

Ultrastructure of Glioblastoma cells in baseline conditions and following mTOR inhibition

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Glioblastoma Multiforme (GBM), a WHO grade IV malignant glioma, is the most common, aggressive and lethal primary brain tumor [1]. GBM poses a unique challenge due to its propensity for proliferation and tissue invasion. Multiple experimental and pathological findings suggest that, at molecular level, the up-regulation of the molecular complex mTOR plays a pivotal role in determining cell growth, stem cell proliferation, infiltration, relapse and resistance to standard treatments [2]. When activated, mTOR controls and modulates, directly or indirectly, several cellular events and biochemical pathways [3,4]; in particular, mTOR acts as a negative modulator of autophagy, resulting in a defective autophagy in GBM.

In the present study we analyzed the ultrastructural correlates of autophagy inhibition in GBM cells and we reverted various alterations by administering the mTOR inhibitor rapamycin. Rapamycin effects were both dose- and time-dependent and consisted in reducing cell proliferation and inducing cell differentiation. In particular, rapamycin was able to restore autophagy vacuoles and it increased specific markers of neuronal differentiation while it inhibited stem cell-like phenotype. The present data lend substance to mTOR and autophagy as critical determinant in astrocytomas and provide the first ultrastructural evidence of autophagy modulation in these brain tumors.

References

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Keywords

Rapamycin, autophagy, electron microscopy, cell differentiation, autophagy vacuoles.