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Butyrate activates the monocarboxylate transporter MCT4 expression in breast cancer cells and enhances the antitumor activity of 3-bromopyruvate.

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Abstract

Most malignant tumors exhibit the Warburg effect, which consists in increased glycolysis rates with production of lactate, even in the presence of oxygen. Monocarboxylate transporters (MCTs), maintain these glycolytic rates, by mediating the influx and/or efflux of lactate and are overexpressed in several cancer cell types. The lactate and pyruvate analogue 3-bromopyruvate (3-BP) is an inhibitor of the energy metabolism, which has been proposed as a specific antitumor agent. In the present study, we aimed at determining the effect of 3-BP in breast cancer cells and evaluated the putative role of MCTs on this effect. Our results showed that the three breast cancer cell lines used presented different sensitivities to 3-BP: ZR-75-1 ER (+)>MCF-7 ER (+)>SK-BR-3 ER (-). We also demonstrated that 3-BP reduced lactate production, induced cell morphological alterations and increased apoptosis. The effect of 3-BP appears to be cytotoxic rather than cytostatic, as a continued decrease in cell viability was observed after removal of 3-BP. We showed that pre-incubation with butyrate enhanced significantly 3-BP cytotoxicity, especially in the most resistant breast cancer cell line, SK-BR-3. We observed that butyrate treatment induced localization of MCT1 in the plasma membrane as well as overexpression of MCT4 and its chaperone CD147. Our results thus indicate that butyrate pre-treatment potentiates the effect of 3-BP, most probably by increasing the rates of 3-BP transport through MCT1/4. This study supports the potential use of butyrate as adjuvant of 3-BP in the treatment of breast cancer resistant cells, namely ER (-).

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Publication Types, MeSH Terms, Substances, Grant Support

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