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New therapeutic strategy for medulloblastoma: μsPulse Electric Field exposure targeting cancer stem cells to promote radiosensitization

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Medulloblastoma (MB) is the most common pediatric malignant brain tumor. Its conventional therapy consists of surgical resection followed by chemotherapy and radiotherapy that often involve severe neurocognitive deficiencies. Cancer stem cells (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. Moreover, the quiescence state is the survival strategy of CSCs responsible for the later recurrence and relapses. Therefore, new therapeutic strategies are necessary to reduce not only long-term toxicity of radiotherapy or chemotherapeutic agents, but also to targeting specifically CSCs. The goal of this study is selectively target quiescent malignant CSCs and subsequently induce a differentiation process to sensitize them to radiotherapy treatment using appropriately modulated pulse electric fields (PEFs).

We started to characterize different MB cell lines in term of CSCs content. The D283 cells resulted a perfect model of MB SCs. They showed almost 100% of CD133 positive cells and this feature defined their high oncogenic potential and a major capacity to form neurospheres and to engraft in nude mice with respect to the other cell lines.

Exposure of living cells to PEFs is able to change the permeability of the cell membrane by modifying its molecular structure opening pores, causes the influx of ion permeation, inducing various cellular reactions, including signal transduction, stress response and cell death. Therefore, EF signal itself may lead to a multiple effect on the unhealthy cell target, thus achieving a potentiation of the anticancer therapy, but a crucial point involves the selective neutralization. To this aim different PEFs are been selected to be effective in D283 cells but not in Normal Human Astrocyte (NHA). In particular the μsPEF-3 (40 μs 0.35 MV/m 5 pulses) exposure induced a different response in term of cell death and cell cycle perturbation. To provide deep insight into the mechanism that differentiates the response we focused our attention in cell cycle network as a molecular point of view, using the RT^2 Profiler PCR Arrays. The molecular analysis showed that μsPEF-3 induced the G2/M arrest via the up-regulation of GADD45a that could be crucial for the choice of the cell fate activating apoptosis, senescence or differentiation mediated by stress-activated p38 MAPK process.

Our results suggest that this new therapeutic approach could be suitable as pre-treatment to promote radiosensitization. Combined μsPEFs treatment with ionizing radiation exposure could represent an innovative strategy that will improve the clinical outcome.

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