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REVIEW & HYPOTHESIS

The Non-uniformity of the Absorption of Ionizing Radiation Energy in the Body Potentiates the Radioprotective Effects of Drugs: Influence on the Post-radiation Recovery of Radiosensitive Tissues with High-Dose Total-Body Irradiation

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Abstract. Purpose: This review proposes a hypothesis of the mechanism of potentiating the radioprotector effect with non-uniform irradiation. Conclusion: Preventive application of radioprotectors provides a radioprotective effect not only by means of partially neutralising the "oxygen effect" but also by their pharmacological action on mesenchymal and hematopoietic stem cell progenitors. The stem cells that survive at the site of shielding in the irradiated body may become an object for the radioprotector's action via the stimulation of stem cell proliferation and expansion. Shielding radiosensitive tissues increases the spectrum of radioprotector action and is the basis of the potentiation of combined radioprotector + shielding protection. Significant non-uniformity of the absorption of ionizing radiation energy in a body increases the effectiveness of radioprotective drugs with lethal and extra-lethal levels of irradiation, which must be considered when providing emergency healthcare to individuals exposed to radiation accidents.

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1. Introduction

The distribution of the absorbed energy of ionizing radiation through the body of animals and humans is characterized by non-uniformity that increases with an increase in body weight [1]. The maximum absorption of ^{60}Co and ^{137}Cs γ radiation energy occurs at a depth of ~10 mm from the surface of the body [2] and shifts to a larger depth with an increase in ionizing radiation energy [3]. The screening of potential radioprotective compounds has been performed in mice, an experimental model with a low body weight that provides a relatively uniform distribution of γ radiation throughout the body. Sixty years ago, Bacq et al. [4] discovered the first radioprotector, cysteamine, in mice.

However, the clear non-uniformity of absorption of γ radiation energy through an animal's body is observed when radioprotector studies are performed on large animals, such as dogs and monkeys. Moreover, because of the greater mass of the human body, this effect should be considered when data from radiobiological experiments are extrapolated from animals to humans who have been exposed to lethal doses of acute radiation during a nuclear accident.

2. Local Shielding, the Abscopal Effect, and Stem Cell Migration: History and the Present

For years, the partial shielding of individual animal body parts has been used as a model of the influence of the non-uniform distribution of ionizing radiation through an animal's body on the course of acute radiation sickness. Investigations in this field included studies by Jacobson and coworkers [5-9] on mice that found a protective effect of shielding the spleen, liver lobe, intestinal loop, and hind limb. All of the cases observed an accelerated postradiation recovery of the hemopoietic system. Shielding of the spleen provided 55% survival of the animals exposed to lethal doses of radiation, indicating the role of the spleen in these processes. These findings allowed the authors [9] to hypothesize that the observed effect might be caused by the impact of a humoral factor (or factors) secreted by the reticuloendothelial tissue contained in the shielded tissues. Subsequent time-dependent removal of the spleen performed after exposure of the animals to radiation showed that the influence of this individual organ began 1 h later, with a maximal effect observed 24 h after radiation exposure.

Maisin and coworkers [10-15] confirmed a protective effect of shielding the spleen, intestine, liver, and bone marrow in rat studies and found that the liver played an essential role in the increase in the radioresistance of the body. The same observation was made by Gershon-Cohen et al. [16]. Additionally, early investigations by Craves [17] and Edelman [18] showed that shielding the adrenal glands mitigated radiation toxicity. A significant radiation-protective effect was observed with shielding of the abdomen from exposure to high-energy γ-neutron and proton radiation [19-25]. Further studies confirmed a significant impact of locally shielding small sections of the bone marrow on the course of acute radiation syndrome both in small and large animals (dogs) [26-33].

The first evidence of a distant (abscopal) effect was discovered by Barakina [34] and confirmed by more recent studies [35-37]. They reported accelerated postradiation recovery of hemopoietic tissue in intestine-shielded mice exposed to lethal doses of whole-body irradiation. These data were based on the quantitative analysis of bone marrow cellularity, the accelerated elimination of chromosomal aberrations in bone marrow, and an increase in the number of hemopoietic stem cells in the spleen of the animals.

Nonetheless, a reduction of the radiation dose delivered to the shielded intestine at lethal doses of whole-body radiation partially or completely eliminated the intestinal syndrome and toxemic radiation component of acute

radiation sickness and may mitigate the development of bone marrow syndrome. Our studies [38] fully confirmed the existence of the abscopal effect in studies of guinea pigs and rats exposed to non-lethal low-dose γ irradiation (1 and 2 Gy, respectively). Shielding the upper third of the abdomen of animals accelerated the elimination of chromosomal aberrations in bone marrow to levels equivalent to a two-fold reduction of the radiation dose. The effect was registered 2-3 days after irradiation.

The abscopal effect was also manifested as an acceleration of dermal injury healing in animals exposed to whole-body irradiation with small shielded sections of bone marrow [39]. Hanks [40] was the first to suggest that a shielded area of bone marrow might be a source of endogenous colony-forming units in the spleen (CFUs) in irradiated mice, although no direct data that support this possibility was yet provided. The emergence of CFUs after partially shielding the bone marrow in irradiated animals was confirmed [41, 42]. Petrov et al. [43] obtained convincing evidence of stem cell migration from the bone marrow shielding site to further the process of cell repopulation. They used a gene marker in experiments in two different inbred irradiated parabiotic mice, in which one had shielding of the paw. The time necessary for completing hematopoietic cell expansion from the bone marrow shielding through the entire hematopoietic tissue of the irradiated body was 6 and 14 days in rats and dogs, respectively, and allowed the survival of the animals after lethal radiation exposure [44, 45] .

Nothdurft et al. [46,47] performed a similar study in dogs exposed to radiation of the upper half of the body at a dose of 11.7 Gy, resulting in the loss of 70% of the bone marrow, and discovered the concurrent activation of the hematopoietic system in the non-irradiated part of the body and emergence of granulocyte/macrophage (GM) progenitor cells in the blood flow and irradiated segment of hematopoietic tissue 1 week after irradiation. Under the same experiment conditions, they also discovered that recombinant human granulocyte colony-stimulating factor (rhG-CSF) application increased the number of GM progenitor cells in the blood flow and significantly accelerated the hematopoietic recovery of the irradiated sites of the body, particularly within the first 7 days after exposure [48].

The most significant parts of the body for shielding against radiation were established in experiments that used equal weights and absorbed radiation doses of shielded body parts in dogs and rats [22-25]. The greatest protective effect, with a dose reduction factor (DRF) of 2.4, was found in the animals exposed to lethal doses of irradiation when the upper half or third of their abdomen was shielded [23]. A mathematical model that evaluates the effectiveness of the partial local shielding of the abdomen as a function of the width and thickness of a shield and absorbed dose has been developed [49]. Shielding the upper parts of the abdomen protected the liver, spleen, adrenal glands, one third of the intestine, and a small portion of the bone marrow in four vertebrae and partially in the lower ribs. Notably, this is an area where a large part of the reticuloendothelial system of the body (e.g., liver, spleen) is located. Lowering radiation exposure in these tissues to sub-lethal doses by means of partial shielding is likely to generate active stromal foci that are essential for the post-radiation restoration of hematopoiesis in animals exposed to lethal doses of whole-body irradiation [50-52]. Additionally, partially shielding the abdomen reduces the development of post-exposure primary radiation syndrome [53], namely primary hypercorticism that suppresses stem cell migration [54-58]. Lowering radiation exposure in the adrenal glands by shielding the abdomen may be favourable for the mitigation of acute radiation syndrome [17, 18, 59].

Intensive and comprehensive investigations of the biochemical and cellular mechanisms of hematopoietic stem cell (HSC) traffic from the bone marrow to blood flow and from the

circulation to stem cell niches to continue hematopoiesis at new sites have been performed over the past decade [60]. Although many issues have not yet been resolved, some common features of these processes are discussed below. First, anatomical microsites of the bone marrow where HSCs are preserved and reproduced are niches with a complex three-dimensional structure of the bone marrow microenvironment, consisting of stromal cells and capillary endothelia. The niche regulates the adequate level of hematopoiesis through cytokine production (G-CSF, stem cell factor, interleukin-6, leukaemia inhibitory factor, and so on), thereby providing long-term HSC proliferation, especially the proliferation of the cells responsible for myelopoiesis and thrombocytopoiesis. Niches also work as a barrier to adjust hematopoietic stem and progenitor cell (HSPC) traffic and homing. Reciprocal SDF-1/CXCR4 interactions between hematopoietic and bone marrow stromal cells play a crucial role in HSPC retention in the niche. Chemokine SDF-1 is produced in the bone marrow, spleen, and other tissues exclusively by endothelial and stromal cells. The level of SDF-1 concentration and expression of the CXCR4 receptor determine HSPC and mesenchymal stem cell (MSC) homing and proliferation [61, 62]. G-CSF also plays an important role as the major factor that mobilizes stem cells. G-CSF creates beneficial conditions for the egress of HSPC from the bone marrow by decreasing CXCR4 expression in HSPC [63, 64].

The physiological importance of HSPC and MSC migration through repopulation is clearly associated with the repair of radiation-induced hematopoietic system damage [65, 66]. Irradiation increases the expression of HSPC mobilization factors, including G-CSF [67-70]. The activation of reticuloendothelial tissues induced by radiation is the most important for these processes [50-52]. A study by Francois et al. [71] provided evidence that whole-body irradiation increases the homing of intravenously injected human MSC in the tissues of nude (-/-) mice. MSCs support the expansion of HSCs after irradiation [72, 73]. In another study, the transplantation of irradiated CD34 (+) cells together with MSC in irradiated baboons greatly rescued CD34+ cells from radiation-induced apoptosis and enhanced the therapeutic effect of CD34 (+) cells [74]. Therefore, the beneficial effect of preliminary whole-body irradiation on the repair of local radiation-induced skin injury and diabetic wounds can be explained by the increased migration of mesenchymal stem cells [75, 76].

Overall, the reduction of radiation absorption up to sub-lethal doses by shielding individual parts of the body during whole-body irradiation preserves a certain number of viable hematopoietic or mesenchymal stem cells that further migrate through the body under the influence of radiation-induced humoral factors, thereby providing conditions for the repair of damaged tissues.

3. Potentiation of the radioprotective effect of the combined application of local shielding and radioprotectors

Presently, the pharmacological classification of radioprotective agents reflects the most significant historical advances in the screening of various chemical compounds and theoretical knowledge of their radioprotective mechanism. With the exception of pharmaceutical countermeasures against radioactive nuclide incorporation or primary radiation syndrome, radioprotective agents can be referred to as the following: (1) radioprotectors ("chemical protection" by Bacq) that exert their effects on physicochemical and biochemical levels in cells during exposure to ionizing radiation, (2) radiomitigators (e.g., oestrogens, androgens, cytokines, and immunological adjuvants) that promote the acceleration of the post-radiation restoration of myelopoiesis by stimulating HSPC and MSC mobilization, and (3) radiomodulators (e.g., vitamins and nutritional supplements) that increase the resistance of the body to irradiation

and other unfavourable environmental factors by adaptively shifting the effectiveness of the antioxidative protection of the organism [77].

The mechanism of the radioprotector effect is based on the realization of the "oxygen effect," a radiobiological phenomenon. Radioprotectors either induce lower oxygen content in cells by means of pharmacological action via specific receptors (e.g., serotonin, mexamine, indralin) or directly provide thiol groups (i.e., sulphur-containing radioprotectors, such as cysteamine and amifostine) in competitive chemical reactions with oxygen for products from DNA radiolysis [78, 79].

The first data on the combined application of local shielding and radioprotective agents were reported by Jacobson [9]. He noted an additive protective effect of both cysteine (or estradiol) and the shielding of the spleen in mice exposed to lethal doses of radiation. The first investigation of combined protection that applied both shielding and the radioprotective drug cysteamine was performed by Maisin and coworkers [80, 81]. They discovered a synergistic effect of shielding the liver and intraperitoneal cysteamine administration in rats exposed to lethal doses of radiation. Saxonov and coworkers [82, 83] later estimated the efficiency of combined protection for various groups of radioprotectors and shielding various parts of animals' bodies. In studies of rats exposed to lethal doses of 10 Gy whole-body γ irradiation, partially shielding the abdomen or head provided 30% survival of the animals. Under this condition, cystamine or mexamine at non-protective doses potentiated the radioprotective effect of shielding, with up to 80% survival of the animals [82]. The potentiation and synergism of the protective action of the combined application of radioprotectors and shielding of radiosensitive tissue have been repeatedly confirmed by other investigations [84-87].

To extrapolate these data to humans, experiments on large animals have been performed. Clearly marked non-uniform absorption of ionizing radiation energy in the animal's body must be considered. Partially shielding both the abdomen and head and administering the emergency radioprotector indralin pre-irradiation revealed a strongly pronounced effect of the combined protection in studies on irradiated dogs. With 10-12 Gy whole-body γ irradiation, a dose that is 2.5- to 3-fold higher than the lethal dose of irradiation for this species, 75% of the animals with combined protection survived compared with 100% mortality in the experimental groups that received either the shielding or radioprotector alone [88].

Furthermore, the potentiating effect of bone marrow (pelvis) shielding together with indralin administration was confirmed in experiments on dogs exposed to 5 Gy high-energy proton (~240 МэВ) irradiation [89]. The absorbed radiation dose in all of the experimental groups was identical. Under these conditions, the combined protection provided 57% survival of the dogs, compared with 100% mortality in the experimental groups that received either shielding or indralin alone.

4. Plausible mechanism of the potentiating effect of combined protection

A possible mechanism of the observed potentiation of the effect of combined protection is based on the concept of augmenting the reproduction and migration of MSC and HSPC from the shielding site under the influence of the pharmacological action of radioprotectors, causing their further expansion to radiation-damaged hematopoietic tissues. Therefore, the influence of radioprotectors on these processes may be detected if radioprotectors are applied after radiation exposure, when they fail to exert a protective effect as antagonists of the "oxygen effect" [77].

Rixon et al. [90] first revealed the therapeutic properties of serotonin repeatedly injected in rats 1 h after irradiation. This effect was later confirmed not only with receptor-mediated radioprotectors (e.g., serotonin,

mexamine, and indralin) but also with sulphur-containing radioprotectors (e.g., cystamine and AET) [91-93]. With liver shielding in rats, Masin et al. [80, 81] found a protective effect of cysteamine administered after whole-body lethal-dose irradiation when the radioprotector alone was ineffective. In our studies in rats exposed to 10 Gy radiation with shielding of the upper quarter of the abdomen, including protection of the liver, indralin administered after irradiation increased survival by as much as 55%, whereas the radioprotector alone had no protective effects [94]. Indralin applied after whole-body irradiation also increased the amount of CFUs in mice with paw shielding [88]. The therapeutic effects of radioprotectors have been confirmed in large animals. Indralin used within 30 min after whole-body absolutely lethal irradiation increased survival in irradiated dogs by as much as 30% and 60% when applied alone and coupled with acute radiation sickness therapy accodingly [88, 95]. In this condition preventive application of indralin provided 90% animal survival, in contrast to the therapeutic post-exposure effect [88].

Orbeli [96], an adherent of Pavlov, was the first to discover the adaptation-trophic role of the sympathetic nervous system. Adrenergic agents and serotonin were later found to stimulate hemopoiesis and stem cell mobilization and migration [60, 97-101]. Moreover, norepinephrine, mexamine (i.e., the 5-methyl-derivate of serotonin), and indralin as a direct α_1-adrenergic agent [102] significantly reduced the hemotoxicity of carboplatin [103-105]. The proposed direct action of these tested agents on the hematopoietic system was confirmed by recent discoveries of α_1-, α_2-, β_2-adrenoceptors and serotonin 5-HT_2 receptors on HSPC [106, 107].

Indralin was also shown to activate ribonucleotide reductase in the bone marrow and spleen in "viable animals," which catalyses the inclusion of ribonucleotide-5-diphosphate in DNA through the synthesis of desoxyribonucleotide triphosphate [108-110]. A similar action of norepinephrine on nucleotide metabolism was shown in bone marrow MSC by increasing cell DNA synthesis through α_1-adrenergic receptors [111]. A stimulatory effect of adrenergic agents and serotonin on hematopoietic tissue is likely realized through the hematopoietic microenvironment by means of stromal cell activation. The therapeutic effect of sulphur-containing radioprotectors is likely to be indirectly initiated by the stimulation of the adrenergic system through its vasodilative action [112] and carried out by mesenchymal cells [113].

5. Conclusion

The stem cells that survive at the site of shield protection of the irradiated body may become the object for the action of radioprotectors via stimulation of MSC and HSC proliferation and expansion. Therefore, without shielding, radioprotectors have only therapeutic effects in small animals that are exposed to whole-body ~LD_{70-80} acute irradiation and consistently demonstrate a lack of effectiveness at lethal radiation doses [93] that likely result in the complete radiation-induced damage of the substrate of radioprotector action (i.e. HSPC). A more favourable scenario can be observed with irradiation in large animals (e.g. dogs) [88] and may be extrapolated to humans because of their larger size, greater heterogeneity, and non-uniformity of absorption of ionizing radiation energy.

The preventive application of radioprotectors is likely to provide a radioprotective effect not only by partially neutralizing the "oxygen effect" but also by their pharmacological stimulatory action on mesenchymal stem and hematopoietic stem cell progenitors. Shielding radiosensitive tissues increases the spectrum of radioprotector action and is the basis of combined protection. The significant non-uniformity of the absorption of ionizing radiation energy in a body increases the effectiveness of radioprotective drugs to extra-

lethal levels of irradiation and should be considered when providing emergency healthcare to individuals exposed to radiation accidents.

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