA) blockade produced the most robust decrease in glycolysis, HIF-1 activity, and cancer cell proliferation. Furthermore, either RNAi-mediated silencing of ALDOA or systemic treatment with a specific small-molecule inhibitor of aldolase A was sufficient to increase overall survival in a xenograft model of metastatic breast cancer. In establishing a novel glycolysis-HIF-1α feed-forward mechanism in hypoxic tumor cells, our results also provide a preclinical rationale to develop aldolase A inhibitors as a generalized strategy to treat intractable hypoxic cancer cells found widely in most solid tumors.