An in vitro study of the mTORC1/2 inhibitor PP242 in glioblastoma multiforme

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mTOR is a kinase complex involved in cell growth, proliferation, survival, metabolism and migration. The aberrant activation of mTOR has been previously demonstrated in glioblastoma multiforme (GBM), making it an interesting target for therapeutic approaches [1]. Unfortunately, the attempts to block mTOR activity made so far had disappointing clinical efficacy, as the mTOR inhibitor Rapamycin and analogs only target mTOR complex 1 (mTORC1) while mTOR actually exists in two distinct complexes, namely mTORC1 and mTOR complex 2 (mTORC2) that differ in terms of both regulation mechanisms and functions [2,3]. mTORC1 is inhibited by Rapamycin and acts as a downstream effector of the PTEN/PI3K/Akt pathway, linking growth factors, amino acids, ATP and O₂ signals to protein translation, cell growth, proliferation and survival. Differently, mTORC2 is insensitive to Rapamycin and acts as an upstream activator of Akt via phosphorylation of serine 473 [3]. To analyze the contribution of mTORC1/2 to GBM biology, we studied the in vitro effect of PP242, a novel mTORC1/2 inhibitor, on glioma cell lines of different malignancy degree, and compared it to the effect of Rapamycin and of the irreversible PI3K inhibitor, Wortmannin.

Our results suggest that the inhibition of both mTOR complexes with PP242 induces sustained levels of autophagy that causes G0/G1 cell cycle arrest and a significantly reduction of cell viability, proliferation and migration. Additionally, we observed that administration of PP242 in U87MG cell line prevents stem cell growth, which results in the inhibition of neurospheres formation. This data confirms the pivotal role of mTOR in glioblastoma cells biology and expand upon this evidence suggesting a prominent role of the mTOR complex 2 in glioblastoma cell growth, migration and survival, and indicate that the mTORC2 might represent clinically valuable target in GMB.

References