Symposia

Contact points of cell and molecular research between carcinogenic and carcinostatic radiation effects

S-I-1 Signal transduction pathway to radiation-induced apoptosis
Norio MITSUHASHI1, Tetsuo AKIMOTO2, Hitoshi ISHIKAWA1, Hideyuki SAKURAI1, Katsuya MAEBAYASHI1, Masatoshi HASEGAWA1 and Hideo NIIBE1

Trp53 has been thought to be one of the key genes for cytotoxicity and apoptosis of tumor cells. The wild-type Trp53 protein was shown to be important in a signal transduction pathway mediating the G1 phase cell cycle checkpoint in DNA-damaged cells and in apoptosis of unreplicated cells. Apoptosis may be the primary mode of death of the tumor cells in which mutation of the TP53 gene or depletion of the TP53 allele have been found. Tumor in which many apoptotic cells were observed after irradiation are more sensitive to radiation than those in which less apoptotic cells were observed. Functioning Trp53 protein has been reported to be important in triggering apoptosis induced by radiation and some chemotherapeutic agents. A loss or mutation of Trp53 has been shown to decrease not only radiosensitivity but also chemosensitivity including cisplation which induced apoptosis through a Trp53-dependent pathway. Therefore, chemotherapeutic agents including Paclitaxel which induce apoptosis through a Trp53-independent mechanisms should be combined with radiation for tumor cells with a mutant-type Trp53 to enhance the radiosensitivity. Caffeine is also effective to increase radiosensitivity of tumor cells with a mutant-type Trp53 because apoptosis is induced by irradiation in combination with caffeine in tumor cells with a mutant-type Trp53 through a Trp53-independent pathway. In this paper, the advances in investigation of a signal transduction pathway to radiation-induced apoptosis are reviewed and the place of radiation therapy in malignant tumors with a different Trp53 status is also discussed.

S-I-2 Apoptosis-inhibitory effect of vascular endothelial growth factor (VEGF)
Osamu KATO (Dept. Environ. & Mutat., RIRBM, Hiroshima Univ.)

We have found that vascular endothelial growth factor (VEGF) can inhibit apoptosis induced by exposure to gamma-rays or anti-tumor drugs. To elucidate the molecular mechanism underlying this inhibitory effect of VEGF, we identified MCL1 and ZK7 as genes induced by VEGF in a human leukemia cell line, CMKBE using arbitrary PCR technique. The MCL1 protein has high homology to BCL2 and acts to protect from apoptosis. ZK7 is a Kruppel-type zinc finger gene. We generated clonal U937 myeloid leukemia cell lines transfected with vectors that promoted the constitutive expression of MCL1 or ZK7. MCL1 or ZK7 increased viability of the transfected cells after exposure to ionizing radiation or etoposide anti-tumor drug. Therefore, MCL1 or ZK7 may be involved in the inhibitory effect of VEGF on apoptotic cell death. Moreover, patients with ovarian cancer expressing higher level of the mcl1 mRNA had poor prognosis than those expressing lower level. The expression levels of ZK7 mRNA in human head & neck cancers after radiotherapy and chemotherapy were higher than those before therapy. MCL1, ZK7 and signaling pathway following VEGF receptor may be associated with acquisition of resistance on cancer cells against radiotherapy or chemotherapy.
S-I-3 Possible Role of the Insulin-like Growth Factor I Receptor (IGF-IR) in Carcinogenesis and Cellular Radioreistance
Masahiko MIURA, Molecular Diagnosis and Therapeutics, Dept. Oral Restitution, Graduate School, Tokyo Medical and Dental University

It is well established that insulin-like growth factor I receptor (IGF-IR) plays a pivotal role in cell growth, inhibition of apoptosis, and transformation. The purpose of this study was to discuss the possibility whether overexpression of the IGF-IR, which indeed occurs in some tumors such as breast cancers, leads to carcinogenesis and clonogenic cellular radioreistance. For this, IGF-IR⁺/⁻ (R⁺) and R⁺ cells overexpressing the human IGF-IR derived from R⁻ cells were utilized. R⁺ cells grew in monolayer with a significantly higher growth rate than R⁻ cells. R⁺ cells also possessed colony forming ability in soft agar and tumorigenicity when subcutaneously inoculated into nude mice, while R⁻ cells exhibited none of them. We further showed that R⁺ cells were significantly more radioreistant than R⁻ cells in terms of clonogenicity. Mutational analysis of the IGF-IR revealed that domains required for cell growth in monolayer, antiapoptotic activity, and colony forming activity in soft agar are not the same, implying that signal transduction pathways are dissociated at the receptor level among those closely related biological phenomena. Interestingly, all the mutants exhibiting transforming activity acquired antiapoptotic activity. This strongly suggests that antiapoptotic activity may be prerequisite for carcinogenesis. Collectively, these results provide evidence that IGF-IR-induced antiapoptotic activity may cause carcinogenesis and resultant tumor cells may be refractory to radiotherapy.

S-I-4 Molecular pathological prediction of radiation sensitivity of human cancers

Background: Recently, correlation between oncogene and radiation effect has been intensively investigated with human tumors. Especially, oncogenes associated with cell cycle regulation, apoptosis and cell proliferation are regarded as important biological keys for radiation response. Impact of these genes on clinical radiation oncology is investigated and discussed. Methods: We investigated association of p53, p21, bax, bcl-2, and Mn-SOD with radiation response or prognosis in cervical cancer patients treated with radiation therapy. The expression of these proteins on tumor cells were detected with immunohistochemical methods. Apoptosis was detected using in situ nick end labeling methods. Results: The expression of c-erbB2 oncogene was inversely correlated with local control and long survival. The mitotic index of proliferating population (PMI) which assess cell cycle speed was a strong indicator of local control and long survival. The tumors with Mn-SOD overexpression had high local recurrence probability after radiation therapy. The high p27 and low p53 expression in cancer cells before radiation therapy are regarded as a preferable predictive factor for the prognosis of patients with cervical squamous cell carcinoma treated with radiation therapy alone. The expression of Bax protein in cervical cancer was associated with radiation-induced apoptosis in fractionated radiation therapy. However, p53 and p21 expressions were negatively associated with radiation induced apoptosis. Radiation biologic nature on High LET carbon beam therapy for cervical cancer was investigated according to p53 and p21 expressions, oxygenation, and cell cycle speed of tumor cells. The results indicated that high LET beam carbon irradiation may reduce radiation resistant nature originated from hypoxia of tumor and p53 and p21 overexpressions, but could not overcome radiation resistance for tumors with faster cell cycle speed. Conclusion: Molecular pathological prediction of the proliferative activity and radiation sensitivity of tumors is important for tumor local control and long term survival in patient with human cancers.