Intracellular signalling pathways as potential target in Glioblastoma treatment

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Glioblastoma (GBM) is the most frequent and malignant primary brain tumor. The limited success with temozolomide (TMZ) appears to be related with several mechanisms, namely the activity of O6-methylguanine-DNA methyltransferase (MGMT), the expression and activity of P-glycoprotein (PGP), the presence of GBM stem cells, which are known to be chemo- and radioresistant, and to the occurrence of gene mutations that cause permanent activation of several survival signalling pathways, such as the AKT, ERK1/2 MAP kinase and protein kinase C (PKC).

Previous studies reported that the activity of PKC in GBM cells is increased but it contribution in the aggressiveness of GBM is unclear. One of the PKC inhibitors is tamoxifen (TMX). Considering that GBM shows resistance to TMX and to TMZ, and that these drugs have different mechanisms of action, we investigated the potential synergistic therapeutic effect of that combination in the reduction of GBM aggressiveness.

For that, we used three different GBM cell lines and determined the MGMT methylation pattern, the PGP expression and the expression of stem-like cell markers. After that, the cells were incubated in absence and presence of TMX and/or TMZ and it was evaluated the cytotoxic effect, cell survival and proliferation, the cytoskeleton organization, the migration capability and the phosphorylated amount of p-PKC, p-AKT and p-ERK1/2 MAP kinases.

The results of this study showed that the cell lines have different susceptibilities to TMZ and TMX. The combination of TMX and TMZ reduces the amount of the p-PKC-pan and contributes to the reduction of the aggressive behaviour of the GBM cells, namely due to a decrease in cell migration, proliferation and cell cycle arrest. Together, the results suggest that PKC could be a therapeutic target, emphasizing the importance of combined therapeutic protocols including TMZ with PKC inhibitors in GBM treatment.

Keywords: Glioblastoma; p-PKC; Synergism.