METALLACARBORANES FOR PROTON THERAPY USING RESEARCH ACCELERATORS

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The use of energetic proton beams offers advantages in cancer treatment including tumor confinement, higher LET (linear energy transfer), and higher RBE (relative biological effectiveness). Recently, new drugs with greater selectivity for tumor cells that enable increasing the RBE for protons have been investigated. These new drugs are constituted by carborane boron clusters [1] coordinated by a central metal ion. The presence of B may increase the effect of protons on cell death, due to the $p + {}^{11}B \rightarrow 3\alpha$ nuclear fusion reaction, with a resonance at 675 keV and a high cross section (1.2 barn). The emitted α-particles have a broad spectrum with a predominant energy of 4 MeV. Due to these characteristics, the reaction has become very attractive in the context of medical applications of proton therapy as emitted α- particles range in water is of the order of a cell dimension.

Herein we report on the impact in the viability of U87 glioblastoma cells treated with Fe carborane (FeC) and its iodinated analogue (I_2FeC) compounds after proton irradiation, as a function of deposited dose. The nuclear microprobe external beam facility at the Van de Graaff accelerator at CTN/IST was used to perform the U87 cell's irradiations. The focused proton beam was scanned over a monolayer of U87 cells seeded in 96-well plates. The energy deposited in cells was tuned to reach the resonance energy of the B nuclear fusion reaction in the cell layer (SRIM simulation: for 30 μm cell layer thickness, medium transmitted energy=470 keV and LET=26 keV/μm [2]).

As the therapeutic effectiveness relies on the cellular amount and distribution of compounds, we have evaluated quantitatively the net Fe uptake in U87 cells. PIXE results showed that the Fe uptake in U87 treated cells were 5-fold higher than the control (non-treated cells).

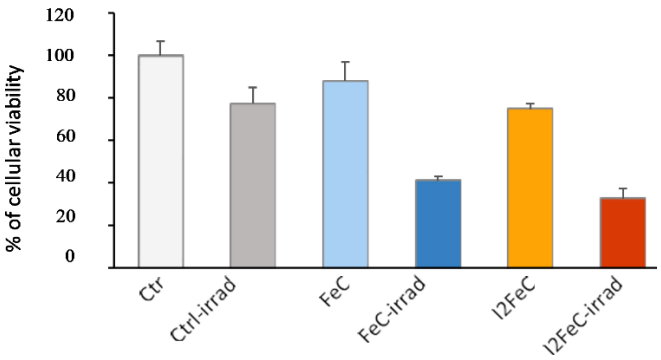

Fig. 1 – Viability of U87 cells under control (Ctr) and treated conditions and their response to proton irradiation for 10s with a dose of 3.7 kGy.

In non-irradiated U87 cells the treatment with FeC and I_2FeC caused a small decrease in viability relative to controls as measured by MTT assay. However, after proton irradiation U87 cells exposed to FeC and I_2FeC compounds showed a 50% increase in lethality contrasting with a 16% increase in irradiated controls as can be depicted in Fig. 1. The magnitude of lethality achieved evidenced the potential of FeC and I2FeC compounds to increase cellular killing following proton irradiation.

References

[1] T. García-Mendiola, V. Bayon-Pizarro, A. Zaulet, I. Fuentes, F. Pariente, F. Teixidor, C. Viñas, E. Lorenzo. Metallacarboranes as tunable redox potential electrochemical indicators for screening of gene mutation. Chem. Sci., 2016, 7, 5786-5797.
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