Genetic disease in human

117 Role of WRN exonuclease in repair of DNA double strand breaks

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Werner syndrome (WS) is an autosomal recessive disease characterized by multiple progeroid features. The gene responsible for WS, *WRN*, is a member of human *RecQ* helicase family. The WRN helicase is unique within the RecQ family because it also shows an exonuclease activity. In the present study, we examined radiosensitivity in immortalized human 293 cell lines defected in a WRN exonuclease activity by the introduction of a WRN gene deleted in a part of WRN exonuclease domain. The radiosensitivity in the WRN exonuclease negative (WRNexo (–)) 293 cell lines was 2.5-fold higher than that in the control 293 cell lines. Also, the induced frequency of micronuclei by X-rays with 4 Gy in the WRNexo (–) 293 cell lines was 1.5-fold higher than that in the control 293 cell lines. These results suggest that the defect in WRN exonuclease enhances the radiosensitivity.

118 Relationship between dysfunction of WRN protein and radiosensitivity

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Werner syndrome (WS) is an autosomal recessive disorder with multiple features of premature aging. The gene responsible for WS, *WRN*, encodes a DNA helicase and exonuclease. In the present study, we examined radiosensitivity in an immortalized WS cell line (WS3RGB) and an immortalized human 293 cell line (293del231) defected in a WRN exonuclease activity. WS3RGB cells were more sensitive to X-rays than a control cell line in an assay for cell killing and a radiosensitization ratio by wortmannin was lower than that of the control cell line. Similarly, 293del231 cells were more sensitive to X-rays than a control cell line in an assay for G_2 chromosome aberrations and a radiosensitization ratio by wortmannin was lower than that the control cell line. These results suggest that dysfunction of WRN protein contributes to the enhanced radiosensitivity and that WRN protein may play a role in non-homologous end-joining.

119 Mismatch Reair deficiency and Radiosensitivity in Colon Cancer Call Lines

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Microsatellite instability resulted from mismatch repair (MMR) deficiency is found in about 15% of human colon cancer cases. This type of colon cancer prefers local recurrence to distant metastasis and is resistant to some kinds of anticancer drug. Therefore we are interested in an efficiency of radiotherapy for MMR deficient colon cancers. In this study, we examined radiosensitivity of six colon cancer cell lines with or without MMR deficiency using colony formation assay and micronuclei assay. The results showed all MMR deficient cell lines were more radiosensitive than MMR preserved ones in colony-formation assay. Tow of them exhibited microsatellite instability in *Rad50* gene. The production of micronuclei was associated with the mutation status of *APC* gene but not MMR deficiency. In conclusion, MMR deficiency may result in an increase of radiation sensitivity.