Mechanism Of HZE Particles Induced Chromosome Instability

Aroumougame Asaithamby and David J Chen

Molecular Radiation Biology Division, Department of Radiation Oncology,
University of Texas Southwestern Medical Center at Dallas, Dallas, Texas 75390

Convincing evidence indicates that High charge and energy (HZE) linear energy transfer (LET) ionizing radiation (IR) induced complex DNA lesions are more difficult to repair in mammalian cells than isolated lesions 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. However, the mechanism by which these unrepaired clustered DNA lesions induce chromosome aberrations is not well understood. In this study, we found that exposure of cells to iron (Fe) particles resulted in the induction of higher levels of chromosomal aberrations compared with those irradiated with lower-LET radiation. Further, the extent of chromosome aberrations directly correlated with the levels of unrepaired clustered DNA lesions both in low- and high-LET irradiated cells. To further investigate the reason for the formation of elevated levels of chromosomal aberrations in Fe ion-irradiated cells, we examined checkpoint arrest mechanisms. We found that the length of G2/M arrest was directly proportional to the reparability of the clustered DNA damage. Although Fe ion-irradiated cells remained in the G2 phase of the cell cycle for a prolonged period relative to γ-ray- or Silicon-irradiated cells, but the G2 accumulation was not a permanent arrest. Further, the presence of chromosomal aberrations in mitotic cells that were released from the G2 checkpoint arrest suggests that the release occurred before the completion of clustered lesion repair. To further confirm that clustered lesion repair was incomplete at the point of checkpoint release, we evaluated the number of clustered lesions remaining during G2 arrest (8 and 12 h) and after G2/M release (24 h). There were about seven clustered DNA lesions per cell at 8h and 12h time points and about six unrepaired lesions at 24 h in ~95% of Fe-irradiated cells. Thus, the G2 checkpoint was not maintained until the completion of lesion repair. There were fewer unrepaired clustered lesions in cells exposed to Silicon ions at 24h than at 12h. Together, these results clearly demonstrate that cells released from the G2 checkpoint do enter mitosis with unrepaired clustered lesions, which presumably results in formation of chromosomal aberrations. Thus, difficulties associated with clustered DNA lesion repair and checkpoint release before the completion of DNA repair contribute to the formation of chromosome aberration