Melanocortin receptor-4 as a novel therapeutic target in glioblastoma

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Background. Our group has recently published new findings suggesting a possible role of melanocortin receptor-4 (MC4R) genotypes in the survival of treated glioblastoma (GBM) patients. In particular, the MC4R rs489693 AA genotype was significantly associated with a shorter progression-free survival and overall survival in patients treated with a standard combined radiotherapy and temozolomide schedule (Pasqualetti et al., 2017). Currently no description of melanocortin receptor-4 (MC4R) expression or activity is available in human cancer cells, including GBM. The aim of this study is to evaluate the presence of MC4Rs in GBM cells and the selective inhibition of their activity through the MC4R antagonist ML00253764 alone and in association with temozolomide.

Methods. MC4R genotyping and gene expression were performed on human U-87 and U-118 cells with real time PCR. MC4R immunohistochemistry were obtained in both cell lines. Proliferation and apoptotic assays were performed with ML00253764, temozolomide or their simultaneous combination for 72h to evaluate their synergistic effects by the combination index (CI) method. ERK1/2 and Akt phosphorylation were quantified by ELISA.

Results. Both GBM cell lines expressed MC4R receptors, although in different extent. The selective antagonist ML00253764 determined an antiproliferative and pro-apoptotic activity through the inhibition of the phosphorylation of ERK1/2 and Akt. The simultaneous combination of temozolomide and ML00253764 determined a highly synergistic effect on GBM cells, corresponding to a CI<1 for percentages of affected cells higher than 60% with a favorable dose reduction index>1 for both drugs.

Conclusion. This is the first study ever to suggest that the MC4R is present in GBM cells and its selective inhibition determined antiproliferative and pro-apoptotic effects and the synergistic enhancement of temozolomide effects. These findings may represent a new relevant field of research for future translational studies for the treatment of GBM.

References.

Pasqualetti F, Orlandi P, Simeon V, Cantarella M, Giuliani D, Di Desidero T, Gonnelli A, Delishaj D, Lombardi G, Sechi A, Sanson M, Zagonel V, Paiar F, Danesi R, Guarini S, Bocci G. Melanocortin Receptor-4 Gene Polymorphisms in Glioblastoma Patients Treated with Concomitant Radio-Chemotherapy. Mol Neurobiol. (2017) doi:10.1007/s12035-017-0414-9