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Quantitative analysis of clustered DNA damages induced by silicon beams of difference kinetic energy; abstract

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Quantitative Analysis of Clustered DNA Damages Induced by Silicon Beams of Different Kinetic Energy

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Humans may be exposed to highly energetic charged particle radiation as a result of medical treatments, occupational activities or accidental events. In recent years, our increasing presence and burgeoning interest in space exploration beyond low Earth orbit has led to a large increase in the research of the biological effects of charged particle radiation typical of that encountered in the space radiation environment. The study of the effects of these types of radiation qualities in terms of DNA damage induction and repair is fundamental to understand mechanisms both underlying their greater biological effectiveness as well as the short and long term risks of health effects such as carcinogenesis, degenerative diseases and premature aging. Charged particle radiation induces a variety of DNA alterations, notably bistranded clustered damages, defined as two or more closely-opposed strand breaks, oxidized bases or abasic sites within a few helical turns. The induction of such highly complex DNA damage enhances the probability of incorrect or incomplete repair and thus constitutes greater potential for genomic instability, cell death and transformation.

Our previous results using megabase-scale genomic analyses indicates higher efficiency per particle to induce clustered DNA damages as a function of increasing linear energy transfer (LET). Using charged particle beams of different atomic number but similar kinetic energies, we have shown that yields and spectra of complex DNA damages vary both with LET and the DNA milieu (radioquenching versus non-radioquenching conditions) [Keszenman D.J. *et al* (2010) *Radiat Res*, 174, 238–250]. Also, the yields of DNA double strand breaks (DSBs), Nfo-sensitive abasic clusters or Fpg-sensitive oxypurine clusters following 50–1000 MeV proton radiation directly correlate with the kinetic energies of the proton beams in non-radioquenching solutions. However, in radioquenching solution the yields of oxypurine clusters induced directly correlate with the proton beam kinetic energy while the yields of DSBs or abasic clusters show an inverse correlation. For ions of higher atomic number (HZE particles), we hypothesize that the dependence between induction level of different types of clustered DNA damages and kinetic energy of the beams would be similar to that observed for protons in both non-radioquenching and radioquenching conditions.

To test this hypothesis, we used silicon beams of different energies delivered at the NASA Space Radiation Laboratory (NSRL) at Brookhaven National Laboratory. The kinetic energy values of the Si beams ranged from 300 to 850 MeV/n (with corresponding LETs from 45.2 to 69.8 keV/μm). Genomic DNA samples were irradiated at room temperature in 10 mM phosphate buffer (non-radioquenching) or 10 mM TRIS (radioquenching) solutions. Bistranded clustered DNA damage frequencies (DSBs, abasic sites and oxypurine clusters) were quantified using gel electrophoresis, electronic imaging and number average length analysis. As hypothesized, our results demonstrate a similar direct correlation between the yields of clustered DNA damages and the kinetic energies of the Si ions in non-radioquenching conditions. Interestingly, contrary to protons, in Si ion-irradiated DNA in TRIS radioquenching solution, the yields of DSBs and abasic clusters increased as a function of the kinetic energy, while the yields of oxypurine clusters decreased. These results suggest the involvement of different mechanisms at the physico-chemical level in the formation of different types of clustered DNA damages as a function of a particular ion species' track structure.

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