

ALTERED DNA DOUBLE STRAND BREAK RESPONSE IN THE WERNER HUMAN PREMATURE AGING SYNDROME

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DNA damage in the form of double strand breaks (DSBs) compromises the integrity of cells and accumulates during the aging process. Individuals with premature aging Werner syndrome (WS) show increased genomic instability, cancer predisposition, and defective DNA DSB repair and response. The finding of a 91% similarity in the expression patterns of the affected genes between WS and normal aging greatly supports the notion that WS is an ideal model to study human aging. Increasing evidence suggests that the WS protein (WRN) protects against DNA DSBs and telomere dysfunction. Interestingly, DNA DSB repair machinery tends to avoid recognizing telomeric ends as DNA DSBs. Therefore, understanding the detailed mechanisms of how WRN functions in the process of DNA DSB repair and response could help uncover the mystery of how we age. The WRN protein belongs to the RecQ DNA helicase family. In addition to helicase activity, WRN also exhibits an exonuclease activity. In normal cells, WRN mainly resides in the nucleoli. WRN contains the unique RQC domain that seems to be the focal point for its protein-protein and protein-DNA interactions. Homologous recombination is the error-free pathway to repair DNA DSBs, and it has become clear that WRN participates in this pathway at the resolution stage. Resolving recombinational intermediates requires helicase activity, and we found that WRN helicase activity is stimulated in the presence of Nbs1 and BRCA1, two proteins that play important roles in homologous recombination. Another linkage of WRN and homologous recombination is based on the Abl tyrosine kinase-dependent WRN re-localization in cells treated with bleomycin. High Abl tyrosine kinase is a hallmark of chronic myeloid leukaemia, and this kinase activity stimulates homologous recombination repair. Thus, delineation of WRN's function in the repair and recognition aspects of DNA DSBs appears to be critical to understanding the pathogenesis of WS and normal aging, and perhaps some forms of cancer.