present study are murine thymic lymphoma and rat mammary cancer. The mode of modification of radiation effect by chemicals in terms of interaction between X-rays and alkylating agents will be discussed from the viewpoint of molecular mechanisms of cancer development.

42 Tumor Induction Sensitivity of Transgenic Mice with a Bacterial Plasmid Error-Prone Repair Gene mucAB

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A bacterial plasmid gene mucAB has an error-prone activity and is widely used for sensitive detection of mutagens as Ames test. The mucAB gene (1.7 Kbp) was cloned into a vector carrying the mammalian metallothionein promoter (pTE40), which enhanced transformation of cultured mouse cells in the previous study. In this study, mucAB was introduced into an embryo of C57Bl mouse to obtain mucAB transgenic mice. Among 93 mice from 439 injections, we found only one mice in which genome mucAB was integrated. Heterogenic mucAB mice from this founder were examined for tumor induction efficiency by subcutaneous injection of 0.02 mg methylchoranthrene. The mice developed fibrosarcomas with an elevated efficiency (24%) as compared with control mice without mucAB (8%) until the present moment.

43 Age dependency of X ray-induced mammary carcinogenesis in *Apc*$^{Min/+}$ mice

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The risk of radiation carcinogenesis is influenced by various factors, including genetic and age factors. The human *Apc* gene was originally identified as a tumor suppressor gene in both sporadic and hereditary (familial adenomatous polyposis; FAP) colorectal cancers. Recently, missense mutations and promoter hypermethylations of *Apc* gene have been reported in human breast cancers, suggesting an involvement of *Apc* mutation in their development. Moreover, FAP model mice with germline *Apc* mutations have an increased susceptibility to mammary carcinogenesis. To investigate the effect of age at exposure on X ray-induced mammary carcinogenesis in the FAP model *Apc*$^{Min/+}$ mice, we examined the mammary tumor development after X irradiation (2 Gy) at various weeks of age. We found that, whereas no tumor was seen in the wild-type littermates, *Apc*$^{Min/+}$ mice developed mammary tumors, with significantly higher incidence in those irradiated at 7 and 10 weeks than those irradiated at 5 weeks. Histologically, all tumors were adenoacanthomas. We discuss the possibility that age dependency of the risk of radiation carcinogenesis is modulated by genetic factors.

44 Radiation effect on internal chromosomal deletion in gamma ray-induced mouse thymic lymphomas

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Mouse thymic lymphomas induced by gamma-irradiation exhibited homozygous deletions of *Rit1/Bcl11b* at a high frequency. Loss of one allele was due to internal chromosomal deletions of mostly exon 2 and exon 3 and the loss of the remaining allele due to allelic loss. To elucidate the mechanism of these internal deletions, we examined break and rejoining points by PCR-mapping and determined sequences in the vicinities. The mapping in lymphomas revealed clustering of recombination sites and subsequent sequencing showed the presence of cryptic sequences recognized by the RAG1/2 recombinase and the P and/or N nucleotides in the rejoining sites. This suggests that these deletions of Rit1 involve an illegitimate V(D)J recombinase activity in radiation-induced mouse thymic lymphomas. Interestingly, such aberrant recombination was detectable in the thymus of wild-type mice, but not of RAG2-deficient mice, and the recombination frequency was not increased by gamma-irradiation. Possible mechanisms for radiation lymphomagenesis will be discussed.

45 Analysis of Loss of Heterozygosity (LOH) in Thorotrast-induced liver angiosarcoma

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Thorotrast is colloidal solution of natural alpha-emitter, thorium dioxide, which was used as a radiological contrast medium during World War II. Decades after injection, it caused hepatic tumors by local exposure to alpha-particles. Histological examination revealed that about 1/3 cases of Thorotrast-induced cancers consist of angiosarcoma (AS). In order to elucidate carcinogenic mechanisms of radiation-induced cancers, we performed genome wide scan of loss of heterozygosity (LOH) in Thorotrast-induced AS. As well as ICC, Thorotrast-induced AS showed more LOH frequency compared with non-Thorotrast cases. LOH frequency at loci common to liver cancer was low in AS. We found a Thorotrast-induced cancer specific locus on chromosome 8q. These indicate that LOH loci specific to the origin of cancer cells and Thorotrast-induced cancers exist, respectively.