SUPPRESSION OF GENOME INSTABILITY IN RESPONSE TO SPACE RADIATION IS MEDIATED BY FANCONI ANEMIA PATHWAY

J. Zhu, F. Su and A. Asaithamby*

[1]Division of Molecular Radiation Biology, Department of Radiation Oncology, University of Texas Southwestern Medical Center, Dallas, Texas, USA.
E-Mail: Asaithamby.Aroumougame@UTsouthwestern.edu

Convincing evidence indicate that high-linear energy transfer (LET) ionizing radiation (IR) induced complex DNA lesions are more difficult to repair than isolated DNA lesions induced by low-LET IR and, in some instances, irreparable; this has been associated with the increased relative biological effectiveness for cell killing, chromosomal aberrations, mutagenesis, and carcinogenesis in high-LET irradiated cells compared to those treated with low-LET radiation. Though both non-homologous end-joining (NHEJ) and homologous recombination (HR) pathways are partially involved in high-LET IR induced DNA lesions repair, it is not clear whether multiple DNA repair pathways collaborate during clustered DNA lesions repair. In this study, using Fanconi Anemia (FA) pathway, a multi protein complex that govern the decision to channel DNA double-strand breaks (DSBs) into HR in favor of the competing error-prone NHEJ pathway, deficient human cells as a model system, we show that FA pathway play a key role in the cellular responses to iron (Fe) particles irradiation. Using a novel live cell imaging technology, we find that FA pathway factors are recruited to the sites of clustered DSBs only in a specific phase of the cell cycle. Further, in the absence of FA pathway, cells become hypersensitive to Fe particles irradiation and exhibit higher number unrepaired clustered DSBs. Using a DNA combing approach, we identified at single molecule level that defect in FA pathway affects recovery of DNA replication forks following Fe particles irradiation. Furthermore, we provide molecular evidence that the inefficient clustered DNA lesions repair in FA pathway defective cells is due to defective binding of RPA2 and RAD51 at the sites of clustered DNA lesions induced by Fe particles. Importantly, exposure of FA pathway deficient cells to Fe particles results in the induction of increased levels of chromosomal aberrations, and the extent of chromosome aberrations directly correlates with the levels of unrepaired clustered DNA lesions. Significantly, using a soft-agar transformation assay, we find that the elevated levels of chromosomal aberrations results in higher frequencies of cellular transformation. Thus, FA factors coordinate the processing of clustered DNA lesions to maintain genome stability in humans following galactic cosmic rays exposure.

Key words: Clustered DNA lesions, Fanconi Anemia pathway, chromosome aberrations, homologous recombination, soft-agar colony and transformation

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