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Rapamycin promotes trans-differentiation while inhibiting mTOR activity in glioblastoma cells

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Glioblastoma multiforme (GBM; grade IV glioma) is the most common and highly malignant primary brain tumor [1]. GBM cells feature mammalian target of rapamycin (mTOR) up-regulation which relates to biological properties of normal stem cells, such as self-renewal, pluripotency and marked proliferation. Thus, they are key in tumor initiation, relapse and resistance to standard treatments [2-4].

Therefore, in the present study we show the effects of different doses of rapamycin on (i) the phenotype of different GBM cell lines; (ii) the number and the ultrastructural morphology of mitochondria. By means of genetic, immunoblotting and morphological analysis at light and electron microscopy, we demonstrate that rapamycin reduces the stem-like phenotype, promotes the neuronal differentiation of GBM cells, and increases the amount of mitochondria by enhancing the mitochondrial fission and mitochondriogenesis. This induced a marked reduction of the stemness marker Nestin, while stimulating gene transcription related to neuronal differentiation, namely the early (beta-III tubulin) and late (NeuN) neuronal markers. No effects were produced for GFAP glial marker. Remarkably, in these experimental conditions, cell phenotype shifts towards a pyramidal neuron-like shape owing long branches.

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Key words

Rapamycin, mTOR, stem cells, neuronal differentiation, transmission electron microscopy.