Theme: Pre-clinical Research and Mechanisms of Disease

Proton therapy for glioblastoma multiforme: in vitro studies and evaluation of gold nanoparticles as radiosensitizers

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Abstract:
Glioblastoma multiforme (GBM) is the most frequent primary brain malignancy in adults and still persists a fatal condition. Hence, proton therapy has been introduced as an alternative to standard radiotherapy treatment in GBM, since its dose-depth curve provides efficient tumor damage while minimizing unwanted radiation exposure to normal brain tissue. Including an extra FLASH effect to proton irradiation would also reduce neurotoxicity as opposed to standard low-dose exposure. Complementarily, the use of gold nanoparticles (AuNPs) to improve radiotherapy effectiveness has also been proposed for glioblastoma tumors, since AuNPs act as local radiosensitizers upon interaction with external radiation due to the release of Auger electrons.
In this work, we developed a PET cyclotron-based FLASH proton beam for in vitro research, whose optimization involved radiochromic film dosimetry methods and FLASH measurements. A direct relationship between the measured integrated beam charge and the absorbed dose at the target was established and a FLASH dose rate of 13.5 Gy/s was obtained. Later on, U373 glioblastoma cells were exposed to proton and photon radiation to quantify their clonogenic survival, revealing to be less sensitive to Co-60 γ-

radiation (1 Gy/min) than to 160 kVp X-rays (2.65 Gy/min) and FLASH protons. Finally, U373 cultures were subjected to proton therapy combined with GBM targeted AuNPs (AuNP-Bombesin AuNP-BBN). These targeted AuNPs were able to produce a radiosensitizing effect for proton doses of 1 and 2 Gy.
In summary, a PET cyclotron-based FLASH proton beam line was successfully assembled for radiobiological in vitro research. We also introduced concomitant GBM-targeted AuNP-BBN and radiotherapy as a potential novel treatment modality for glioblastoma, as AuNP-BBN induced selective radiosensitization. Future work will include proton irradiation studies with other cancer cell lines and complementary radiosensitizing studies.

Keywords: FLASH proton therapy, radiotherapy, glioblastoma, gold nanoparticles, radiobiology