Molecule Nutlin-3a activates a signal inducing cell death and senescence in primary brain tumors

April 20 2011

Researchers of Apoptosis and Cancer Group of the Bellvitge Biomedical Research Institute (IDIBELL) have found that a small molecule, Nutlin-3a, an antagonist of MDM2 protein, stimulates the signalling pathway of another protein, p53. By this way, it induces cell death and senescence (loss of proliferative capacity) in brain cancer, a fact that slows its growth. These results open the door for MDM2 agonists as new treatments for glioblastomas. The study has been published at the journal *PLoS ONE.*

Glioblastoma multiforme is the most common brain tumour in adults and the most aggressive. Despite efforts on new treatments and technological innovation in neurosurgery, radiation therapy and clinical trials of new therapeutic agents, most patients die two years after diagnosis. Avelina Tortosa, IDIBELL and University of Barcelona (UB) researcher, coordinator of the study, explained that one objective of her group is "to find substances that sensitize tumour cells to radiotherapy for more efficient treatments".

New therapeutic targets

There is evidence that several genetic alterations promote the growth, invasion and resistance to stimuli that induce programmed cell death (apoptosis). In this sense, the pilot project TCGA (The Cancer Genome Atlas) has sequenced the genome of up to 25 glioblastomas noting that

14% of patients have an increased expression of MDM2 and 35% had alterations in p53 expression (apoptosis-inducing). That is why research is now focused on the development of new therapeutic strategies that target the apoptosis in gliomas.

The aim of this study was to investigate the antitumor activity of Nutlin-3a in cell lines and primary cultures of glioblastoma. Researchers have shown that Nutlin-3a induces apoptosis and cellular senescence by stimulating the p53 pathway in cells, because cells with mutations in this protein don't produce this response. They have also discovered that the use of Nutlin-3a enhances the response of glioblastoma cells to radiotherapy. "The radiation induced DNA damage of tumour cells", explained Tortosa, "the cells activate repairing mechanisms and, if they are unable to repair, they destruct themselves (a mechanism known as apoptosis). With Nutlin-3a we have seen that increases tumour cell death and therefore increases the effectiveness of radiotherapy treatment. "

In conclusion, the results suggest that the MDM2 antagonists may be new therapeutic options for the treatment of glioblastoma patients.

More information: Villalonga-Planells R, Coll-Mulet L, Martínez-Soler F, Castaño E, Acebes J-J, Giménez-Bonafé P, Gil J and Tortosa, A. (2011) Activation of p53 by Nutlin-3a Induces Apoptosis and Cellular Senescence in Human Glioblastoma Multiforme. PLoS ONE 6(4): e18588. doi:10.1371/journal.pone.0018588

Provided by IDIBELL-Bellvitge Biomedical Research Institute