Retinoic Acid Enhances Drug-Induced Cell Death in Anticancer Drug-Resistant Cancer Cells

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Background Radiation therapy and chemotherapy, in conjunction with surgical operations, have been commonly employed for the treatment of various types of tumors. However, a significant number of tumors are often failed to respond to these therapies, because many forms of tumors appear to be less sensitivity or become resistance to radiation and anticancer drugs after consecutive treatments. Retinoid (RA), a group of vitamin A derivatives, is known to be important for regulation of normal cellular growth and differentiation. Therefore, it has been examined its chemotherapeutic and chemopreventive activity in various types of tumors. Biological actions of RA are mediated through nuclear receptors, including the retinoic acid receptors (RARs) and retinoid X receptors (RXRs) families. Among them, RARβ has been suggested to play an important role in the biological functions of RA in many different types of cancer cells. RARβ expression is also suggested to associate with the cellular sensitivity to retinoid in those cancer cells. Treatment of various types of cancer cells with RA resulted in cell growth inhibition and apoptosis. Therefore, we examined the effect of all-trans-retinoic acid (atRA) as an anticancer drug-sensitizer in cancer cell lines and its cellular mechanism for enhanced drug-sensitivity.

Methods Cells were maintained by RPMI medium containing 10% fetal bovine serum. Cells were treated with 1μM atRA for 48 h and then treated with a desired anticancer drug for 24 h. Cell viability was measured spectrophotometrically at 540 nm using MTT assay. atRA and anticancer drug-treated cells were harvested with ice-cold PBS and were centrifuged at 12000 rpm, 4°C for 10 minutes. The cells were lysed with 200μl of ice-cold RIPA buffer containing protease inhibitors. Total cell lysates(30–50μg) were resolved on 8–12% SDS-PAGE gel and transferred to PVDF membrane. Blots were reacted with desired antibodies.

Results we investigated whether atRA pre-treatment enhanced a drug-sensitivity of various cancer cell lines to 5-fluorouracil (5-FU), Adriamycin (ADR), or cisplatin (CDDP), and a radiation-sensitivity. 5-FU, ADR, and CDDP are commonly used anticancer drugs for various types of tumors, especially stomach cancer, and ovarian cancer. 5-FU (SNU638-F2) and CDDP-resistant cell (SNU638-Cis) lines were established from a Korean gastric cancer cell line (SNU638) and the ADR-resistant cells (AD600) were established from a colon cancer cell line (SW620). The resultant cell lines showed an increased resistance to 5-FU, ADR, or CDDP, compared to their parent cells. Treatment of each cell lines with 10μM atRA before drug treatment resulted in an enhanced cell death in every cell lines tested here. Furthermore, the effect of atRA on growth inhibition in each drug-resistant cell lines (SNU638-F2, SNU-Cis, and AD600) was more obvious than in their parent cell lines.

Conclusion Based on our data, we suggest that atRA enhanced drug-induced cell death and reversed drug-sensitivity of the drug-resistant cancer cell lines.