A GENOMIC STRESS RESPONSE AS A NOVEL MECHANISM LEADING TO CHROMOSOMAL INSTABILITY IN HEAVY PARTICLE-IRRADIATED CELL POPULATIONS

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BACKGROUND

High charge and energy (HZE) particles are a component of galactic cosmic rays. They cause complex damage to DNA and other cellular components, leading to both direct and indirect biological effects. Here, we investigate the hypothesis that one of these indirect effects is to compromise the accuracy of the DNA repair machinery, reducing the ability to cope with subsequent genotoxic insults.

METHODS

We used a new human reporter cell line with single copy integrated fluorescent reporter cassettes that allow measurement of the frequency of mutagenic repair. Introduction of the rare cutting I-SceI nuclease stimulates both translocations (joining of two I-SceI sites on different chromosomes), and deletions (joining of two I-SceI sites after deletion of an intervening fragment) (1). These can be measured simultaneously in the same cell population using different color reporter genes. To test the effect of HZE exposure on the frequency of translocations and deletions in this assay, cells were exposed to 600 MeV/u ^{56}Fe ions or 1000 MeV/u ^{48}Ti ions at doses of 0.3 Gy or 1.0 Gy. They were allowed to recover and challenged with I-SceI at 1, 7, 14, 21 and 28 days post-irradiation. To further explore the mechanism underlying the mutagenic DNA repair phenotype, we performed genome wide expression profiling on cells that were harvested 7 days post ^{56}Fe ion exposure.

RESULTS

Results showed that HZE particle irradiation significantly increased the frequency of I-SceI translocations and deletions above baseline levels. There was an increase in translocations by up to three-fold, seen in both ^{56}Fe and ^{48}Ti-treated populations. There was also a more modest, but significant increase in I-SceI mediated deletions seen in a population that received the higher dose (1.0 Gy) of ^{56}Fe particles. The increased frequency of I-SceI induced translocations and deletions persisted for 2-3 weeks with ^{56}Fe (but not with ^{48}Ti). The increased frequency of translocations and deletions was not observed in populations treated with low-LET radiation at doses up 3 Gy. Thus, the phenomenon, which we term the “mutagenic repair phenotype” is dependent on both dose and radiation quality. The mutagenic repair phenotype closely correlated with the persistence of micronuclei and excess DNA repair foci in the dividing cell population, suggesting that persistent genomic stress might be one causative factor. (2). Gene expression profiling showed that Results showed significant alterations in 234 genes. Many of the most highly induced genes encode secreted proteins that have previously been implicated in cellular senescence or pro-inflammatory processes. These findings suggest that a paracrine mechanism (induction of a set of senescence or inflammation-related proteins) contributes to the mutagenic repair phenotype.

CONCLUSIONS

A persistent genomic stress response, leading to an increased reliance on an error-prone pathway as well as widespread changes in gene expression, is a novel mechanism leading to chromosomal instability in heavy particle-irradiated cell populations. The persistent stress response is seen only in heavy particle irradiated cells, and not in low-LET irradiated populations, suggesting that it may underlie both the increased cancer risk and distinctive degenerative changes characteristic of space radiation exposure.

REFERENCES

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