Symposia

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

S-I-1  Signal transduction pathway to radiation-induced apoptosis
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Trp53 has been thought to be one of the key genes for cytotoxicity and apoptosis of tumor cells. Th 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 unrepaird cells. Apoposis 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 or some chemotherapy agents. A loss or mutation of Trp53 has been shown to decrease not only radiosensitivity but also chemosensitivity including cisplatin which induced apoptosis through a Trp53-dependent pathway. Therefore, chemotherapeutic agents including Paclitaxel which induce apoptosis through a TP53-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)
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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, CMK8E 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 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 Radiosensitivity
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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 radiosensitivity. For this, IGF-IR+/ (R-) and IGF-IR+
+ (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 radiosensitive 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 ability 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 to be 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,
p27, 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 immuno-histochemical
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
humancancers.