68 Association of cells from Fanconi anemia patients with radiation sensitivity

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Fanconi anemia (FA) is an autosomal recessive disorder characterized by skin pigmentation, high incidence of cancer, and a diverse variety of congenital malformations. The cells from FA patients display chromosome instability, and hypersensitivity to DNA cross-linking agents such as mitomycin C. At least 7 complementation groups (FA-A to FA-G) have been described. Among these, *FANCA*, *FANCC*, *FANCD2*, *FANCE*, *FANCF* and *FANCG* genes have been identified. It has been reported that FANCG is identical with XRCC9, suggesting FA genes might be involved in repair from DNA damage. These reports suggest that study on the FANC genes might help understanding the repair mechanisms of DNA damage.

In order to examine the sensitivities of FA cells to MMC and IR, we have immortalized the skin fibroblasts from FA patients. We tested four cell lines belonging to different complementation groups. Although these sensitivities were varied with complementation groups. Our results indicated possible radiation sensitivity but is needed to confirm by further experiments.

69 Establishement of mouse *Nbs1*-deficient cell lines by gene targeting

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Nijmegen breakage syndrome is an autosomal recessive disorder characterized by microcephaly, growth retardation, 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. The gene, *Nbs1*, encodes a protein of 754-amino acids. The Nbs1 protein interact with hMre11 and forms a hRad50/hMre11/Nbs1 complex. To generate a potential model for Nijmegen breakage syndrome, we have created a mouse line carrying a mutation in one *Nbs1* allele. Mice heterozygous for the mutant allele were normal and fertile, whereas mice homozygous for the mutant allele was not created, and these mice died in utero between 8.5 and 9.5 dpc. The results cleary demonstrates that *Nbs1* is critical for normal development. On the other hands, MEFs from 8.5 dpc *Nbs1*-/- embryo were viable, and showed radio-sensitivity and chromosomal instability, similar to those of cells from Nijmegen breakage syndrome patients.

70 Complementation studies of immortalized cell lines from infants with total PCS

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Chromosomal instability syndrome is a human genetic disorder, characterized by chromosomal instability and high risk of malignancy. It includes Fanconi anemia, Bloom syndrome, ataxia-telangiectasia, and Nijmegen breakage syndrome. Kajii et al reported a chromosomal instability syndrome characterized by total premature chromatid separation (total PCS), and mosaic variegated aneuploidy. The infants both showed severe pre- and postnatal growth retardation, profound developmental retardation, severe microcephaly, hypodysplasia of the brain, Dandy-Walker anomaly, and bilateral cataract. Out of four patients reported, three developed Wilms tumor. Last year, we reported that the infants'fibroblast cells were defective in mitotic-spindle checkpoint. Here we have carried out the functional complementation assays using immortalized cell lines from the two infants. There was no restoration on the basis of mitotic index and total PCS configuration in these fused clones, suggesting genetic homogeneity in these two infants.