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Glioblastoma stem cells and radiation: metabolism and radiation sensitivity

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Among brain cancers, glioblastoma multiforme (GBM) is the most aggressive form with a very poor prognosis. Surgery is the first-line treatment for GBM patients, followed by combined radio- and chemotherapy. In the most recent models of cancer, the presence of cells with stem-like properties is deemed to contribute to high recurrence rate and failure of conventional treatments. Literature data reports that gamma irradiation of GBM cells produced an increased fraction of stem-like cells in the residual tumour population compared with that in non-irradiated tumours. This was attributed to activation of DNA damage checkpoint response and increase in DNA repair capacity.
Recent studies on gliomas based on microarray expression profiling as well as gene analysis have identified molecular subtypes associated with tumour grade, progression, and patient survival. Although these studies could not reach conclusive statements nor were able to predict more precise clinical outcomes for GBM patients, their relevance consists in revealing that gliomas can be divided into subtypes of different prognostic significance. In this framework, we have identified and characterized the "metabolite phenotypes"of thirteen glioblastoma stem cell (GSC) lines by 1H NMR spectroscopy through unsupervised analysis of spectral features. This study yielded two clusters with six lines belonging to a more "neural-like"and seven to a more "glioma-like"metabolic phenotype. Two GSC lines belonging to the two different metabolic clusters identified by 1H NMR, namely line 1 and line 83, were then examined after gamma irradiation with a Cs-137 source. Viability and cell death were analyzed in the dose range 1-10 Gy by colorimetric methods and cytotoxicity assays while apoptosis was evaluated in parallel by flow cytometry measurements using Propidium Iodine and Annexin-V. The overall results have shown that line 83 cells are much more radioresistant than line 1. Moreover, cell metabolism monitored by 1H NMR 48 hr after 10 Gy irradiation showed changes in mobile lipid signals and in signals of glu-gln metabolic pathway related to cell cycle check points and to oxidative stress response, respectively, for line 1 while no differences between irradiated and control cells appeared for line 83.
These preliminary results suggest the presence of different mechanisms of radioresistance acting in the two GSC lines studied.

Primary author: Dr ROSI, Antonella (Departement Technology and Health, Istituto Superiore di Sanità, Rome, Italy; INFN, Sez. Roma1-gruppo collegato Sanità, Rome, Italy)

Co-authors: Dr PALMA, Alessandra (Departement Technology and Health, Istituto Superiore di Sanità, Rome, Italy; INFN, Sez. Roma1-gruppo collegato Sanità, Rome, Italy); Dr CAMPA, Alessandro (Departement Technology and Health, Istituto Superiore di Sanità, Rome, Italy; INFN, Sez. Roma1-gruppo collegato Sanità, Rome, Italy); Dr LUCIANI, Anna Maria (Departement Technology and Health, Istituto Superiore di Sanità, Rome, Italy; INFN, Sez. Roma1-gruppo collegato Sanità, Rome, Italy); Dr FRATINI, Emiliano (Centro studi e ricerche e museo storico della fisica "E. Fermi", Rome, Italy); Dr PELACCHI, Federica (Department of Hematology, Oncology and Molecular Medicine, Istituto Superiore di Sanità, Rome, Italy); Dr ESPOSITO, Giuseppe (Departement Technology and Health, Istituto Superiore di Sanità, Rome, Italy; INFN, Sez. Roma1-gruppo collegato Sanità, Rome, Italy); Dr PECCHIA, Ilaria (Departement Technology and Health, Istituto Superiore di Sanità, Rome, Italy); Dr GUIDONI, Laura (Departe-

ment Technology and Health, Istituto Superiore di Sanità, Rome, Italy; INFN, Sez. Roma1-gruppo collegato Sanità, Rome, Italy); Dr RICCI-VITIANI, Lucia (Department of Hematology, Oncology and Molecular Medicine, Istituto Superiore di Sanità, Rome, Italy); Dr TABOCCHINI, Maria Antonella (Departement Technology and Health, Istituto Superiore di Sanità, Rome, Italy; INFN, Sez. Roma1-gruppo collegato Sanità, Rome, Italy); Dr BALDUZZI, Maria (Departement Technology and Health, Istituto Superiore di Sanità, Rome, Italy; INFN, Sez. Roma1-gruppo collegato Sanità, Rome, Italy); Dr BELLI, Mauro (Departement Technology and Health, Istituto Superiore di Sanità, Rome, Italy; INFN, Sez. Roma1-gruppo collegato Sanità, Rome, Italy); Dr BIFFONI, Mauro (Department of Hematology, Oncology and Molecular Medicine, Istituto Superiore di Sanità, Rome, Italy); Dr PALLINI, Roberto (Department of Neurosurgery, Catholic University of Rome, Rome, Italy); Dr GRANDE, Sveva (Departement Technology and Health, Istituto Superiore di Sanità, Rome, Italy; INFN, Sez. Roma1-gruppo collegato Sanità, Rome, Italy); Dr DINI, Valentina (Departement Technology and Health, Istituto Superiore di Sanità, Rome, Italy; INFN, Sez. Roma1-gruppo collegato Sanità, Rome, Italy); Dr VITI, Vincenza (Departement Technology and Health, Istituto Superiore di Sanità, Rome, Italy; INFN, Sez. Roma1-gruppo collegato Sanità, Rome, Italy)

Presenter: Dr ROSI, Antonella (Departement Technology and Health, Istituto Superiore di Sanità, Rome, Italy; INFN, Sez. Roma1-gruppo collegato Sanità, Rome, Italy)

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