Carcinoma hepatocelular e 3-bromopiruvato : aumento da apoptose

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3-Bromopyruvate induces endoplasmic reticulum stress, overcomes autophagy and causes apoptosis in human HCC cell lines.


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Abstract

BACKGROUND: Autophagy, a cellular response to stress, plays a role in resistance to chemotherapy in cancer cells. Resistance renders systemic chemotherapy generally ineffective against human hepatocellular carcinoma (HCC). Recently, we reported that the pyruvate analog 3-bromopyruvate (3-BrPA) promoted tumor cell death by targeting GAPDH. In continuance, we investigated the intracellular response of two human HCC cell lines (Hep3B and SK-Hep1) that differ in their status of key apoptotic regulators, p53 and Fas. Methods and

RESULTS: 3-BrPA treatment induced endoplasmic reticulum (ER) stress, translation inhibition and apoptosis based on Western blot and qPCR, pulse labeling, Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay and active caspase-3 in both the cell lines. However, electron microscopy revealed that 3-BrPA treated SK-Hep1 cells underwent classical apoptotic cell death while Hep3B cells initially responded with the protective autophagy that failed to prevent eventual apoptosis.

CONCLUSION: 3-BrPA treatment promotes apoptosis in human HCC cell lines, irrespective of the intracellular response.

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Hypoxia stimulates proliferation of human hepatoma cells through the induction of hexokinase II expression.


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Abstract

BACKGROUND/AIMS: In a hypoxic state, a glycolytic system is operating as a salvage pathway of generating ATP, and hexokinase II, the first enzyme in this system, might be over-expressed in hepatocellular carcinomas (HCCs). This study was to evaluate if hexokinase II is participating in HCC cell survival in a hypoxic state, and to analyze the mechanism of cell death caused by hexokinase II-specific inhibition.

METHODS: Human hepatoma cell lines were grown either in a normoxic or hypoxic condition. Hexokinase II and hypoxia-inducible factor-1alpha (HIF-1alpha) expression were evaluated using immunoblot techniques. Cell growth was assessed using the MTS assay. Apoptotic signaling cascades were explored by immunoblot analysis. RESULTS: Hypoxia stimulated HCC cellular growth through HIF-1alpha-dependent induction of hexokinase II expression. The hexokinase II-specific inhibitor, 3-bromopyruvate, significantly suppressed cellular growth in a hypoxic state compared to cells in a normoxic condition. This suppression was due to the induction of apoptosis through activating mitochondrial apoptotic signaling cascades.

CONCLUSIONS: This study demonstrates that hypoxia stimulates HCC cellular growth through hexokinase II induction, and its inhibition induces apoptotic cell death. Therefore, hexokinase II induction may participate in HCC progression and the blockage of this enzyme may therapeutically be efficacious in human HCCs.

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