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Targeting SLC25A10 alleviates improved antioxidant capacity and associated radioresistance of cancer cells induced by chronic-cycling hypoxia

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Abstract

High tumor heterogeneity and increased therapy resistance acquired in a hypoxic tumor microenvironment remain major obstacles to successful radiotherapy. Others and we have shown that adaptation of cancer cells to cycling severe hypoxia and intermittent reoxygenation stress (chronic-cycling hypoxia) increases cellular antioxidant capacity thereby supporting resistance to chemotherapy and radiotherapy. Here we explored the involvement of antioxidant-associated mitochondrial transport-systems for maintenance of redox-homeostasis in adaptation to chronic-cycling hypoxia and associated radioresistance.

Genetic or pharmacological inhibition of the mitochondrial dicarboxylate carrier (SLC25A10) or the oxoglutarate-carrier (SLC25A11) increased the cytotoxic effects of ionizing radiation (IR). But only targeting of SLC25A10 was effective in overcoming chronic-cycling hypoxia-induced enhanced death resistance *in vitro* and *in vivo* by disturbing increased antioxidant capacity. Furthermore, *in silico* analysis revealed that overexpression of SLC25A10 but not SLC25A11 is associated with reduced overall survival in lung- and breast-cancer patients.

Our study reveals a role of SLC25A10 in supporting both, redox- and energy-homeostasis, ensuring radioresistance of cancer cells with tolerance to chronic-cycling hypoxia thereby proposing a novel strategy to overcome a mechanism of hypoxia-induced therapy resistance with potential clinical relevance regarding decreased patient survival.