115 Werner Syndrome-Associated Abnormal Phenotypes in Relation to WRN Mutation

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Werner syndrome (WS) is an autosomal recessive disease whose phenotype mimics premature aging. WS gene (*WRN*) was isolated and recently shown to encode DNA helicase and exonuclease activities. We have recently reported that a SV40-transformed WS cell line (WS780) is hypersensitive to 4-nitroquinoline-1-oxide (4NQO) and that this abnormal phenotype is not corrected by introduction of the *WRN* gene, suggesting that *WRN* mutation may not directly result in 4NQO hypersensitivity. Here, we demonstrate that WS780 cells show normal sensitivity to cell killing by exposing to X-rays, UV and camptothecin. So far, 4NQO is the only agent to which WS780 cells are hypersensitive. To know the reason for the 4NQO hypersensitivity of WS780 cells, we constructed several whole cell hybrids between a WS780 cell and a control cell and examined the 4NQO sensitivity of them. We report that a whole cell hybrid shows an intermediate sensitivity, indicating that the 4NQO hypersensitivity of WS780 cells is not a dominant trait and can be partially rescued by some cellular factors.

116 Functionally important domain analysis of the Nijmegen breakage syndrome gene, *NBS1*

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Nijmegen breakage syndrome (NBS) is a rare autosomal recessive disorder characterized by microcephaly, combined immunodeficiency, and a high incidence of lymphoid cancer. Cells from NBS patients display chromosome instability, hypersensitivity to ionizing radiation, and abnormal cell cycle regulation after irradiation. We have cloned *NBS1*, the NBS gene, by complementation assisted positional cloning. The NBS1 protein consists of 754 amino acids and it shows a weak homology to the yeast Xrs2 protein in the N-terminus region. It has been reported that the NBS1 protein interacts with MRE11 and that a RAD50/MRE11/ NBS1 complex or foci can be seen in the nucleus after irradiation. It has also been suggest-ed that this complex may be active in processing the ends of DNA double-strand breaks to permit non-homologous end-joining and also for homologous recombination. In this study, we have assayed for functionally important domains of the NBS1 protein by transfecting mutated NBS1 cDNA into NBS patient cells. We found that several deletion mutants were able to restore radiation resistance in NBS cells. The relationship between *NBS1* deletion mutants, restoration of radiation resistance and NBS1 foci formation will be discussed.

117 Mutation screening of the *NBS1* gene in sporadic malignant lymphoma

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Recently, the *NBS1* gene for Nijmegen breakage syndrome (NBS) has been positionally cloned and mapped at 8q21.3. NBS (also called as an ataxia-telanigiectasia variant) is an autosomal recessive disorder characterized by microcephaly, growth retardation, severe combined immunodeficiency and a high incidence of lymphoid cancers. Cells from NBS patients display chromosome instability, hypersensitivity to ionizing radiation and abnormal cell-cycle regulation after irradiation. Out of 55 NBS patients registered, 15 patients have developed a lymphoma. On the other hands, sporadic lymphomas are highly genetically unstable and show radio-hypersensitivity. To address whether *NBS1* gene is involved in carcinogenesis of sporadic lymphomas, we screened the *NBS1* mutation in 48 DNA Japanese samples from patients with B-cell lymphoma using PCR-SSCP and direct sequencing. We found several kinds of single-base substitutions, which are likely to be neutral polymorphisms. No mutations were detected in the coding regions of *NBS1* gene. Our results suggested that *NBS1* gene might not be involved in carcinogenesis of sporadic B cell lymphomas.