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Control of Glycolytic Flux by AMPK and p53-mediated Signaling Pathways in Tumor Cells Grown at Low pH

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Introduction

Tumor cells grow in nutrient and oxygen deprived microenvironments and adapt to the suboptimal growth conditions by altering metabolic pathways. This adaptation process characteristically results in a tumor phenotype that displays upregulated Hif-1α anaerobic glycolysis, chronic acidification, reduced rate of overall protein synthesis, lower rate of cell proliferation and aggressive invasive characteristics. Most transplantable tumors exhibit a pHe of 6.7-7.0; the DB-1 melanoma xenografts used here have a pHe=6.7. Understanding tumor cell reaction to the microenvironment is a critical factor in predicting the tumor response to radiotherapy. The glucose regulatory molecule, 6-Phosphofructo-2-Kinase/Fructose-2,6-Biphosphatase Isoform-3 (PFKFB3), is a bifunctional enzyme central to glycolytic flux and downstream of the metabolic stress sensor AMP-activated protein kinase (AMPK), which we show activates an isoform of phosphofructokinase (PFK-2).

Methods

All techniques including the growth of the early passage DB-1 human melanoma and the U87 human glioma cells were standard and have been published.

Results

As hypothesized, our results demonstrated that growth at chronic pH 6.7 in air induced AMPK activation resulting in the upregulation of PFKFB3 and p53 and the downregulation of mammalian Target-Of-Rapamycin (mTOR) in both human tumor cell lines. Conversely, inhibition of AMPK resulted in downregulation of PFKFB3 and inhibition of glycolysis. When PFKFB3 was transfected and overexpressed in DB-1 melanoma cells growing at pH 7.3, it induced a high rate of glycolysis and inhibited oxygen consumption, which could lead to tumor acidification and oxygenation. By contrast, cells growing at low pH did not display an increased rate of glycolysis after PFKFB3 expression because the level of the TP53-induced Glycolysis and Apoptosis Regulator (TIGAR) was increased. Cells growing at low pH also were resistant to radiation-induced apoptosis despite upregulation of p53. This was partially explained by the expression of the anti-apoptotic proteins, Bcl-2 and Bax; TIGAR's ability to reduce lactate production; and downregulation of mTOR. Conversely, growth at low pH blocked GSH production and reduced bioreduction.

Conclusion

These results indicate that growth at tumor-like low pH activates AMPK and PFKFB3 and induces a high glycolytic and apoptotic potential that is countered by TIGAR and anti-apoptotic proteins, respectively. Alterations in these pathways lead to predictable alterations in lactate and oxygen levels, mTOR, GSH and redox state, and response to radiation. The control of glycolysis can thus alter acidification, oxygenation and state of bioreduction and modify tumor cell death pathways. These metabolic pathways that respond to the microenvironment require incorporation in radiation treatment strategies.

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