Ultrashort pulsed electric fields as specific radiosensitizers of medulloblastoma cancer stem cells

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Abstract

The SUMCASTEC project aims to isolate and neutralize brain cancer stem-like cells (CSC) using electromagnetic stimulations.We present an in vitro and in vivo study on the effects of pulsed electric fields as a new therapeutic strategy to promote CSCs radiosensitization.

Medulloblastoma (MB) is the most common pediatric malignant brain tumor. Its conventional therapy ofteninvolves severe neurocognitive deficiencies. Therefore, new therapeutic strategies are necessary to reduce not only long-term toxicity of radiotherapy or chemotherapeutic agents, but also to target specifically cancer stem cells (CSCs), responsible for the later recurrence and relapses. In fact, CSCs seem to be candidates in the onset of the disease and constitute an endless reserve for the maintenance and progression of the tumor and it could be the reason of conventional therapy failure. The goal of this study was to test the ability of microsecond pulsed electric fields (μsPEFs) to selectively target malignant MB CSCs and induce a process to sensitize them to radiotherapy treatment.

Presented Work

We started to characterize different MB cell lines in term of their stemness phenotype. The D283 cells showed almost 100% of CD133 positive cells, a major capacity to form neurospheres and a higher oncogenic potential, thus resulting a perfect model of MB CSCs [1]. A crucial point of this study was to investigate a selective action of the μsPEFs exposure on CSCs. To this aim a suitable pulsing protocol has been selected.

It resulted to be effective on D283 cells but not in Normal Human Astrocytes (NHAs) in term of cell membrane. permeability, cell death, cell cycle perturbation and proliferation.

To provide deep insight into the molecular mechanism driving the selective cell targeting, we focused our attention on the cell cycle network, using the RT2 Profiler PCR Arrays. Results showed that the exposure to μsPEFs induced the G2/M arrest in D83 cells via the up-regulation of GADD45a, a gene that could be crucial for the choice of the cell fate activating apoptosis and senescence processes.

The efficacy of combined treatment (i.e. μPEFs and ionizing radiations) have been also validated both in vitro and in vivo. Our results suggest that exposure to μsPEFs could represent a new therapeutic strategy as pretreatment to promote CSCs radiosensitization, overcoming their radio-resistance and improving future clinical outcomes.

References:

1: Casciati A, Tanori M, Manczak R, Saada S, Tanno B, Giardullo P, Porcù E, Rampazzo E, Persano L, Viola G, Dalmay C, Lalloué F, Pothier A, Merla C, Mancuso, M. Human Medulloblastoma Cell Lines: Investigating on Cancer Stem Cell-Like Phenotype. Cancers (Basel). 2020 Jan 17;12(1). pii: E226. doi:10.3390/cancers12010226. PubMed PMID: 31963405.

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