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Investigation of regularities of clustered DNA damage repair after dense-ionizing irradiation

High-order clustered DNA lesions is the hallmark of the dense-ionizing radiation. It is defined as the combination of two or more individual lesions (single-strand and double-strand breaks (DSB), DNA base damage, etc.) within one or two DNA helix turns, created by the passage of a single radiation track. Clustered DNA DSBs which contains DSB and other DNA lesion(s) represent specific interest for investigation. This type of DNA damage is the most difficult for repair and can lead to the formation of severe genetic disorders in cell nuclei with higher probability. Currently regularities of clustered DNA DSB repair are not investigated properly. It is important to study the issues about mutual influence of DNA lesions included in cluster on the effectiveness of their recognition and reparation; existence of a hierarchy in repair of closely spaced DNA damage; identification of proteins involved in the repair of clustered DNA lesions, and the mechanisms used by the cell to eliminate them.

For investigation of clustered DNA DSBs formation and repair, human fibroblasts were irradiated with accelerated 15N ions (LET = 181.4 keV/μm, E= 13 MeV/nucleon) at the angle of 10° between the ion beam and the plane of the cell monolayer. The key proteins of DNA DSBs (53BP1) and base damage (OGG1) repair, which form foci at the damage sites, were visualized by immunofluorescence staining and high-resolution microscopy. The quantitative analysis of 53BP1 and OGG1 foci, which included in colocalized 53BP1/OGG1 foci and characterize the structure of clustered DNA lesions, was completed. It was shown that a number of formed OGG1 foci on average in 1.5 times more than 53BP1 foci during the whole post-radiation period. A detailed analysis of the 53BP1/OGG1 foci clusters showed the most complicated structure after 24h post-irradiation, while the total number of clusters decreased. The obtained results apparently indicate a difficulty in repairing of clustered DNA damage.

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