MedicalXpress

Biochemical alteration responsible for brain tumour resistance identified

February 19 2016

Researchers from the Institute of Neuroscience (INc) of the Universitat Autonoma de Barcelona (UAB) have identified the biochemical and molecular alteration that causes resistance to radiotherapy and chemotherapy in the glioblastoma , the most aggressive of brain tumours. This finding could enable new, more effective therapies.

Glioblastoma is the most aggressive manifestation of brain tumours. Due to its high invasive capacity and uncontrolled, infiltrating growth, it is particularly difficult to manage. Currently, the treatment consists of a combination of surgery (when possible), radiation and chemotherapy. Although current therapy raises the overall survival of patients by around 15 months, it remains inefficient at eradicating tumour cells and unfortunately, recurrences are typical.

A team of researchers has identified a common molecular alteration in glioblastoma. The researchers observed that the cells of this type of tumour harbour a common intrinsic defect that prevents them from degrading their genetic material during apoptosis, the most important form of programmed cell death induced by radiotherapy and chemotherapy.

This defect is related to an enzyme: the endonuclease DFF40/CAD (Death Fragmentation Factor, 40 kDa subunit / Caspase-Activated DNase). This enzyme, which is essential for degrading DNA during apoptosis, appears both downregulated and improperly located inside the tumour cells when compared with non-tumoural cells. The researchers

observed that overexpression of the enzyme allows the glioblastoma cells to properly degrade their DNA content as expected in an apoptotic cell death.

DNA degradation during apoptosis is an essential step that facilitates the subsequent removal of cellular debris from malignant cells. In fact, the lack of degradation and removal of genetic material from malignant cells could have detrimental consequences, including new tumour processes more aggressive than the initial ones.

Despite the efforts made in the last decade to understand the biology of these tumours, until now, no common genetic or biochemical defect had been found in glioblastoma cells. The low levels of expression observed in the enzyme endonuclease DFF40/CAD and the deficiency in degrading and properly compacting its genetic material constitute a potential molecular marker in this tumour. In addition, the fact that this alteration was observed in all the cases points to its importance as a possible explanation for the aggressiveness of this cancer. The researchers hope these new results will improve our understanding of what goes on inside the tumour, and perhaps enable new, more effective therapies to be designed in the future.

More information: María Sánchez-Osuna et al. An intrinsic DFF40/CAD endonuclease deficiency impairs oligonucleosomal DNA hydrolysis during caspase-dependent cell death: a common trait in human glioblastoma cells, *Neuro-Oncology* (2016). DOI: 10.1093/neuonc/nov315

Provided by Universitat Autonoma de Barcelona