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Control of Glycolytic Flux by AMPK and p53-Mediated Signaling Pathways in Tumor Cells Adapted to Grow 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 anaerobic glycolysis, chronic acidification and aggressive tumor characteristics. Understanding the tumor cell reaction to the microenvironment is a critical factor in predicting the tumor response to hyperthermia. 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 has been shown to activate an isoform of Phosphofructokinase (PFK-2).

Results

As hypothesized, our results demonstrated that exposure to chronic low pH induced AMPK activation which resulted in the upregulation of PFKFB3 and p53, and the downregulation of mammalian Target-Of-Rapamycin (mTOR) in two tumor cell lines, DB-1 human melanoma and U87 human glioma. Conversely, inhibition of AMPK resulted in downregulation of PFKFB3 and inhibition of glycolysis. When PFKFB3 was over-expressed in DB-1 melanoma, it induced a high rate of glycolysis and inhibited oxygen consumption. By contrast, cells adapted to growth at low pH did not display an increased rate of glycolysis after PFKFB3 induction because the level of the TP53-induced Glycolysis and Apoptosis Regulator (TIGAR) was increased. Low pH adapted cells also were resistant to apoptosis, despite upregulation of p53. This may be partially explained by the induction of anti-apoptotic proteins and TIGAR's ability to reduce lactate production.

Conclusion

These results indicate that growth at tumor-like low pH activates AMPK and induces a high glycolytic and apoptotic potential that is countered by TIGAR and anti-apoptotic proteins, respectively. The control of glycolysis can thus minimize acidification and further protect tumor cells from death. These metabolic pathways in response to the microenvironment need to be incorporated in hyperthermia treatment strategies.

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