

Inhibition of LAT1 activates GCN2-ATF4 survival pathway in Breast cancer cells.

Takashi Yamaga, Junichi Suehiro, Hiroyuki Sakurai

Dept. Pharmacol., Sch. Med., Kyorin Univ.

LAT1 overexpressed in many cancer cells is an attractive therapeutic target because it provides cancer cells with essential amino acids required for proliferation. JPH203, a specific competitive inhibitor for LAT1, has been reported to suppress proliferation of cancer cells. Recently, we found that anti-tumor effects of JPH203 between MDA-MB-231 cells, a model of highly malignant breast cancer cells (=TNBC) and T-47D cells(=non-TNBC) were different. To investigate the difference in JPH203 sensitivity, we analyzed global gene expression change in JPH203-responsive T-47D cells in the presence or absence of JPH203. Among them, we focused on ATF4, a master transcription factor for stress response, which activates anti-apoptotic pathway. Knockdown of ATF4 in MDA-MB-231 cells, enhanced JPH203 induced cell death. Furthermore, some reports showed that ATF4 elicits CTH, the biosynthetic enzyme for cysteine, which protects TNBC from nutrient stress. Knockdown of CTH in MDA-MB-231 cells, also enhanced growth inhibition by JPH203 treatment. These results suggest that nutrient stress caused by JPH203-treatment activated anti-apoptotic signaling via ATF4 in MDA-MB-231 cells and that CTH inhibition could be a novel way of breaking resistance to anti-LAT1 therapy in MDA-MB-231 cells.