PROTECTIVE ASPECT OF MITOTIC DIVISION DELAY

V.G. Tyazhelova, I.G.Akoev
Institute of Biological Physics, Acad.Sci.USSR,
Pushchino, Moscow Region, USSR, 142292

In mammalian cells under small dose irradiation an unspecific complex of reactions develops involving inhibition of DNA synthesis and cell division, decrease of the common level of endogenic thiols and accompanied by an increase in radiosensitivity of the whole organism (I). The high doses of irradiation cause blocking of cell division. The end of the cell delay period in the radiosensitivity system in time coincide with the hightened radioresistance of the organism. For example, the periods of higher resistance to repeated irradiation of mice were observed for haemopoietic death on the 8th - 14th day after irradiation (2,3). This permitted us to discuss the protecting role of cell division delay.

In order to use in practice the cell division delay it is necessary to know its temporal regularities for each stage of the cell cycle. As defined by the analysis of the experimental data on mitotic activity of rodent small intestine epithelium, the block duration increases with the dose. This indicates that the cells need more and more time to restore their structure and function. Each cell cycle stage of the tissue under study has its characteristic limit values of block duration. The revealled regularity is expressed as follows:

$$T_i(D) = t_i + T_{limi}(I-\exp(-a_iD))$$

t_I = Ih, T_{lim_I} = IO hs, A_I = 0.0034 for stage G_2,

t_2 = 5.5 hs, T_{lim_2} = 27 hs, A_2 = 0.00I7 for stage S,

t_3 = I3.5 hs, T_{lim_3} = 42 hs, A_3=0.00I2 for stage G_I (4).

As for the haemopoietic system, there are no such detailed data on temporal changes in the mitotic index. We can be guided only by the maximal times of depletion of marrow and the data on beginning of restoration of blood leucocyte kinetics (on the 35th day - for humans, on the 20th day - for dogs, on the 12th - 20th day - for rats, on the 8th - 14th day - for mice) (3,5).

By calculation of mitotic activity data we obtained the cell survival curves for different stages of cell cycle and showed that the shoulder on the survival curve is observed as long as the stage becomes longer. As the stage duration reaches its maximum the cells die, this pointing to the protective character of stage elongation (6).

All the aforesaid supports our earlier suggestion that the organism "widely uses" the time factor for a more optimal repair of injury since the rate of repair changes little (7,8). However, the time factor has limitations. It is due to that inhibition

of all vital functions exept the repair process cannot last an extended time. Besides, it is known that the prolonged blocking of mitotic division results in depletion of the tissue and in break of its function.

During the mitotic delay the cell system seems to be in isolation from the necessities of the organism because of break of the connections with supernal control levels. This viewpoint is supported by the analysis of biochemical changes in the cell. These changes are directed to repairing the interacellular structure and do not enable the cell to fulfil its function.

At this period the cells lose their glycogen almost completely, the lipase activity decreases appreciably, a sharp drop in the activity of alkaline and acidic phosphatase is observed the succinatedehydrogenase activity reduces to a minimum. At the recovery stage the succinatedehydrogenase activity rises and becomes higher than that in the control. By that time the nucleoli and the nucleous membranes are normalized and most of the mitochondria recover. By the end of mitotic delay the alkaline and acidic phosphatase are highly active which coincides in time with the maximal and supernormal development of agranular reticulum. The intracellular structure is characterized by a great number of free ribosomes and hypertrophy of the Golgi complex producing lysosomes. The development of granular plasmatic reticulum is minimal, its recovery correlates with the start of cell regeneration (8).

The fact that the cell division delay takes place when the organism is affected by ACTH, corticosteroids, radioprotectors also testifies to its protecting role.

Another positive feature of cell division delay was revealed when modelling the recovery process in tissue (9). It was proposed that some quantity of cells repair during the mitotic delay, start to divide thus contributing to cell repopulation. The computations showed that some values of mitotic blocks extend the stability zone of cellular repopulation thus permitting higher values of feedback coefficient to be used. Due to that the intial level of the stationary state is reached with higher accuracy. The stability zone is extended at relatively small blocking time values whereas at great values it sharply narrows. It is found for the white and red blood systems as well as for intestinal epithelium that their experimental values of mitotic block duration extend the stable zone (9).

Thus, inspite of the fact that the cell division delay causes temporal depletion of the functioning tissue it is still positive for the final stage of tissue recovery since it provides higher accuracy of homeostasis.

REFERENCES

(I) KALENDO, G.S. "On possibility of adaptational syndrom-stress on the cellular level and its role in response of the cell to irradiation". Uspekhy sovremennoi biologii, 73, NI; 59-80 (I972).

(2) KOVALEV,V.P., PLOTNIKOVA,E.D., EIDUS, L.Kh. "Study of restoration of mammalian critical systems responsible for different forms of radiation death". Radiobiologiya, II, N 2, I95-200 (I97I).

(3) AKOEV I.G. "Problems of postirradiation recovery". M., Atomizdat (I97O)
(4) TYAZHELOVA, W.G., SAWELYEV,A.P., AKOEV,I.G. "Quantitative analysis of curves of postirradiation mitotic activity as a method for studying the process of intracellular repair" Studia biophysica, 42, (I974) 87-98.
(5) KILLMAN S.A. "Radiation effects on the myelocytic cell renewal system" in Manual on Radiation Haematology, IAEA Vienna, (I97I) 89-98.
(6) TYAZHELOVA V.G. "Theoretical and model description of repair of cell system depending on age of mitotic cycle phase and damage degree", Studia biophysica, 46, I (I974) I-8.
(7) AKOEV I.G. "Some results of theoretical analysis of radiation injury of organisms" Izvestiya AN SSSR, N I, (I976) 4I-5I.
(8) TOKIN I.B. "Problems of radiational cytology", Leningrad, "Meditsina" (I974).
(9) TYAZHELOVA V.G., AKOEV I.G. "Model description of proliferating tissue recovery as a two-level hierarchical system" Studia biophysica (in print).