The Role of Apoptosis in the Development of Radiation-Induced Genome Instability under Chronic Radiation Expos

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Apoptosis resulting from a high frequency of damage to the cell's genetic material and manifested at late time after exposure is regarded as an evidence of radiation-induced genomic instability. On the other hand, apoptosis disruption may lie behind preservation of cells with genetic anomalies, and become thereby one of the mechanisms of genomic instability. Techa riverside residents, have been chronically exposed to radiation since 1949 as a result of the Mayak PA activities. Maximum dose rates were 0.4-0.5 Gy/year during the early years. Two groups (168 exposed individuals and 118 unexposed controls) were studied with the aim to assess the intensity of peripheral blood lymphocyte apoptosis 55-58 years after the onset of radiation exposure. Apoptosis was assessed based on morphological criteria, using the TUNEL assay, by typing CD95 positive lymphocytes. To assess the apoptotic reserve of the peripheral blood lymphocytes, in-vitro additional irradiation at a dose of 1 Gy, and 24-hour incubation was used. Increase of apoptosis in exposed individual was revealed based on morphological criteria (â) (12.3±0.6 in exposed vs 9.1±0.8 control subjects) and the findings of the TUNEL assay (â) (2.4±0,3 in exposed vs 0.9±0.2 control subjects). No dependence of CD95 positive lymphocytes on radiation factor was registered (8.0±0.4 in exposed vs 7.4±0.6 control subjects). A modeling approach was used to estimate the fraction of cells with broken apoptosis from these two groups. In this approach dynamics of cell states after in vitro irradiation is modeled by the 4-compartment model with compartments of i) cell with deficient apoptosis, ii) normal cells, iii) damaged cells, and iv) cells identified as apoptotic. The estimation of model parameters resulted in identifying the fraction of cells with broken apoptosis from the initial blood sample. It can be concluded based on the study results that: (1) chronically exposed individuals manifest an increased rate of peripheral blood lymphocyte apoptosis decades after dose rates returned to the background level, (2) using the method of genotoxic exposure (standard in-vitro irradiation), it was possible to detect a higher frequency of apoptotic abnormalities in chronically exposed individuals vs that in the controls. Thus, the study has provided a convincing evidence of the important role played by apoptosis in the development of radiation-induced genomic instability in man.

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