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Spatiotemporal dynamics of repair proteins at DNA damage induced by particles of different energy and LET

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Energetic charged particles (HZE) are encountered in spaceflight as part of the galactic cosmic rays, where they pose a health risk to astronauts. However their destructive potential can be used in heavy ion tumour therapy. The deposition of energy of these HZE particles occurs mostly along the trajectory of the particle itself, but depending on its energy, there is some probability for energy deposition relatively far from the nominal trajectory, due to long-ranged delta rays. These delta rays are considered to induce non correlated DNA damage similar to low-linear energy transfer (LET) radiation (like X-rays), whereas the dense ionizing track of HZE particles is assumed to produce more complex and clustered DNA damage, which is slowly repaired or is even irreparable. To study the spatiotemporal protein dynamics during charged particle irradiation, a remote controlled microscope was established at the accelerator facility of GSI. The system enables the acquisition of high-resolution fluorescence images of living cells during ion irradiation. The microscope allows studying early radiation effects without the time lag of minutes presently conditional on limitations of access to the irradiation devices. GFP-tagged repair proteins like NBS1 were used for the spatio-temporal characterization of DNA damage in respect to the particle trajectory in cell nuclei. To compare high LET (ions) and sparsely ionizing radiation (X-rays) induced DNA damage, the microscope can alternatively be equipped with a 35 kV x-ray tube operated at high dose rate (40 Gy/min).
Time-lapse series of repair proteins like XRCC1 proved accumulations within seconds along the ion tracks indicating a fast recognition of DNA damage in combination with a quite stable location of damage processing. In the study presented here, we used a spectrum of different particles over a broad range of LETs in addition to x-rays to address the dynamics of the early DNA damage response in regards to the damage density in living cells. The detailed analysis of NBS1-GFP revealed differences in the recruitment kinetics and retention at damage sites in connection to the LET and radial track structure of the particles.

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