Abstract

Malignant brain tumors are characterized by destructive growth and neuronal cell death making them one of the most devastating diseases. Neurodegenerate actions of malignant gliomas resemble mechanisms also found in many neurodegenerative diseases such as Alzheimer's and Parkinson's diseases and amyotrophic lateral sclerosis. Recent data demonstrate that gliomas seize neuronal glutamate signaling for their own growth advantage. Excessive glutamate release via the glutamate/cystine antiporter xCT (system xc-, SLC7a11) renders cancer cells resistant to chemotherapeutics and create the tumor microenvironment toxic for neurons. In particular the glutamate/cystine antiporter xCT takes center stage in neurodegenerative processes and sets this transporter a potential prime target for cancer therapy. Noteworthy is the finding, that reactive oxygen species (ROS) activate transient receptor potential (TRP) channels and thereby TRP channels can potentiate glutamate release. Yet another important biological feature of the xCT/glutamate system is its modulatory effect on the tumor microenvironment with impact on host cells and the cancer stem cell niche. The EMA and FDA-approved drug sulfasalazine (SAS) presents a lead compound for xCT inhibition, although so far clinical trials on glioblastomas with SAS were ambiguous. Here, we critically analyze the mechanisms of action of xCT antiporter on malignant gliomas and in the tumor microenvironment. Deciphering the impact of xCT and glutamate and its relation to TRP channels in brain tumors pave the way for developing important cancer microenvironmental modulators and drugable lead targets.

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