THE G4 LIGAND RHPS4 INDUCES CHROMOSOMAL INSTABILITY AND INCREASED SENSITIVITY TO X-RAYS IN GLIOBLASTOMA CELLS

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It is well known that one of the phenotypic hallmarks of cancer, *i.e.*, unlimited replicative potential, is intimately related to the maintenance of telomeres, the nucleoproteic complexes located at the end of eukaryotic linear chromosomes. A number of published works revealed that uncapped/dysfunctional telomeres can be obtained by pharmacological stabilization of specific secondary structures that are physiologically present at telomeres known as G-quadruplex (G4). G4 interacting compounds, such as the RHPS4 drug, destabilize telomere architecture leading to end-to-end telomeric fusions and consequently to chromosomal instability.

In addition, in recent years telomeres have been recognized as a new player in radiation sensitivity and in particular telomere loss or dysfunction were indicated as critical parameters in the cellular response to ionizing radiation.

The aim of the present study is to shed light on the possible synergistic effect of the combined treatment with RHPS4 and ionizing radiation on radioresistant U373 human glioblastoma cells. Percentage of dysfunctional telomeres progressively increased with time of exposure whereas Q-FISH analyses revealed that telomere length did not decrease as response to RHPS4-treatment. To investigate the effect on chromosomal stability of the drug alone or in combination with IR, cytogenetic experiments were performed using direct labeled FITC-pancentromeric and Cy3-telomeric PNA probes. Dicentrics and telomere fusions were higher in the combined treatment samples if compared to X-irradiated samples. In addition, it was observed a higher percentage of unrejoined DSBs and a reduced surviving fraction in the combined treatment with respect to the only X-ray exposure.

Further experiments are in progress to support the hypothesis of a direct correlation between the number of dysfunctional telomeres induced by RHPS4 and the cellular radiosensitivity measured by the induction of unstable rearrangements such as dicentrics and telomere fusions.