Bistranded Dna Damage Clusters Induced By Low Let Radiation And Heavy Charged Particles: Formation And Repair[§]

B. M. SUTHERLAND, P. BENNETT, A. GEORGAKILAS and M. HADA
Biology Department, Building 463, 50 Bell Ave., Brookhaven National Laboratory
Upton NY 11973-5000 USA (E-mail bms@bnl.gov)

INTRODUCTION

Clustered DNA damages—two or more oxidized bases, abasic sites or strand breaks on opposing strands within about two helical turns—are formed in DNA in solution and in mammalian cells by radiation exposure [1]. The biological impact of such clusters depends on the number and identities of the constituents of the cluster, the spacing of the constituent lesions, and their polarity with respect to each other. For example, some oxidized bases block polymerases and are thus potentially lethal lesions, whereas other lesions direct the incorporation of incorrect bases, making them potentially mutagenic.

METHODS

We have developed sensitive, quantitative methods for measuring clustered damages using gel electrophoresis, electronic imaging and number average length analysis [2]. These approaches allow the quantification of damages at levels as low as a few per gigabase pair, and their accuracy and use on clustered damages has been validated [3]. We have also developed a novel method for distinguishing among configurations of abasic clusters that allows us to evaluate possible differences in complexity among abasic clusters [4]. We are using three approaches to evaluating the induction and repair of complex damages by high LET radiation.

RESULTS

We have measured the cluster levels induced by Fe (1 and 5 GeV/amu) and Si (600 MeV/amu), as well as 50 kVp X-rays and ^{137}Cs γ-rays in genomic DNA in solution. We have also measured the cluster levels and relative yields induced by Fe particles (1 GeV/amu) vs. those induced by photons in human cells. Using DNA from these two cell types, we are evaluating the relative levels of abasic clusters recognized by Nfo protein (lower lesion density) vs. those recognized by putrescine (higher lesion density). These data should indicate whether the type of radiation as well as the DNA environment affect the absolute yields and relative levels of specific cluster types in model systems and in human cells. We are also using these approaches to evaluate repair in human cells of specific clustered lesions induced by high LET radiation, and comparing the rates and ease of repair of high LET-induced clusters with our current data for repair of low LET-induced clustered damages.

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References

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