LET-dependence of lesion clustering in irradiated DNA

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Abstract

It is well accepted that the most relevant radiation effects, in biological matter, are those occurring in the DNA molecule. Clustered lesions, within a short segment of DNA are the main progenitors of radiation-induced cancer and cell death. Conventional microdosimetric techniques rely on the averaging of radiation interactions within micrometric volumes, and cannot account for the stochastic nanometer-scale clustering of lesions within irradiated DNA. We have proposed and implemented a novel dosimetric technique, ion-counting nanodosimetry, which precisely measures clustering of ions formed within a gas model of the DNA.

We present here the first-ever correlated results of biological and physical measurements of the clustering of radiation damage at the nanometer level. We compare physical data of ion clusters within a gas model of DNA (described on the right) to biological data, measured by irradiating thin films of plasmid DNA (in-vitro) and quantifying the strand-break and base-damage clustering (described on the left).

The results of these extensive studies, carried out with protons, Helium nuclei and gamma rays over a broad LET range, clearly indicate a strong correlation between ion-clusters and clustered DNA damage. Furthermore, it is demonstrated that protons and He nuclei, both having the same LET value (26 keV/μm in water), yield significantly different effects. The physical measurements reflect an increase in the frequency of large ion clusters induced by protons compared to He nuclei, it is clearly attributed by model simulations to the different range of 8-electrons, leading to a more compact proton-induced track structure. The biological measurements reflect twice as frequent proton-induced clustered lesions compared to that in plasmid DNA irradiated by He nuclei.

These results clearly establish the relevance of nanodosimetry as a tool for evaluating radiation effects in DNA targets, which cannot be described by macroscopic parameters. The availability of combined physics and biology results permit, for the first time, establishing a model for predicting the molecular effects of radiation on DNA.

Figure 1( TOP): The yield of SSIS induced in DNA, irradiated by protons of varying LET, gammas (γ) and Helium nuclei (He).

Both the yield of SSIS and the yield of isolated base lesions (not shown) decreases with increasing LET due to the recombination of radicals.

There is a clear difference for the SSIS yield between the protons and the Helium nuclei of same LET. This is due to higher frequency of clusters containing one SSIS and one or more base lesions. Such clusters are identified by the casy as SSIS although they are, in reality, clustered.

At 2 mM glyceral, single strand breaks are mainly due to radicals formed far away from the DNA and therefore are more affected by radical recombination, resulting in a stronger decrease with increasing LET.

Figure 2 (BOTTOM): The yield of DSBS and clustered lesions induced in DNA irradiated by protons of varying LET, gammas (γ) and Helium nuclei (He).

Yields decrease between LET 0.4 to ~2.7 keV/μm for proton irradiations.

After 2.7 keV/μm these yields increase slowly. The decrease at low LET is probably due to a change in the radical recombination, which does not exist to the same extent in the physical system.

The rise at high LET and the difference between Helium nuclei and protons is due to a change in the nanometric clustering and is in good correspondence with the nanodosimetric prediction. References:


