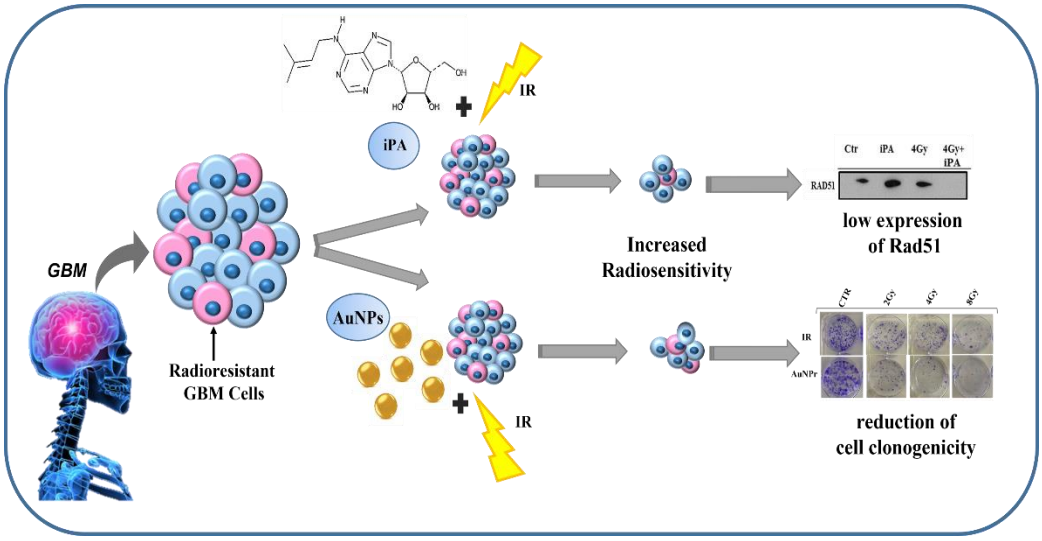
UNIVERSITY OF NAPLES FEDERICO II

DOCTORATE IN
MOLECULAR MEDICINE AND MEDICAL BIOTECHNOLOGY

XXXV CYCLE

Giovanna Navarra

DEVELOPMENT OF NEW THERAPEUTIC APPROACHES TO RADIOSENSITIZE GLIOBLASTOMA CELLS



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DEVELOPMENT OF NEW THERAPEUTIC APPROACHES TO RADIOSENSITIZE GLIOBLASTOMA CELLS

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“Nothing in life is to be feared, it is only to be understood.
Now is the time to understand more, so that we may fear less”.

-Marie Curie-

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LIST OF ABBREVATIONS

ADK: adenosine kinase
AMP: monophosphate adenosine
AMPK: AMP-kinase
ATM: ataxia telangiectasia mutated
ATR: ataxia telangiectasia and Rad3-related protein
AuNPs: Gold nanoparticles
BBB: blood-brain barrier
CAT: computerized axial tomography
CDKs: cyclin-dependent kinases
CSCs: cancer stem cells
DDR: DNA damage response
DMAPP: dimethylallyl diphosphate
DSB: double-strand break
EGFR: epidermal growth factor receptor
EPR: enhanced permeability and retention
FDPS: Farnesyl diphosphate synthase
GBM: Glioblastoma Multiforme
GSCs: Glioblastoma stem cells
HMGCR: HMG-CoA reductase
HR: homologous recombination repair
HT: Hyperthermia
IDH1/2: isocitrate dehydrogenase 1/2
iPA: N^6-isopentenyladenosine
iPAMP: 5'-iPA-monophosphate
IPT: isopentenyl transferase
IR: Ionizing Radiation
ITH: intra-tumoral heterogeneity
MGMT: O6-methylguanine-DNA methyltransferase
MVA: mevalonate pathway
NF1: neurofibromin 1
NHA: normal human astrocyte
NHEJ: non-homologous end-joining
NK: natural killer
NMR: nuclear magnetic resonance
NPrs: Nanoprism
NPs: nanoparticles
NSCs: neural stem cells
OPCs: oligodendrocyte precursor cells
PDGFRA: platelet-derived growth factor receptor A
PEG: polyethylene glycol
PTEN: phosphatase and tensin homolog
PTT: photothermal therapy

ROS: reactive oxygen species
RT: radiotherapy
RTK: Receptor tyrosine kinase
SSB: single-strand break
TCGA: The Cancer Genome Atlas
TMZ: temozolomide
TP53: tumor protein P53
WHO: World Health Organization

ABSTRACT

Glioblastoma multiforme (GBM) is the most common primary brain cancer in adults with poor prognosis due to the bad response to therapeutic regimens such as radiotherapy and chemotherapy. Ionizing radiation (IR) has been identified as a crucial treatment for GBM following surgical resection to improve both local control and survival. Unfortunately, radiotherapy resistance is frequently observed in GBM patients, which is the main reason for the high mortality rate of cancer patients. Tumours typically recurs due to robust DNA repair, so the mechanisms underlying the intrinsic radio-resistance in GBM are rigorously studied.
In the present work are investigated two different approaches to evaluate their radiosensitizer effects in GBM cells. A first study, more detailed, in which a natural molecule is used, and a second, still ongoing, in which nanotechnology is tested. Previous studies of my research group reported N^6-isopentenyladenosine (iPA), a naturally modified adenosine harboring an isopentenyl moiety, has shown several antiproliferative effects on GBM cell lines.
In this study has been shown the potential of iPA treatment at micromolar concentration, in combination with IR, enhance radiotherapy sensitivity of GBM cells. The combined treatment significantly attenuated the repair of radiation-induced DNA damage by inhibiting both the expression and irradiation-induced *foci* formation of RAD51, a key player in the homologous recombination repair process, leading to persistent DNA damage, as reflected by an increase of ɣ-H2AX *foci*. These data suggest that iPA could function as a promising radiosensitizer agent for GBM cells.
We are currently evaluating the effectiveness of new approaches such as the use of gold nanoparticles (AuNPs). AuNPs are actively under study and hold promise to improve the treatment response to radiotherapy. AuNPs, specifically nanoprisms (NPrs) have been tested in two several GBM cell lines. The AuNPs act by photothermal therapy (PTT), an efficient method of inducing localized hyperthermia aiming to selectively kill tumor cells. Preliminary data, show that AuNPrs at low concentrations have no toxic effects in GBM cells and when combined with different radiation doses, have an encouraging radiosensitizing effect. Therefore, it is our interest to study the synergistic effects of iPA together with AuNPs in order to develop a promising strategy to extend the efficacy of radiotherapy in GBM cells.