The Japan Radiation Research Society

86 The PI3 kinase/Akt Survival Pathway Is Not Required for IGF-I Receptor-mediated Clonogenic Radioresistance

Dong YU[1], Mikio TEZUKA[1,2], Hitoshi SHIBUYA[2], Masahiko MIURA[1], [1]Mol. Diag. Ther. Grad. Sch. Tokyo Med. Dent. Univ. [2]Diag. Ther. Radiol. Grad. Sch. Tokyo Med. Dent. Univ.

The insulin-like growth factor I receptor (IGF-IR) induces clonogenic radioresistance when expressed in R- cells derived from mouse embryo fibroblasts deficient in IGF-IR. We have examined if the PI3 kinase/Akt survival pathway is required for this biologic event because the pathway is strongly activated through the IGF-IR. For this purpose, cell lines were established from R- cells expressing the IGF-IR with mutations at either Y950 or Y1316, or both. These tyrosine residues are required to activate PI3 kinase. All these cell lines demonstrated exactly the same radiosensitivity as cells expressing the wild type IGF-IR. Akt was activated in wild type IGF-IR-expressing cells, but not in R- cells following irradiation. A PI3 kinase inhibitor, wortmannin, inhibited this activation at concentrations specifically inhibiting PI3 kinase. Radiosensitivity, however, was not influenced in both cell lines under these conditions. Collectively, these results suggest that the PI3 kinase/Akt survival pathway is not required for IGF-I receptor-mediated clonogenic radioresistance.

87 Lack of Relationship between Expression of the Insulin-like Growth Factor I Receptor and Radiosensitivity in Ataxia Telangiectasia (A-T) Cells

Hiroshi WATANABE[1], Dong YU[3], Takehito SASAKI[1], Hitoshi SHIBUYA[3], Yoshio HOSOI[4], Masahiko MIURA[2], [1]Oral Maxillofac. Radiol. Grad. Sch. Tokyo Med. and Dent. Univ. [2]Mol. Diag. Ther. Grad. Sch. Tokyo Med. and Dent. Univ. [3]Radiol. Oncol. Grad. Sch. Tokyo Med. and Dent. Univ. [4]Dept. Radiat. Oncol. Grad. Sch. Univ. Tokyo

Ataxia telangiectasia (A-T) is an autosomal recessive disorder with a pleiotropic phenotype including high radiosensitivity. The promoter activity of the insulin-like growth factor I receptor (IGF-IR) gene has been reported to be dependent on ataxia telangiectasia mutated (ATM) and thereby IGF-IR expression is decreased in A-T cells. Using RT-PCR, ^{125}I-IGF-I binding assay, Scatchard analysis, and Western blotting, we demonstrate here that the IGF-IR expression levels are essentially the same among several cell lines of normal and A-T cells. Even under these conditions, radiosensitivty of A-T cells was still remarkably high compared to that in normal cells. Furthermore, overexpression of the IGF-IR did not influence radiosensitivity of A-T cells. The present data thus do not favor the hypothesis that low expression of the IGF-IR in A-T cells is an important contributor as a cause of the high radiosensitivity.

88 Mechanism of p53 Accumulation and Activation by Ionizing Radiation and Telomere Shortening

Masatoshi SUZUKI[1], Keiji SUZUKI[1], Seiji KODAMA[1], Masami WATANABE[1], [1]Lab.Radiat.Life Sci.,Sch.Pharm.Sci.,Nagasaki Univ.

Telomeres, telomeric DNA specific nucleoprotein complexes, play an important role in protection of DNA termini and avoidance of checkpoint mechanism. p53 protein regulates checkpoint mechanism and is activated by both ionizing radiation and telomere shortening. We studied whether the same signal transduction pathway is involved in p53 accumulation and activation by ionizing radiation and telomere shortening. p53 was accumulated and activated in normal human diploid cells having short telomeres by phosphorylation at Ser15 in a similar manner that detected in X-irradiated cells. Similar results were obtained in wtp53-deficient lung carcinoma cells with short telomeres when they were expressed the wtp53 gene by an Ecdysone-inducible expression vector. We also found that the treatment with wortmannin reduced phospholyration level of p53, suggesting that wortmannin-sensitive ATM-kinase is involved in the activation of p53. These results indicate the similarity between the pathways activated by DNA damage and by telomere shortening.

NII-Electronic Library Service