【S-17】

Allelotypes Analyses on the Radiation Induced Lymphomas on the Hybrid F1 Mice

Doo-Pyo Hong, Ph.D.
Department of Pathology, Hanyang University

Malignant lymphoma cells are considered to develop through a multi-step genetic processed and to be efficiently induced by genetic events brought about by irradiation. In an epidemiology study, few events are supposed to be directly involved in the leukemogenesis compared with those which occur in solid tumors. To identify the genes involved in the development of leukemia/lymphoma, we studied radiation-induced lymphomas in mice. Also, to detect tumor-suppressor genes involved in the lymphomagenesis, we analyzed allelotypes in the tumors from F_1 hybrid mice.

First, to examine possible contributions of individual tumor-suppressor genes to tumorigenesis in p53 heterozygous deficiency, we investigated the genome-wide distribution and status of LOH in radiation-induced lymphomas from F_1 mice with different p53 status. In this study, we found frequent LOH (more than 20%) on 4, 9, 11, 12, 16, 19 chromosomes and especially it suggested that tumor-susceptibility gene region exist on the 4, 9 chromosomes. The two hybrids, (SXM)F_1-p53$^{KO/+}$ and (SXM)F_1-p53$^{+/+}$ used in this study, differed considerably in the latent period of lymphoma development. (SXM)F_1-p53$^{+/+}$ mice first developed thymic lymphomas about 4 months after the last irradiation. On the other hand, that of (SXM)F_1-p53$^{KO/+}$ developed 3 months. Thus, p53 heterozygous deficiency shortened the latent period of tumor development. Second, we analyzed the LOH related to the genetic background of different strains respectively. The genome wide patterns of LOH in F_1 mice on the radiation-induced thymic lymphomas differ with the parental combinations, even if the histopathological feature of the tumor and the oncogenic treatment are the same. The most frequent LOH on chromosome 12 occurred in all crossed tested. Frequent of LOH in 4, 19 chromosomes depended on the combinations of strains. Loss of STS/A-derived allele on chromosome 4 may predispose the animals to lymphomas. Therefore, tumor-suppressor gene modifying resistance to radiation lymphomagenesis may reside on chromosome 4. The frequency on chromosome 19 in (CXS)F_1 hybrid mice was

markedly high compound with other strains, one of the parents of the allele was MSMMs. Third, to elucidate the nature of allelic losses, we refined the loss regions on chromosomes 4, 12 and 19 of the tumors from the F_1 mice and then analyzed them cytogenetically. The results represent evidence of a wide range of allelic losses owing to mitotic recombination on chromosomes 4 and 19 in the tumors, possibly reflecting functional losses of putative tumor-suppressor genes. It is suggested that the generation of these large homozygous chromosomal segments probably containing the affected genes is one of the genetic alterations responsible for tumorigenesis.