ABSTRACT

Gliomas are the most malignant tumors of the central nervous system and present an extremely important therapeutic problem affecting people around the world. Currently available treatments allow only to improve the quality of life and prolong survival. High resistance to applied therapy is based on the very high proliferative, migration and infiltration potential of cells. The malignant nature of gliomas and their resistance to the induction of programmed death is closely related to the overexpression of the TrkB receptor and its regulated pathways: PI3K-Akt/PKB-mTOR, Ras-Raf-MEK-ERK, and PLCγ1-PKC. Therefore, the search for new therapeutic strategies based on blocking survival signal transmission through these pathways gives hope for the elimination of the disease using novel targeted therapies.

The aim of the study conducted on human anaplastic astrocytoma (MOGGCCM) and glioblstoma multiforme (T98G) cell lines was to determine the anti-tumor activity of LY294002 (PI3K inhibitor), sorafenib (Raf inhibitor), U-73122 (PLCγ1 inhibitor), and LOXO-101 (TrkB inhibitor) as well as Temozolomide in a single and simultaneous application by the induction of programmed cell death.

The results showed that the studied compounds effectively eliminitaed both cel lines on the way of programmed death and inhibited their migration also. Autophagy was associated with an increase of its markers expression - beclin-1, while in apoptotic cells an increase in the expression and activity of caspases 3, 8 and 9 were observed.

Simultaneous application of the studied substances was more effective in the elimination of glioma cells by programmed cell death in comparison to single treatment, while glioblastoma multiforme appeared to be more sensitive to the used therapy than anaplastic astrocytoma. MOGGCCM cells were mostly sensitive to the apoptosis initiation after simultaneous incubation with of LY294002, U-73122 and Temozolomide, which indicates the involvement of PI3K-Akt/PKB-mTOR and PLCγ1-PKC pathways in anaplastic astrocytoma resistance. In turn, the largest number of apoptotic cells were observed in the T98G line after simultaneous incubation with LY294002, sorafenib, and Temozolomide, what suggests that the resistance of glioblastoma multiforme is associated with the stiumulation of PI3K-Akt / PKB-mTOR and Ras-Raf-MEK-ERK pathways.

Blocking the expression of PI3K, Raf, PLCγ1 and TrkB with specific siRNAs provided direct evidence of the involvement of studied pathways in gliomas resistance to programmed cell death initiation and confirmed the effectiveness of studied inhibitors in blocking the survival signal and sensitizing cancer cells to the induction of apoptosis.

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