CANNABINOIDS IN THE TREATMENT OF GLIOBLASTOMA: ROLE OF CB1 AND CB2 RECEPTORS.

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Herein we evaluated the expression of cannabinoid receptors type 1 and 2 (CB1/2) in a wide panel of human brain tumors (GBM) and in normal human astrocytes (NHA). A majority of the brain tumor sample over-expressed protein levels of CB1 as compared to NHA in an aggressiveness-related manner, while uniformly expressed low levels of CB2. This finding prompted us to investigate the therapeutic exploitation of CB1 inactivation by Rimonabant treatment, with regard to its direct and indirect cell-mediated effect against GBM.

Functional studies, using GBM primary cell lines derived from patients expressing different levels of CB1, highlighted that its levels determine Rimonabant efficacy at inducing cell cycle arrest and block of TGF-β1 secretion through a mechanism that involves STAT3 inhibition. According to the role of STAT3 in the promotion of survival, proliferation, but also in the immune escape of cancer cells, interestingly Rimonabant lead also to the functional and selective expression of MICA/B on the surface of responsive malignant glioma cells, but not on NHA. This make Rimonabant treated-glioma cells potent targets for allogeneic NK cell-mediated recognition through a NKG2D restricted mechanism, thus stimulating cytotoxicity and IFN-γ production of co-cultured NK cells. In vivo the treatment with Rimonabant caused a significant reduction of tumor size in mice xenografted with human U87 glioma cells. This correlates with a higher expression of MICA/B and a Ly49G2 + NK cells infiltrate in murine tumor tissue sections, suggesting that, in addition to the direct anti-proliferative effect, Rimonabant can also make GBM immunovisible priming it for NK cell antitumor reactivity.

Keywords: Glioblastoma, CB1 receptor, NK, STAT3.