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Measurements of primary and secondary particle tracks in live cells

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Carbon (C-) ion beams undergo nuclear interactions with tissue, producing secondary nuclear fragments. Thus, at the depth where the tumor and critical structures are located, C-ion beams are composed of a mixture of different particles with different linear energy transfer (LET) values. Indeed, at the middle of a typical spread-out Bragg peak of a C-ion beam, only about 35% of the particles are primary particles. To understand the biological consequences of C-ions it is important to elucidate how single cells coupe with damage induced by C-ions and their fragments. Particularly, it is important to understand at the molecular level the kinetics of DNA repair proteins after damage from C-ions and their fragments. Here we describe a technique that enables isolation of DNA damage response (DDR) in mixed radiation fields using beam line microscopy coupled with fluorescence nuclear track detectors (FNTDs).

We first constructed a portable confocal microscope that could be transported to and placed in any beam line. We then cultured HT1080-eGFP-53BP1 cells on coverslips made of FNTDs, which in turn where imaged before, during and right after C-ion, proton or photon irradiation using an in-house built confocal microscope placed in the beam path. The HT1080-eGFP-53BP1 cell construct allowed us to monitor the spatiotemporal behavior of 53BP1, a double strand break repair protein. The FNTD allowed us to link single particle track traversals to their damage sites and separate DNA damage induced by primary particles from fragments in the HT1080-eGFP-53BP1 cell nucleus.

We were able to spatially link physical parameters of radiation tracks to DSB sites in live cells to investigate DSB repair induced by a clinical C-ion beam in real time, which was previously not possible. We demonstrated that the lesions produced by the high-LET primary particles associate most strongly with cell death in a multi-LET radiation field, and that this association is not seen when analyzing radiation induced DSB lesions in aggregate without primary/fragment classification.

We report a new method that uses confocal microscopy in combination with FNTDs to provide submicrometer spatial-resolution measurements of radiation tracks in live cells. Our method facilitates expansion of the radiation-induced DNA damage research because it can be used in any particle beam line including particle therapy beam lines.

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