TELOMERE REPAIR AND CHROMOSOME INSTABILITY AFTER HIGH LET PARTICLE RADIATION.

John P. Murnane and Bijan Fouladi, Radiation Oncology Research Laboratory, University of California, San Francisco, 1855 Folsom St., MCB 200, San Francisco, CA 94103, USA

Chromosome instability plays an important role in human cancer by providing the genome plasticity required for tumor cell progression. We have previously demonstrated that the spontaneous loss of the ends of chromosomes, termed telomeres, is a mechanism for initiating chromosome instability in human cells. We have also demonstrated the effectiveness of high LET particles, a component of the space radiation environment, in generating non-rejoined DNA double-strand breaks (DSBs) in the genome of human cells. Based on these preliminary results, we present the hypothesis that high LET particles generate DNA DSBs in the telomeric regions of the genome and that a fraction of these breaks do not rejoin. The loss of the ends of chromosomes due to these un-rejoined DSBs may not be lethal to the cell, but may instead result in the loss of functional telomeres, chromosome fusion, and initiating of breakage/fusion/bridge cycle-induced chromosome instability. Therefore, this study will present a molecular mechanism for the initiation of high LET particle-induced chromosome instability in human cells and hence a better understanding of the factors involved in predicting carcinogenesis in humans during space flight. To test our hypothesis, we will conduct experiments that will 1) determine the rate of induction and capacity to repair high LET particle-induced DNA DSBs near the ends of chromosomes in primary human fibroblasts, 2) determine the influence of telomerase in the "healing" of chromosomes that have broken near their telomeres, 3) determine the rate of telomere loss and the spectrum of events following telomere loss after high LET particle irradiation in a human cell line containing a selectable marker integrated directly adjacent to a telomere, and 4) determine the consequences of telomere loss and its role in chromosome instability after high LET particle irradiation.