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Ultrashort electric pulses: an effective way to target cancer stem cells

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Medulloblastoma (MB) is the most common pediatric brain cancer. 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 [1]. CSCs seem also to be the reason of conventional therapy failure. Moreover their quiescence state is responsible for the later recurrence and relapses of the pathology. Therefore, new therapeutic strategies are necessary to reduce not only long-term toxicity of radiotherapy or chemotherapeutic agents, but also to targeting specifically CSCs. To this aim, in this work we applied different sets of ultra-short electric pulses (both microsecond and nanosecond) to understand if malignant and quiescent CSCs can be targeted by this exposure and which type of molecular alterations (associated with senescence, cell dead or differentiation) occurs after this treatment. Indeed, the electric treatment could sensitize CSCs to radiotherapy.

First of all, we started to characterize different MB cell lines in term of CSCs content; the D283 cells resulted a perfect model of MB CSCs. They showed 95% of CD133 positive cells, high oncogenic potential and a major cell capacity to form neurospheres and to engraft in nude mice with respect to other tested MB cell lines [1].
After cell exposure, in standard electroporation cuvette using a suitable pulsing buffer, we analyzed different end points at different times after the exposure as: i) cell viability, ii) cell permeabilization, iii) cell cycle, iv) reactive oxygen species formation, as well as a panel of different genes involved in cell cycle, apoptosis and differentiation.

However, a crucial point for the effectiveness of this novel therapeutic strategy involves the selective neutralization of CSCs. To this aim normal human astrocyte (NHA), as a model of non-transformed cells, were exposed to similar electric stimulations. NHA presented different responses with respect to D283 in term of cell membrane permeabilization, cell viability and cell cycle perturbation. The evidenced selectivity of the electric treatment is very interesting for its potentiality in therapeutic applications. Therefore, different molecular pathways are under investigation to disclose selective mechanism of ultra-short electric pulses in brain cells.

References

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