125 The Mechanism of Increase in Drug Resistance in Polyploid Hamster Cells Induced by Cell Cycle-Perturbing Agents

[1]Mitsumasa W. HASHIMOTO, [2]Osamu NIKAIDO, [1]Keizo TANO, [3]Keiji SUZUKI, [3]Masami WATANABE and [4]Toshio MORI; [1]Kyoto Univ., [2]Kanazawa Univ., [3] Nagasaki Univ., [4] Nara Medical Univ.

Three cell cycle-perturbing agents, K-252a (protein kinase inhibitor), colcemid (mitotic inhibitor) and aphidicolin (DNA synthesis inhibitor), produced polyploid cells in Chinese hamster V79 cells in a concentration-dependent manner. The agents also increased the frequencies of methotrexate-resistant (MTX^r), doxorubicin-resistant (DOX^r) and paclitaxel-resistant (TAX^r) cells. In colcemid-induced MTX^r and DOX^r colonies, the concentration-dependent emergence of cells with polyploid DNA contents was observed. Moreover, two new-established tetraploid clones proved to be more resistant to DOX and MTX than diploid V79 cells. Thus, polyploidization was strongly suggested as a main mechanism for enhancement of the frequency of drug resistance by cell cycle-perturbing agents. Tetraploid clones grew with similar speed to parental cells. They had two times more DNA than parental cells, but had only 1.6-1.8 times more cell volume and DOX accumulation. The values of DOX accumulation per cell volume were found to be almost same between cells. But, the values of DOX accumulation per DNA were 80 and 87% in tetraploid clones, compared with parental cells. The values between cells were inversely correlated with their DOX sensitivities. Thus, the present results suggested that 13-20% decrease in DOX accumulation per DNA correlated with increase in DOX resistance in tetraploid and near-tetraploid DOX^r clones.

126 Correlation between Radiosensitivity and Radiation-induced Cell Cycle Pattern in γ- Ray Irradiated Human Melanoma Cells

Tetsuro.TAMAMOTO[1], Hitoshi.YOSHIMURA[1], Kazuo.IWATA[1], Hajime.OHISHI[1], Hideo.UCHIDA[1], Ken.OHNISHI[2], Akihisa.TAKAHASHI[3], Xinjiang.WANG[3] and Takeo.OHNISHI[3]
Dep. of [1]Oncoradiol. and Radiol., [2]Physiol., [3]Biol., Nara Medical University

It has been already found that there are different grades of radiosensitivity in human melanoma cells. In this study we found that in HMV1 the 10 percents' survival dose (D_{10}) was 10Gy and the 50 percents' one (D_{50}) was 4 Gy and that in MeWo its D_{10} was 4Gy and its D_{50} was 2Gy. MeWo was about two times sensitive to γ- rays as compared with HMV1. Moreover we examined radiation-induced cell cycle pattern by flowcytometer (FACScan) whether the sensitivity to γ- rays may depend on any cell cycle stage or not. We found that both HMV1 and MeWo showed a little increase in the percentage of cells in G_2/M phase after 4Gy-irradiation and that, in contrast, HMV1 showed much increase in the percentage of cells in G_2/M phase after γ- ray irradiation at 10Gy.

These results indicate that HMV1, hyposensitive cells for γ- rays, may have a certain ability to repair DNA damage in G_2/M phase. It will be necessary to examine whether the two melanoma cells have different repairbility for DNA damage induced with γ- rays or not, and the difference in a signal transduction pathway through *p53*.