H1

ATM-induced Radiosensitization *in vitro* and *in vivo*

E.K.Choi[3], S.D.Ahn[3], Y.H.Rhee[3], H.S.Chung[2], S.W.Ha[4], C.W.Song[1], R.J. Griffin[1], H.J.Park[1,2]
[1]Radiobiology Laboratory, Department of Therapeutic Radiology, University of Minnesota Medical School, [2]Department of Microbiology, College of Medicine, Inha University, [3]Department of Radiation Oncology, Asan Medical Center, College of Medicine, University of Ulsan, [4]Department of Therapeutic Radiology, College of Medicine, Seoul National University

It has been known that ATM plays a central role in response of cells to ionizing radiation by enhancing DNA repair. We have investigated the feasibility of increasing radiosensitivity of tumor cells with the use of ATM inhibitors such as caffeine, pentoxifylline and wortmannin. Human colorectal cancer RKO.C cells and RKO-ATM cells (RKO cells overexpressing ATM) were used in the present study. The clonogenic cell survival in vitro indicated that RKO-ATM cells were markdely radioresistant than RKO.C cells. Treatment with 3 mM of caffeine significantly increased the radiosensitivity of cells, particulary the RKO-ATM cells, so that the radiosensitivity of RKO.C cells and RKO-ATM cells were almost similar. The radiation induced G2/M arrest in RKO-ATM cells was noticeably longer than that in RKO.C cells and caffeine treatment significantly reduced the length of the radiation induced G2/M arrest in both RKO.C and RKO-ATM cells. Pentoxifylline and wortmannin were also less effective than caffeine to radiosensitize RKO.C or RKO-ATM cells. However, wortmannin was more effective than caffeine against human lung adenocarcinoma A549 cells indicating the efficacy of ATM inhibitor to increase radiosensitivity is cell line dependent. For in vivo study, RKO.C cells were injected s.c. into the hind-leg of BALB/c-nuslc nude mice, and allowed to grow to 130mm^3 tumor. The mice were i.p. injected with caffeine solution or saline and the tumors irradiated with 10 Gy of X-rays. The radiation induced growth delay was markedly increased by 1-2