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Morphology demonstrates similar autophagy alterations in neurodegeneration and brain tumors

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Malignant glioma are the most malignant brain tumors. Frequent genetic alterations involve PTEN (Phosphatase homolog deleted on chromosome Tensin and Ten), a lipid phosphatase that after mutation is not able to convert phosphatidylinositol (3,4,5)-triphosphate (PIP3) into phosphatidylinositol (4,5)-bisphosphate (PIP2) and thereby inhibiting AKT, which in turn activates the apoptotic factors, mutations of p53 and retinoblastoma, both responsible of controlling the phase transition G1 / S of cell cycle under physiological conditions and prevent the replication of DNA when the cell is altered. Recently a dramatic uptake of the amino acid glutamine was reported in malignant glioma. This amino acid produces a marked inhibition of the autophagy pathway. Consistently, autophagy is defective in human glioblastoma similar to neurodegeneration. Autophagy is the main clearing system to remove damaged or potentially harmful organelles and misfolded proteins. Autophagy progresses through several stages: (i) the phagophore (ii) the autophagosome (iii) the amphisomes; (iv) the autophagolysosome and (v) the autophagoproteasome. The last stages involves the fusion of amphisome with lysosome which originates autophagolysosome that contains the elements to be removed and lytic enzymes necessary for this degradation process, while the autophagoproteasome derives from the fusion with component of the proteasome.

The autophagy machinery can be measured by several specific markers such as beclin1 and LC3, the occurrence of stagnant autophagy vacuoles.

In the present study we characterized the consistency and relevance of autophagy failure in glioblastoma by using human cell lines, primary human cell cultures and in vivo human glioblastoma cells implanted in the brain of nude mice.

In baseline conditions we observed in cells obtained from surgery of human patients a marked inhibition of the autophagy pathway. This was associated with an increase in autophagy substrates overlapping with neurodegenerative disorders.

In keeping with the ongoing autophagy inhibition we found that activation of the autophagy pathway reduced cell proliferation and promoted cell differentiation dose-dependently in vitro while the systemic administration of a powerful autophagy activator reduced the volume of brain tumor in vivo by 96.6%.

These data indicate a relevant role of autophagy failure in glioblastoma and suggest potential approaches to contrast tumor growth.

Keywords: synucleinopathy, glioblastoma, autophagy, neurodegeneration