Comparing DNA Damage Responses to Low- and High-LET Radiation: Is Laser Micro-Irradiation a Valid High-LET Model?

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Ionizing radiation induces complex DNA damage whose nature and repair depend strongly on linear energy transfer (LET). Low-LET radiation (e.g., X-rays, γ-rays) predominantly generates isolated lesions, whereas high-LET ions produce densely clustered damage that challenges repair pathways and drives distinct cellular outcomes. Laser micro-irradiation is widely used to study DNA damage responses (DDR) with high spatial and temporal control, and is often interpreted as a proxy for high-LET exposure. However, how faithfully it reproduces the physical and biological characteristics of high-LET tracks remains unclear.

In this study, we systematically compare DDR induced by low-LET photons, accelerated high-LET ions, and laser micro-irradiation in mammalian cells. We analyze the initial induction of DNA double stranded breaks (DSBs) and spatiotemporal dynamics of their repair using quantitative imaging of γH2AX and additional DSB markers. We also assess chromatin remodelling at the micro- and nano-scale, and cell fate outcomes to capture broader differences.

Our data reveal both similarities and critical differences between laser-induced damage and bona fide high-LET tracks in terms of lesion density and track structure; differences in the engagement of DSB repair pathways and the impact on repair fidelity remain to be investigated. These findings open a discussion on the conditions under which laser micro-irradiation can be considered a valid qualitative or quantitative surrogate for high-LET radiation in the context of radiotherapy- and space-relevant ion exposures and, conversely, in which aspects it represents a distinct phenomenon with unique biological consequences. Finally, we outline future possibilities for exploiting the capabilities of ELI Beamlines to advance radiobiological research.

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