SLC6A14-Mediated Glutamine Metabolism Reprogramming Enhances Cancer Stemness for Early Onset of Breast Cancer

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**Purpose**

Exposure to environmental substances, especially plasticizers in daily-used products, facilitates breast cancer formation. Young patients with early-onset breast cancer (EOBC), diagnosed before 45 years old, show poor therapeutic responses and short overall survival rates. Yet, the impacts of plasticizer exposure on driving the early tumorigenesis of breast cancer remain obscure.

**Materials and Methods**

We collected full-length hair (25mg) from healthy donor and patients with breast cancer in China Medical University Hospital from January 2024 to June 2024. The levels of DEHP were analyzed by using mass stpectrum analysis.

**Results**

In this study, a higher level of plasticizer di(2-ethylhexyl)phthalate (DEHP) was found in the hair of breast cancer patients and was associated with younger age at diagnosis. DEHP exposure accelerated tumorigenesis by increasing the cancer stem cell subpopulation. This effect was mediated by ER-beta-dependent upregulation of glutamine transporter SLC6A14, which enhanced cancer stemness through increasing glutamine uptake, mitochondrial oxidative phosphorylation, and de novo nucleotide synthesis. Inhibition of SLC6A14 reduced cancer stemness, suppressed tumor progression in vivo, and overcame chemoresistance.

**Conclusion**

Our study highlighted glutamine dysregulation in plasticizer-induced breast cancer initiation and progression and suggested SLC6A14 as a potential therapeutic target for EOBC.