DNA REPAIR DOMAIN MODELING CAN PREDICT CELL DEATH AND MUTATION FREQUENCY FOR WIDE RANGE SPECTRUM OF RADIATION

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Exploration missions to Mars and other destinations raise many questions about the health of astronauts. The continuous exposure of astronauts to galactic cosmic rays is one of the main concerns for long-term missions. Cosmic ionizing radiations are composed of different ions of various charges and energies notably, highly charged energy (HZE) particles. The HZE particles have been shown to be more carcinogenic than low-LET radiation, suggesting the severity of chromosomal aberrations induced by HZE particles is one possible explanation. However, most mathematical models predicting cell death and mutation frequency are based on directly fitting various HZE dose response and are in essence empirical approaches. In this work, we assume a simple biological mechanism to model DNA repair and use it to simultaneously explain the low- and high-LET response using the exact same fitting parameters. Our work shows that the geometrical position of DNA repair along tracks of heavy ions are sufficient to explain why high-LET particles can induce more death and mutations. Our model is based on assuming DNA double strand breaks (DSBs) are repaired within repair domain, and that any DSBs located within the same repair domain cluster into one repair unit, facilitating chromosomal rearrangements and increasing the probability of cell death. We introduced this model in 2014 using simplified microdosimetry profiles to predict cell death. In this work, we collaborated with NASA Johnson Space Center to generate more accurate microdosimetry profiles derived by Monte Carlo techniques, taking into account track structure of HZE particles and simulating DSBs in realistic cell geometry. We simulated 224 data points (D, A, Z, E) with the BDSTRACKS model, leading to a large coverage of LET from ~10 to 2,400 keV/µm. This model was used to generate theoretical RBE for various particles and energies for both cell death and mutation frequencies. The RBE LET dependence is in agreement with experimental data known in human and murine cells. It suggests that cell shape and its orientation with respect to the HZE particle beam can modify the biological response to radiation. Such discovery will be tested experimentally and, if proven accurate, will be another strong supporting evidence for DNA repair domains and their critical role in interpreting cosmic radiation sensitivity.