**Monocarboxylate Transporter 7 Contributes to Anticancer Drug Resistance in Breast Cancer Cells**

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**Background and aims.** Breast cancer is the most common cancer in women globally, with increasing morbidity rates. Various drugs such as anti-estrogens, molecularly targeted drugs, and cytotoxic agents are used in the treatment of breast cancer. Anticancer drug resistance, in which the effects of anticancer drugs diminish after prolonged drug treatment, has become an important clinical issue that affects the prognosis of cancer patients. Monocarboxylate transporter 7 (MCT7/SLC16A6) is a transporter expressed in normal tissues such as human brain and liver, as well as in several cancer tissues, especially breast cancer (1). MCT7 has been reported to be upregulated in ovarian cancer cells resistant to some anticancer drugs (2). However, the pathophysiological role of MCT7 and its contribution to drug resistance in breast cancer cells remains unclear. Therefore, we evaluated the contribution of MCT7 to anticancer drug resistance, and the function of MCT7 as a novel drug transporter in breast cancer cells.

**Methods.** MCF-7 cells with doxycycline-inducible expression of human MCT7 (MCF-7-Tet-MCT7) were established by CRISPR/Cas9 genome editing. The viability of cells exposed to anticancer drugs was assessed by CCK-8 assays. In transport experiments, the intracellular levels of anticancer drugs and endogenous amino acids were examined using HEK293T cells transiently expressing EGFP-tagged human MCT7 and MCF-7-Tet-MCT7 cells. The anticancer drugs and endogenous amino acids in cell extracts were measured by LC-MS/MS.

**Results.** To examine whether MCT7 expression induces chemoresistance in breast cancer cells, we evaluated the effect of MCT7 expression on the anti-proliferative effects of various anticancer drugs using MCF-7-Tet-MCT7 cells. MCT7-induced cells showed higher cell viability than that of the non-induced cells against methotrexate (MTX) and pemetrexed (PMX). To examine whether MTX and PMX are directly transported by MCT7, we performed uptake experiments using HEK293T cells expressing EGFP-tagged MCT7. These drugs were taken up into MCT7-transfected cells, whereas these were not significantly taken up into mock cells. We also examined the uptake of these drugs using MCF-7-Tet-MCT7 cells under the acidic conditions. The uptakes of these drugs in MCT7-induced cells were decreased compared with those in non-induced cells. In addition, we examined the efflux of endogenous L-glutamate in MCF-7-Tet-MCT7 cells, because intracellular MTX and PMX undergo metabolic activation by folylpolyglutamate synthetase, which catalyses the addition of L-glutamates to folate derivatives. The L-glutamate level in MCT7-induced cells was lower than that of non-induced cells.

**Conclusion/Discussion.** Our study revealed that MCT7 expression contributes to MTX and PMX resistance in breast cancer cells. As this mechanism, MCT7 may function as a novel efflux transporter of these drugs and/or L-glutamate in breast cancer cells. Our *in vitro* cancer cell models are useful for evaluation of the physiological and pathophysiological role of MCT7.

**References:**

(1) Kothari, C. et al (2020) Sci Rep. 10:10464

(2) Januchowski, R. et al (2013) Biomed Pharmacother. 67:240-245

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