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A novel effective drug target for treating endocrine therapy resistant breast cancer

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SLC6A14 is a unique amino acid transporter; it transports only positive and neutral amino acids (18 of the 20 amino acids). The importance behind studying this transporter is that SLC6A14 is expressed at high levels in malignant tissues, specifically in estrogen receptor positive (ER+) breast cancer. The up-regulation of SLC6A14 protein in malignant cells is associated with the increased need for essential amino acids to maintain the accelerated cell growth. Glutamine and arginine are the most important amino acids for tumor cells because both are essential for proteins and nucleotides biosynthesis. Here, we demonstrate the relationship between the expression levels of the transporter and ER protein in endocrine sensitive and resistant breast cancer cell lines. Our data shows that which is conflicting with previous studies showing a significant correlation between SLC6A14 protein expression levels and ER protein in regular breast cancer cell lines. Suggesting that resistant breast cancer cells have a different pathway to regulate the transporter expression levels. Moreover, knocking down of SLC6A14 protein by siRNA led to a dramatic death rate (approximately 65%) in resistant breast cancer cells, confirming the importance of the transporter to this type of breast cancer. Consequently, *in vitro* treatment of ER-positive breast cancer cell lines series LCC1 (sensitive), LCC2 (Tamoxifen-resistant), and LCC9 (Faslodex-resistant; Tamoxifen-resistant) with α-methyl tryptophan (αMT), a selective substrate of SLC6A14 that can block the transporter, induces cell death by autophagy and apoptosis. Prolonged treatment stops the autophagosomal lysis process and induces apoptosis. Our study highlights SLC6A14 transporter as an effective drug target that can lead to new strategies for the treatment of endocrine therapy-resistant breast cancers.

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