HYPOXIA AND ACIDOSIS INDEPENDENTLY REGULATE CELL IMMORTALITY IN CANCER CELL

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Abstract: Hypoxia and acidosis are hallmarks of tumors as well as critical determinants of response to cancer treatments. The development of tumor hypoxia has been shown to be a critical step in tumorigenesis and cancer cell metastasis. Low tumor pO₂ has been correlated with poor patient survival and metastasis in several types of cancer. Specifically, cyclical hypoxia was found to be associated with significant increase in metastasis of fibrosarcoma tumors. In one study, we quantified the metabolic end-products produced during routine carbohydrate metabolism in malignant neuroblastoma cells (N2A) under conditions of accelerated glycolysis to delineate differences between anaerobic vs. aerobic cellular metabolism. The data show acceleration of glycolysis instigates a reduction in extracellular pH. The data also show an accumulation of lactic acid, fumarate and alpha-ketoglutarate, while other metabolic organic acids remained undetected. Amino acids were also quantified and the results show production of L-alanine, L-glutamate, L-asparagine and L-aspartate during routine metabolism N2A. Analysis of acetaldehyde / aldehydes using indicate an absence of accumulated alcohol or aldehyde products. The results from this study indicate that carbohydrate metabolism in tumor cells may expand beyond glycolysis and involve peripheral carbon-nitrogen pathways central to the accumulation of diverse acidic and metabolic products. In the present study, we investigated the extent to which changes in O₂/CO₂ gas ratio may affect the pH and subsequently initiate cell death in malignant neuroblastoma. The data indicate that cell death occurred in either a closed chamber containing 100% oxygen or atmosphere (5% CO₂) after 24hrs of exposure at 37°C. These effects were also accompanied by a rise in pH within cell culture medium. Under both conditions, toxicity was potentiated by the addition of sodium bicarbonate but prevented by neutralization with acetic acid. In contrast, cells grown in a closed chamber containing 100% pure CO₂ underwent cell death tantamount to a drop in pH resulted from the buildup of carbonic acid. Under these conditions, toxicity was exacerbated by acetic acid addition and reversed by neutralization with sodium bicarbonate. These data clearly indicate that while O₂ appears to be toxic to cancer cells, the rise in alkalinity is the determining factor in cell death. Moreover, the pH range to which cells thrived was 5.6 to 7.4, where a slight rise in basic pH from 7.4 to 8.0, corresponded to dose dependent cell death mediated by higher levels of O₂. These findings suggest a paramount role for alkalinity rather than O₂ itself in promoting immortality in cancer cells.

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