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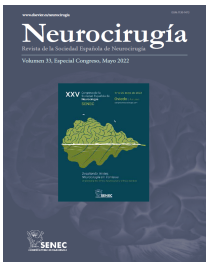

P-182 - OXIDATIVE AND GLYCOLYTIC PHENOTYPES COEXIST WITHIN THE METABOLIC HETEROGENEITY OF GLIOBLASTOMA

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Resumen

Introduction: One of defining characteristics of glioblastoma, at a functional, bioenergetic level, is its ability to exploit glycolytic metabolism even in the presence of oxygen, a phenomenon known as the “Warburg effect"

Objectives: We propose that strategic targeting of dysregulated bioenergetic pathways, after an initial assessment of the metabolic phenotypes coexisting within glioblastoma, could become a valuable stratification and therapeutic tool, improving the efficacy of adjuvant metabolic therapy.

Methods: We performed a Gene Set Variation Analysis (GSVA) for canonical glycolytic/oxidative pathways in The Cancer Genome Atlas (TCGA) GBM datasets. We characterized the basal bioenergetic metabolism and antiproliferative potential of metformin (MF), dichloroacetate (DCA), sodium oxamate (SOD) and diazo-5-oxo-L-norleucine (DON) in three distinct glioma stem cells (GSCs) (GBM18, GBM27, GBM38), in addition to traditional established cell line U87MG.

Results: A clustering of highly oxidative signatures was observed in normal tissues, whereas highly glycolytic tumors matched with the mesenchymal subtype; interestingly, mesenchymal signatures are associated with increased inflammation and wound healing pathways, a higher degree of necrosis and the worst survival when restricting for samples with low transcriptional heterogeneity. GBM27, a highly oxidative cell line, was the most resistant to all treatments, except DON. GBM18 and GBM38, Warburg-like GSCs, were sensitive to MF and DCA, respectively. Resistance to DON was not correlated with basal metabolic phenotypes. In combinatory experiments, radiomimetic bleomycin exhibited therapeutically relevant synergistic effects with MF, DCA and DON in GBM27 and DON in all other cell lines. MF and DCA shifted the metabolism of treated cells towards glycolysis or oxidation, respectively. DON consistently decreased total ATP production.

Conclusions: Our study highlights the need for a better characterization of GBM from a metabolic perspective. Metabolic therapy should focus on both glycolytic and oxidative subpopulations of GSCs.