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Abstracts

DR-06. REACTIVE OXYGEN SPECIES MEDIATE THERAPEUTIC RESPONSE AND RESISTANCE IN GLIOBLASTOMA
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Glioblastoma (GBM) resistance to therapy is the most common cause of tumor recurrence, which is ultimately fatal in 90 percent of the patients five years after initial diagnosis. A subpopulation of tumor cells with stem-like properties are specifically endowed to resist or adapt to the standard therapies (e.g., radiation, chemotherapy) and lead to tumor resistance. We investigated the mechanisms underlying GBM response to treatment using the non-toxic, non-psychoactive cannabinoid derivative cannabidiol (CBD), in primary glioma stem-like cells in culture and in vivo. In culture, CBD induced an increase in reactive oxygen species (ROS) in GSC which lead to inhibition of pro-neural markers, cell survival, p-AKT, and self-renewal, concomitant with upregulation of anti-oxidant response gene products and mesenchymal markers. These phenotypic changes were also measured in GSC-derived xenografts from CBD-treated animals, suggesting this molecular adaptive response contributes to therapeutic response and resistance in vivo. CBD-induced mesenchymal shift was reversible by pretreatment with Tocopherol (vit E), indicating that it is ROS mediated. CBD-induced inhibition of self-renewal was mediated by activation of the AMPK-phosphor-p38-Bmi1 pathway. The anti-oxidant response cellular program was mediated by transcriptional activation of NFE2L2 and resulted upregulation of its target genes, such as xCT. xCT is the enzymatic component of system Xc which regulates GSH levels, the main CNS redox buffering system, and plays a critical role in GBM cell survival. We hypothesized that combining CBD with xCT inhibition will exhibit an enhanced anti-tumor effect. Using genetic knockdown and the pharmacological agents Sulfasalazine and Erastin, we demonstrate that CBD and xCT inhibitors work synergistically to inhibit survival, self renewal and invasion of primary GSC. Taken together our data suggest that combination of CBD and non-toxic small molecules which regulate ROS levels constitute a promising therapeutic approach for glioblastoma.

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