

Gliomas are the most common primary malignant brain tumors in adults. Current treatment for glioblastoma patients is not sufficient – most patients will survive not more than 12-15 months from the time of diagnosis. That is why there is a great need to either for new targets for molecular medicine drugs, which is an expensive venture, or for new uses of the already existing ones.

Recent studies show that glioma cells depend upon fatty acid oxidation (FAO) for aerobic respiration and proliferation and that inhibition of FAO prolongs survival in mouse model of malignant glioma. Modulation of fatty acid metabolism in cancer cells might be a promising therapeutic strategy. Etomoxir, a drug used in those studies, is an inhibitor of FAO rate-limiting enzyme – palmitoyltransferase 1 (CPT1). It was tested in phase II clinical trials but the trials were terminated due to high hepatotoxicity. The efficiency of etomoxir in inducing cancer cell death in lower and less toxic doses could be improved. Carnitine is essential for the proper functioning of CPT1, and SLC22A5 is the only protein capable of efficient transport of carnitine through the plasma membrane that is present in the brain cells. Data published on the subject and our preliminary results show that there is more SLC22A5 in glioma cells than in astrocytes – noncancer equivalent of glioma cells. Moreover, SLC22A5 is able to transport several chemotherapeutics, the process that also often inhibits carnitine transport into the cell. However, there is nothing known about the role of SLC22A5 in glioma and its therapeutic potential in sensitizing the cells to lower, less toxic doses of CPT1 inhibitors has not been tested yet.

The aim of this study is to verify if the chemotherapeutic drugs transported by SLC22A5 can induce cell death by both their regular mechanism of action and inhibition of carnitine delivery into the cell, and whether they may sensitize glioma cells to lower, less toxic doses of CPT1 inhibitors.

To achieve this goal I will first verify, with the use of radiolabeled substrates, whether anticancer drugs that are transported by SLC22A5 are able to inhibit carnitine transport in glioblastoma cells, and by that modify fatty acid metabolism. Subsequently, I will assess the impact of different doses of those chemotherapeutics, administered separately and in combination with CPT1 inhibitor, on the viability and proliferation of cells. I will also compare the responses of glioma cells and astrocytes to the combination of above-mentioned drugs. Finally I will verify if the effects observed after co-administration of SLC22A5 transported drugs with CPT1 inhibitors are indeed due to SLC22A5 activity.

The results of this study would increase the current knowledge on the role of SLC22A5 and CPT1 in cancer cells and on fatty acid metabolism in glioblastoma. What is more, the evaluation of the potential of novel therapeutic approach to sensitize cells to lower doses of CPT1 inhibitors may contribute to the improvement of therapeutic strategies for glioma patients.