Fractionated dose of 60 Gy changes molecular response of HL-60 cells to irradiation

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Objective: The cells of human promyelocyte leukaemia HL-60 lack functional protein p53 and react to ionizing radiation in doses up to 10 Gy by long cell cycle arrest in G2 phase, during which they repair radiation-induced DNA damage. Abrogation of G2 cell cycle arrest has radiosensitizing effect. In this work we evaluated changes in molecular response of HL-60-R cells (HL-60 irradiated by 10 cycles of radiation with total dose of 60 Gy, given over a period of 3 months) to irradiation by the dose of 2 and 8 Gy. Results: Both types of cells (HL-60 and HL-60-R) have high basal level of ERK1/2 phosphorylated on serine 202/204. This corresponds with their quick proliferation. Irradiation by the doses of 2 and 8 Gy induces decrease of ERK1/2 phosphorylation after 4 h in both cell types. However, after irradiation by the dose of 2 Gy in HL-60-R cells ERK1/2 phosphorylation is restored after 24 h, while in HL-60 cells the decrease is longer and ERK1/2 phosphorylation is restored only after 72 h. This may be related to different repair capacity, as the dose of 2 Gy is not lethal. This dose also induces in HL-60-R cells upregulation of cdk inhibitor p21, which is not detectable in HL-60 cells. Increased p21 is responsible for cell cycle arrest. On the other hand, in HL-60 cells the phosphorylation of check-point kinase 2 (chk-2) on threonine 68 occurs, while it is not observed in HL-60-R cells. Apoptosis induction by the dose of 8 Gy was lower in HL-60-R then in HL-60 cells. No difference in expression of anitiapoptotic mitochondrial protein Mcl-1 was found. Conclusion: In contrary to HL-60 cells, the HL-60 irradiated by 10 cycles of radiation with total dose of 60 Gy, given over a period of 3 months (HL-60-R) react to irradiation by p53 independent increase in p21, and not by activation of chk-2. Also kinetics of Erk1/2 phosphorylation is different in these cell types. HL-60-R are more resistant to radiation-induced apoptosis, but significant difference in D0 was not found (HL-60 2.5 Gy, HL-60-R 2.6 Gy). P21 might prevent apoptosis induction and trigger permanent cell-cycle arrest, which can also contribute to regression of this leukemia after therapy.

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