FUNCTIONAL ROLE OF BCL2 IN REGULATING THE REPAIR OF THE HZE PARTICLE-INDUCED DNA DAMAGE

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Space radiation is comprised of high energy protons and high charge (Z) and energy (E) (HZE) nuclei, whose ionization patterns in molecules, cells and tissues, and the resulting initial biological insults, are distinct from typical terrestrial radiation. The relationships between the early biological effects of HZE nuclei and the probability of cancer in humans are poorly understood. Bcl2 not only functions as a potent antiapoptotic molecule but also as an oncogenic protein that can enhance susceptibility to carcinogenesis. We have recently discovered that Bcl2 is associated with increased genetic instability but the mechanism(s) involved remains elusive. The high-LET radiation from HZE particles has been reported to inhibit the Ku-dependent NHEJ pathway but does not affect the HR pathway, suggesting that HR pathway may play a major role in repairing DSBs induced by high-LET radiation. Because the repair of DNA double-strand breaks (DSBs) by HR requires processing of broken ends, the DSBs must first be resected to generate a 3′-single-stranded DNA (ssDNA) overhang, which becomes an essential substrate to initiate the down-stream HR DNA repair pathway. It has been demonstrated that the Mre11 complex (Mre11/Rad50/NBS1) resects DSB ends in preparing for DSB repair via HR pathway. Here we found that expression of Bcl2 inhibits the repair of the HZE particle (*i.e.* ^{56}Fe)-induced DSBs by inhibiting Mre11 complex activity. Exposure of cells to ^{56}Fe promotes Bcl2 to interact with Mre11 via the BH1 and BH4 domains. Purified Bcl2 protein directly suppresses Mre11 complex-mediated DNA resection in vitro. Intriguingly, expression of Bcl2 reduces the ability of Mre11 to bind DNA following exposure of cells to the HZE particle. Our findings suggest that, after exposure of the HZE particle, Bcl2 may inhibit the Mre11complex -mediated DNA resection leading to suppression of the HR-mediated DSB repair in live cells, which may eventually contribute to genetic instability and tumor development.