

- 55 Age Dependence of Radiation-Induced Tumorigenesis in a Genetically-Predisposed Min Mouse  
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- Min(multiple intestinal neoplasia) mice carry a mutant allele of the murine *Apc* locus and are predisposed to adenoma formation in the intestinal tract. The observed tumor phenotype and the involvement of *Apc* have parallels in human colorectal cancer. Tumorigenesis in Min mice is affected by various factors including genetic background and ionizing radiation. In this report, we analyzed the effect of low-dose X rays in tumorigenesis in Min mice, with special interests in its age dependence and modifying effect of genetic background. B6-Min mice of susceptible genetic background and (B6xMSM)F1-Min mice of resistant genetic background were exposed to 0.25, 0.5, 1.0 or 2.0 Gy X-rays at 2, 10, 24, or 40 day-old, or prenatal stage. Tumor multiplicities were determined at 16–20 weeks of age for B6-Min mice and 34–38 weeks of age for F1-Min mice. The results strongly suggested that exposure to X-rays above 0.5 Gy enhanced tumorigenesis in Min mice in a dose-dependent manner, and that the enhancement depends on age at exposure in either genetic background.
- 56 Characteristic changes in mitochondrial DNA in radiation-associated human thyroid tumors  
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- Paired DNA samples of tumor and normal thyroid tissue from adult patients possibly exposed to radioactive Chernobyl fallout and from control samples were examined for the relative mitochondrial DNA (mtDNA) content, prevalence and level of common deletion (CD) and large scale deletions in mtDNA. Relative mtDNA content was elevated in tumor tissue in most cases, but no significant correlation with level of radioiodine contamination of patients residency and/or with clinicopathological data was found. Common deletion was detected in every DNA specimen from any type of tissue regardless of the presence of oxyphilic cell changes. The CD level was not associated with clinicopathological parameters, radioiodine contamination and relative mtDNA content. Quantity of large scale deletions in mtDNA did not correlate with levels of radiopollutant, content of the CD and clinicopathological characteristics, but highly significantly associated with relative mtDNA content specifically in radiation associated tumors. Correlation of these two parameters of mtDNA may comprise a unique molecular feature allowing to distinguish human thyroid tumors of different etiopathogenic groups.
- 57 Novel tumorigenic *rfp/ret* fusion oncoprotein in radiation induced papillary thyroid carcinoma  
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- ??o unknown structural mutation involving the 5' portion of an *rfp* gene juxtaposed upstream of the fragment encoding tyrosine kinase domain of the *ret* gene was identified in the tumor tissue of papillary thyroid carcinoma developed in an externally irradiated patient several years after exposure. At the genomic level, the formation of a fusion gene occurred as a result of balanced chromosomal translocation between short arm of chromosome 6 and long arm of chromosome 10 with the participation of respective introns of *rfp* and *ret* genes. Presence of the mutation was confirmed by extensive molecular, cytogenetic and functional analysis. The fusion protein retained the propensity to form homodimers as assessed by yeast two-hybrid system. The revealed rearrangement is likely to be oncogenic, as NIH 3T3 cells stably transfected with an expression vector encoding full-length cDNA yielded rapidly growing tumors in immunocompromised mice. The finding provides an additional line of evidence of facilitated susceptibility of the *ret* gene to structural mutations in irradiated human thyroid cells.
- 58 Gene Mutations in Second Malignancies after Radiotherapy  
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- Radiotherapy is known to cause secondary malignancies (= post-radiation malignancies), but little is known about genetic changes. In the present study, mutations of *p53*, *K-ras*, *c-kit*, *β-catenin*, *Fas*, and *bak* genes were analyzed on paraffin-embedded specimens from patients with cancer or sarcoma after radiotherapy (50–55 Gy) for uterine cancer by PCR-SSCP followed by direct sequencing.
- There was high frequency of *p53* mutations (67%), and their pattern was very different from that of primary tumors, and there was a tendency of longer survival without *p53* mutations compared to those with mutations. More than 50% of *c-kit* and *β-catenin* mutations were seen in soft tissue tumors but not in colon cancers. *Fas* and *bak* gene mutations were also seen in post-radiation malignancies, indicating apoptotic pathway may play a role for carcinogenesis in post-radiation malignancies.(supported by the grant from the Minist. Edu. Sci. Culture)