W12–3 Involvement of Telonomic Instability in the Formation of Delayed Chromosome Aberrations Induced by Radiation

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Radiation induces delayed chromosome aberrations in the descendants of surviving cells. To know the mechanism of induction of delayed chromosome aberrations, mouse A9 cells containing a human chromosome 11 were irradiated with 6 Gy or 15 Gy of X-rays, and then a human chromosome 11 was transferred into unirradiated mouse m5S cells using a microcell-mediated chromosome transfer. Chromosome aberrations were analyzed by whole chromosome painting specific for human chromosome 11. In the m5S cells transferred with 15 Gy-irradiated chromosome 11, all chromosomes 11 were fragmented and 45% of the chromosomes was rearranged after chromosome transfer. Similarly, in the cells transferred with 6 Gy-irradiated chromosome 11, 25% and 46% of them were rearranged to form rings and telomeric-fusion chromosomes, respectively. The results suggest that the irradiated chromosome *per se* possesses unstable nature and that telonomic instability induced by radiation is possibly involved in the induction of delayed chromosome aberrations.

W12–4 Radiation Sensitivity and Expression of Nucleotide Excision Repair Genes in Peripheral Blood Mononuclear Cells of Atomic Bomb Survivors with Myelodysplastic Syndrome

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A preliminary epidemiological study demonstrated that myelodysplastic syndrome (MDS) has an excess relative risk per sievert of 13 in atomic bomb survivors (Oda et al, 1998). We investigated the micronucleus (MN) frequency in peripheral T lymphocytes of twenty-three atomic bomb survivors with MDS and five normal individuals. The spontaneous- and X-ray-induced-MN frequencies were significantly higher in MDS patients than in normal individuals. Interestingly, radiation sensitivity increased along with the severity of MDS clinical subtypes. To explain the cause of unusual radiation sensitivity, we measured the expression levels of four nucleotide excision repair (NER) genes (ERCC1, ERCC3, ERCC5 and XPC) using a RT-PCR method. The ERCC5 gene was expressed at reduced levels in only one of 10 patients with mild symptom. Reduction of NER genes was expressed in four of 11 patients with severe symptom. Our data suggest that the control of chromosomal stability is impaired in pluripotent hematopoietic stem cells of MDS patients, and that chromosomal instability and DNA repair defects may be involved in the pathophysiology of disease progression.

W12–5 Analysis of Microsatellite Instability in Thorotrast Induced Intrahepaticholangiocarcinoma

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A natural alpfa-particle emitter, Thorotrast (Th) was used for the radiological contrast during 2nd World War and induced intrahepatic cholangiocarcinoma (ICC) several decades after injection. We analyzed microsatellite instability (MSI) in Th induced ICC (Th-ICC). Also methylation status of the promoter region of the hMLH1 and hMSH3 genes, whose inactivation is responsible for MSI, was studied. MSI was positive in 68% of Th-ICC whereas 26% in non-Th-ICC. Either MSI of mononucleotide repeats, BAT25, 26, or targets of MSI such as the hMSH3/6, Bax, TGFbIIR, IGFIIR genes was not observed. Compared with non-tumor part, methylation status of the hMLH1 gene promoter in tumor part was remarkably increased in Th-ICC. The period of carcinoma induction tended to be longer in MSI-H tumors than in MSI-L tumors. Loss of heterozygosity (LOH) frequency in non-Th-ICC was the highest at the p73 locus and the frequency was 73%. LOH frequency of the same locus in Th-ICC was 36%. In conclusion, genomic instability represented by MSI not by chromosomal aberration due to methylation of the hMLH1 gene promoter could be involved in carcinogenesis of Th-ICC. This indirect effect of radiation could be caused during remodeling of the hepatic tissue after defects by alpha-particles emitted from Th.