DOI 10.18699/SBB-2022-601

The novel radioprotective agent. Characterization of the substance and the mechanism of its action

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Key words: RNA internalization, radioprotection, double-stranded RNA, homologous recombination

Motivation and Aim: Nucleic acids are known to exert radioprotective properties, which are believed to be associated with the restoration of the integrity of nuclear DNA [1]. Nevertheless, no studies on determining the cellular and molecular mechanisms of the radioprotective capabilities of nucleic acids have been undertaken yet. In the current report, a stage of the research aimed at clarifying the mechanisms mediating the radioprotective effect of RNA is described.
Methods and Algorithms: Mice were intravenously injected with yeast total RNA and than exposed to an absolutely lethal dose of γ-radiation. The effective parameters of the radioprotective effect of the compound were established. Pathomorphological examination of spleens, as well as analysis of the rate of post-irradiation recovery of hematopoiesis, proved the RNA preparation to facilitate the reconstitution of the hematopoietic and immune systems. Using hydroxyapatite chromatography, it was found that it is double-stranded RNA (dsRNA) that mediates the radioprotective effect of the yeast RNA preparation. Based on two sequenced molecules as a model structure, we have designed and synthesized the fluorescent dsRNA probe. Using the double fluorescent-radioisotope labeling, we have demonstrated the native internalization of dsRNA into hematopoietic stem cells. Molecules of dsRNA were show to be resistant to blood nucleases and, being administered intravenously, accumulate in some "critical" organs. Using bone marrow cells pre-incubated with the radioactive dsRNA probe, we have identified the organs predominantly populated by circulating (i.e. mobilized) hematopoietic stem cells.
Results: Intravenous injection of 7 mg of total RNA 30 minutes prior to exposure to an absolutely lethal dose (9.4 Gy) of γ-radiation increases the survival rate of irradiated mice up to 80–100 % [2]. The acting component, dsRNA, was isolated from S. cerevisiae total RNA. DsRNA was established to exert the radioprotective effect by facilitating the post-irradiation reconstitution of the hematopoietic and immune systems [3]. It was found that radioprotective properties do not depend on the primary structure of dsRNA, but unequivocally depend on the presence of free double-stranded ends. It was demonstrated that dsRNA can be natively internalized into hematopoietic stem cells [4]. P^{32}-labeled dsRNA was shown to remain intact after at least one hour of circulation in blood, after which it can be detected in the bone marrow of the recipient animal. Intravenous injection of bone marrow cells exposed to P^{32}-labeled dsRNA results in detection of P^{32} predominantly in the bone marrow and spleen.
Conclusion: Based on the results obtained, the mechanism for the radioprotective capability of dsRNA, which implies the internalization of intravenously administered dsRNA by hematopoietic stem cells, where it further participates in the post-irradiation repairing of double-stranded DNA breaks, has been hypothesized. Once the repair

process is over, the preserved hematopoietic stem cells exit to the circulatory system and than repopulate the emptied niches in hematopoietic organs, where they proliferate and reconstitute the hematopoietic and immune systems. Due to the greater number of the preserved hematopoietic stem cells, such a reconstitution goes much faster and thus increases the survival rate of irradiated mice.

Acknowledgements: This research was funded by the Russian Ministry of Science and High Education via the Institute of Cytology and Genetics (State Budget Project No. FWNR-2022-0016), LLC “KARANAHAN” and LLC “ACTIVATOR MAF”.

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