Effectiveness of laser accelerated ultra high dose rate protons in DNA DSB damage induction under hypoxic conditions

P. Chaudhary¹, D. Gwynne² D. Doria³ L. Romagnani³, C. Maiorino³, H. Padda³, A. Alejo³, N. Booth³, D. Carroll³, S. Kar³, P. McKenna³ G. Schettino³ M. Borghesi² and K.M. Prise¹

1. Centre for Cancer Research and Cell Biology, Queen’s University Belfast, UK
2. Centre of Plasma Physics, Queen’s University Belfast, UK
3. Laboratoire LULI Ecole Polytechnique, Cedex, France
4. Experimental Science Group, Central Laser Facility, Rutherford Appleton Laboratory, Didcot, Oxford, UK
5. SUPA Department of Physics, University of Strathclyde, Glasgow G4 0NG, UK
6. National Physical Laboratory, Teddington, Middlesex, UK

Background: Particle therapy has been predicted to be an effective treatment modality for killing radioresistant hypoxic tumor cells. However, installation and operational costs of particle facilities makes them less accessible. Technological advances using laser-accelerated ions, emitted in ultra-short bursts, offers a future, cost-effective alternative to conventional accelerators. Characterization of the radiobiological effects at the ultrahigh dose rate delivered by these short ions pulses on human cells under hypoxic conditions is important for the optimization of this technology for future clinical applications.

Materials and methods: Laser accelerated 15-18 MeV protons generated using the Nd:glass VULCAN laser system at the Rutherford Appleton Laboratory, Oxford, UK, were delivered, by a compact magnetic transport system, to cell samples at dose rates exceeding 10⁸-10¹⁰ Gy/s. Dosimetry was validated using gafchromic films and CR-39 track detectors. Human skin fibroblasts (AG01522 cells) were pre-gassed with hypoxic gas mixture (95% N₂/5% CO₂) for 4 hours and irradiated inside portable beam-line hypoxia chambers. Hypoxia induction was validated physically using oxygen sensor and biologically using HIF-1α immunostaining coupled with DNA DSB damage, and repair kinetics measurements quantified using the 53BP1 foci formation assay.

Results: There was a good correlation between 53BP1 foci repair kinetics under oxic conditions from laser and cyclotron accelerated proton beams, with average foci values at 30 minutes of 29.93±1.02 and 27.07±1.20 respectively. Under hypoxic conditions the fast repair component of DSB foci kinetics showed an oxygenation dependency (average foci 16.63 ± 0.65), which could not be seen for the slow repair component. We also observed a non-significant variation in the foci induction at 24 hours post-irradiation with laser-accelerated protons suggesting an OER of about 1 for residual DSB foci.

Conclusions: Here we report for the first time measurements of DNA DSB damage with pulsed protons at ultrahigh dose rate (10⁸–10¹⁰ Gy/s) under hypoxic conditions and a comparison with conventional protons. We observed a close similarity between the foci kinetics induced by laser accelerated and cyclotron accelerated protons under both the oxic and hypoxic conditions.