Analyzing the Effect of Neuropilin 1 Knockdown on Conventional Chemotherapy in GBM

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Despite the advancement in therapy, Glioblastoma Multiforme (GBM) remains to have a very low 5-year survival rate of 27%. Those diagnosed with GBM often only have an average of 14 months to live, making it one of the most deadly diseases in the world. GBM tumor cells are nourished by blood vessels that are formed via angiogenesis (the formation of blood vessels) by the Vascular endothelial growth factor (VEGF). VEGF is a signaling protein that stimulates angiogenesis, causing the GBM cells to reproduce, strengthen, and migrate around the brain. However, VEGF therapy has failed miserably to cure GBM patients. In this study I will look at coreceptor Neuropilin 1, a transmembrane glycoprotein that enhances the effects of many GBM cell receptors such as VEGF, Transforming Growth Factor beta (TGFb), and Semaphorin. In most cases of GBM, Neuropilin 1 is known to be overexpressed. GBM has been proven to be extremely drug resistance and has a high recurrence rate. I used shRNA mediated Nrp-1 knockdown approach and studied the effect of NRP-1 in the GBM drug resistance. I found that Neuropilin depletions in tumor resistant GBM cell lines, caused drug sensitization as observed in the Temozolomide treatment in our studies. Temozolomide mechanism of action is alkylating/methylating DNA at the N-7 or O-6 positions of guanine residues, damaging DNA and triggering the death of tumor cells. I found that Neuropilin knockdown leads to suppression of GBM stem cell marker expressions and also the inhibition of MDM2 expression. Neuropilin knockdown also results in tumor growth inhibition. In conclusion NRP1 Knockdown sensitizes GBM to conventional Temozolomide therapy.

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