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THE INFLUENCE OF A SODIUM BUTYRATE ON PROLIFERATIVE SIGNALING CASCADES IN SENSITIVE AND RESISTANT TO HDAC INHIBITORS ACTION CELLS

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To establish the mechanisms of transformed cells resistance to the histone deacetylase inhibitors (HDACi), we compared the changes of the main proliferative signaling cascades activities in cells that are sensitive or resistant to HDACi-induced apoptosis. The time-dependent dynamics of the ERK kinase activity was shown. Phosphorylation of ERK kinase increased in the first 24 hours of the HDACi sodium butyrate treatment, followed by ERK activity decrease in resistant cells. Whereas in apoptotic cells, an inverse time-dependent dynamics of ERK activity changes was observed. It has been shown that resistance to HDACi can be overcome by inhibiting the MEK/ERK pathway. The resistant cells underwent to apoptotic death after 48 hours of combined treatment with sodium butyrate and the MEK/ERK pathway inhibitor PD098059. The study of the Wnt/β-catenin signaling cascade showed that the accumulation and transcriptional activation of β-catenin occurs only in cells resistant to HDACi-induced apoptosis. Thus, the obtained results indicate that a change in the activity of β-catenin is one of the reasons for the resistance to apoptosis induced by HDACi sodium butyrate, and the increased activity of the PI3K/Akt and MEK/ERK kinase pathways is a prerequisite for the most effective antiproliferative effect of HDACi.

Keywords: tumor cells, histone deacetylase inhibitor (HDACi), apoptosis, resistance, β-catenin, PKB/Akt and ERK kinases