D-Amino acid oxidase-induced oxidative stress, 3-bromopyruvate and citrate inhibit angiogenesis, exhibiting potent anticancer effects.


Source

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Abstract

Angiogenesis is critical for cancer growth and metastasis. Steps of angiogenesis are energy consuming, while vascular endothelial cells are highly glycolytic. Glioblastoma multiforme (GBM) is a highly vascular tumor and this enhances its aggressiveness. D-amino acid oxidase (DAO) is a promising therapeutic protein that induces oxidative stress upon acting on its substrates. Oxidative stress-energy depletion (osed) therapy was recently reported (El Sayed et al., Cancer Gene Ther, 19, 1-18, 2012). OSED combines DAO-induced oxidative stress with energy depletion caused by glycolytic inhibitors such as 3-bromopyruvate (3BP), a hexokinase II inhibitor that depleted ATP in cancer cells and induced production of hydrogen peroxide. 3BP disturbs the Warburg effect and antagonizes effects of lactate and pyruvate (El Sayed et al., J Bioenerg Biomembr, 44, 61-79, 2012). Citrate is a natural organic acid capable of inhibiting glycolysis by targeting phosphofructokinase. Here, we report that DAO, 3BP and citrate significantly inhibited angiogenesis, decreased the number of vascular branching points and shortened the length of vascular tubules. OSED delayed the growth of C6/DAO glioma cells. 3BP combined with citrate delayed the growth of C6 glioma cells and decreased significantly the number and size of C6 glioma colonies in soft agar. Human GBM cells (U373MG) were resistant to chemotherapy e.g. cisplatin and cytosine arabinoside, while 3BP was effective in decreasing the viability and disturbing the morphology of U373MG cells.

PMID:22802136