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Editorial Open Access

Radioprotectors and Mitigators: Current Status

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Editorial

Ionizing radiation (IR) is a known environmental, occupational and medical hazard that can produce dreadful health impairments. Usually, occupational exposure is low (~0.3 mSv per worker per year in the US [1]) and is only slightly higher than the exposure to the environmental radiation. However, occupational exposure could reach excessively high levels due to the accidents at nuclear power plants [2-4], exposure to contaminated waste [5], consequences of nuclear "dirty bombing" [5,6] or due to industrial accidents during mining, milling and processing of radioactive materials [7]. In these situations, the risk of exposure to high doses of radiation increases significantly not only for radiation workers but also for personnel participating in emergency response.

Medical application of IR is used mostly for the treatment of a broad range of malignancies. Multiple lines of evidence indicate that increasing the cumulative radiation dose by as little as 10-20% may facilitate the complete eradication of some tumors [8,9]. Unfortunately, elevated doses of IR cause damage to tumor-surrounding normal tissues, thus inducing detrimental side effects.

The most common therapeutic approach to safeguarding the normal tissue from deleterious effects of IR exposure is the development of radoprotectors and mitigators [10]. Radioprotectors are compounds that are designed to reduce the damage in normal tissues caused by radiation and must be present before or at the time of radiation for effectiveness. Mitigators may be used to minimize toxicity when applied even after radiation has been delivered.

Radioprotective treatments that have been proposed over the past several decades include thiol compounds that can scavenge free radicals; growth factors and cytokines that function through receptor mediated mechanisms to modify cellular response to radiation; and natural antioxidants and extracts [11-14]. Thiol compounds are the most effective and the longest studied radioprotectors. Synthetic thiol Amifostine (Ethyol) is the only FDA approved radioprotective treatment available today [15]. However, it has significant shortcomings including relatively high toxicity, unfavorable routes of administration, and narrow protection time window [14,16]. Because of its adverse side effects in humans, effectiveness of Amifostine in clinical trials is significantly diminished compared to that in animal studies [17]. Another class of radioprotectors, cytokines and immunomodulators, can only be effective if significant fraction of target cell population survives after the radiation exposure, and, thus, should be used with low radiation doses and/or in combination with radical scavengers and antioxidants [18]. These radioprotectors have common adverse side effects related to their proinflammatory activity and immunogenicity [14]. Natural antioxidants, such as vitamin E, melatonin, flavonoids and others, have fewer toxic side effects but also a lower degree of protection compared to thiol agents [14,17]. One approach to address these shortcomings has been the use of combinations of natural and synthetic compounds to increase effectiveness while lowering toxic side effects [14,17]. However, the availability of effective and safe therapeutic strategies to ameliorate radiation-induced damage is still lacking [14,17].

Encouraging pre-clinical data introduce superior and increasingly selective radioprotectors [9,19,20]. The development of some of these new agents is based on the premise that the cytotoxicity of ionizing radiation is cell-cycle dependent and include inhibitors of cyclin-dependent kinases (CDKs), and cell cycle regulators such as tumor suppressors pRb and p53 [20], and glycogen synthase kinase 3β (GSK-3β) [21,22]. Most important, these inhibitors are highly selective and protect only normal cells [21-23]. The other group of novel radioprotectors includes free radical scavenges with the safer profiles compared to Amifostine. For example, pyridoxamine (PM) was shown to be more effective at protecting from radiation-induced damage to normal tissue than Amifostine [24]; at the same time PM is well tolerated, with no significant treatment-related adverse effects [25].

Radiation mitigators aim to interrupt IR-induced damage or intervene to prevent the perpetuation of damage and thus reduce the overall toxicity. Alternatively, radiation mitigators can be the agents delivered during or shortly after exposure to repopulate a critical cell compartment such as the mucosa or bone marrow. In this instance, the mitigator is used to prevent acute toxicity. Many cytokines and growth factors have radiation mitigating effects: granulocyte-colony stimulating factor (G-CSF) [26], keratinocyte growth factor (KGF) [27], agonists for toll-like receptors 5 [28] and 2/6 [29].

These emerging radioprotectors and mitigators present novel strategies for reduction of deleterious consequences of normal tissue irradiation, as well as for radiosensitization of tumors.

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