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Up-regulation of hexokinase II in myeloma cells: targeting myeloma cells with 3-bromopyruvate.

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Abstract

Hexokinase II (HKII), a key enzyme of glycolysis, is widely over-expressed in cancer cells. However, HKII levels and its roles in ATP production and ATP-dependent cellular process have not been well studied in hematopoietic malignant cells including multiple myeloma (MM) cells. We demonstrate herein that HKII is constitutively over-expressed in MM cells. 3-bromopyruvate (3BrPA), an inhibitor of HKII, promptly and substantially suppresses ATP production and induces cell death in MM cells. Interestingly, cocultures with osteoclasts (OCs) but not bone marrow stromal cells (BMSCs) enhanced the phosphorylation of Akt along with an increase in HKII levels and lactate production in MM cells. The enhancement of HKII levels and lactate production in MM cells by OCs were mostly abrogated by the PI3K inhibitor LY294002, suggesting activation of glycolysis in MM cells by OCs via the PI3K-Akt-HKII pathway. Although BMSCs and OCs stimulate MM cell growth and survival, 3BrPA induces cell death in MM cells even in cocultures with OCs as well as BMSCs. Furthermore, 3BrPA was able to diminish ATP-dependent ABC transporter activity to restore drug retention in MM cells in the presence of OCs. These results may underpin possible clinical application of 3BrPA in patients with MM.

FMD: 22298254 [PubMed - indexed for MEDLINE]

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