Biomedicine & Pharmacotherapy 106 (2018) 610–617

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Appraisal of mechanisms of radioprotection and therapeutic approaches of radiation countermeasures

Krishna N. Mishra, Belal A. Moftah, Ghazi A. Alsbeih*

Radiation Biology Section, Biomedical Physics Department, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

ARTICLE INFO

Keywords:
Radioprotection
Radioprotector
Radiation countermeasures
Free radicals
Antioxidants
Ionizing radiation
Radiation effects

ABSTRACT

Radiation countermeasures are radioprotective agents that reduce the harmful effects of ionizing radiation. They have wide range of applications extending from protection of normal tissues of cancer patients during radiotherapy to safeguard people aftermath of radiologic or nuclear accidents. Despite the screening of thousands of natural and synthetic compounds, only few found place in clinic with limited tolerance. Therefore, mechanistic understanding is essential in the development of more suitable and customized radiation countermeasure agents. This review focuses on the mechanisms of radioprotection imparted by these agents.

Radioprotectors are diverse and act through widely varying mechanisms that can be classified in 10 categories: 1) scavenging of free radicals; 2) enhancing DNA repair; 3) synchronizing of cells; 4) modulating redox sensitive genes; 5) modulating growth factors and cytokines; 6) inhibiting apoptosis; 7) repurposing of drug; 8) interacting and chelating of radionuclides; and therapeutic methods of tissue regeneration such as 9) gene therapy; and 10) stem cell therapy. The most common mechanism of radioprotection is the scavenging of free radicals whereas, modulation of growth factors, cytokines and redox genes emerge as effective strategies. Gene and stem cell therapies as therapeutic radiation countermeasures are being developed and can be applied in the near future to minimize the side effects of radiation exposure through tissues regenerations. Thus, the management of radiation exposure may require a holistic multi-mechanistic approaches to achieve optimal radiation protection during radiotherapy of cancer patients and in cases of nuclear eventualities.

1. Introduction

Radiation countermeasures are agents that protect organisms from deleterious ionizing radiation effects and mitigate tissues' injuries caused by planned or unplanned exposure [1]. The development of such countermeasures that can be applied before, during or after intentional or accidental radiation exposure are currently an active areas of research worldwide [2–4]. In general, radioprotectors are the agents used before radiation exposure to protect cells and tissues from being damaged; radiomitigators are the agents that can be applied soon after the exposure to repair and recover tissues before the appearance of symptom; whereas therapeutic agents are applied after radiation exposure to enhance healing of injuries and regeneration of tissues.

These agents have a very important role in enhancing the quality of life of cancer survivors after radiotherapy by alleviating radiation induced side effects [5,6]. The need for efficient and effective agents is also solicited by the increased risks of radiation exposure to different types of radiological sources in medicine and industry. This is because of the tremendous rise in the applications of radiations in various aspects of our daily life with increased probabilities of inadvertent accidental exposure. In addition, the heighten risks of spillage of nuclear material and potential terrorist detonation of dirty bomb pose threat to the society and cause public fear, anxiety and uncontrolled turmoil. Furthermore, human inspiration to invade space and send manned flights to Mars and beyond is complicated by how to protect astronauts from galactic radiation. Invariably, radiation usages and threats in

Abbreviations: AH, antioxidant; APAF-1, apoptotic protease activating factor 1; APE1, apurinic/apyrimidinic endonuclease 1; ARE, antioxidant response element; ATM, ataxia telangiectasia mutated; ATP, adenosine triphosphate; BCl, B-cell lymphoma family of cell death regulatory (apoptosis) proteins; BRCA1, breast cancer gene 1; CDC25, cell division cycle phosphatase 25; cIAP, cellular inhibitors of apoptosis; COX-2, cyclooxygenase 2; CtIP, carboxy-terminal interacting protein; DTPA, diethylenetriaminepentaacetic acid; FDA, Food and Drug Administration; G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte macrophage colony stimulating factor; GPx, glutathione peroxidase; GSH, glutathione reduced; GT3, gamma tocotrienol 3; H_2O_2, hydrogen peroxide; HAT, hydrogen atom transfer; IL, interleukin; IND, investigational New Drug; iNOS, inducible nitric oxide synthase; MSC, mesenchymal stem cells; NF-kB, nuclear factor kappa beta; NRF2, nuclear factor erythroid 2-related factor 2; $ONOO^-$, peroxonitrite radical; ROO·, peroxyl radical; ROOH, alkyl hydro peroxides; ROS, reactive oxygen species; SET, single electron transfer; SOD, superoxide dismutase; TLR5, toll like receptor 5; TNF-alpha (α), tumor necrosis factor alpha; VEGF, vascular endothelial growth factor; X·, free radical; XiAP, X-linked inhibitor of apoptosis protein

* Corresponding author at: Biomedical Physics Department, King Faisal Specialist Hospital and Research Centre (KFSHRC), MBC-03, P.O. Box 3354, Riyadh 11211, Saudi Arabia.
E-mail address: galsbeih@kfshrc.edu.sa (G.A. Alsbeih).

https://doi.org/10.1016/j.biopha.2018.06.150
Received 6 June 2018; Received in revised form 24 June 2018; Accepted 27 June 2018
0753-3322/ © 2018 Published by Elsevier Masson SAS.

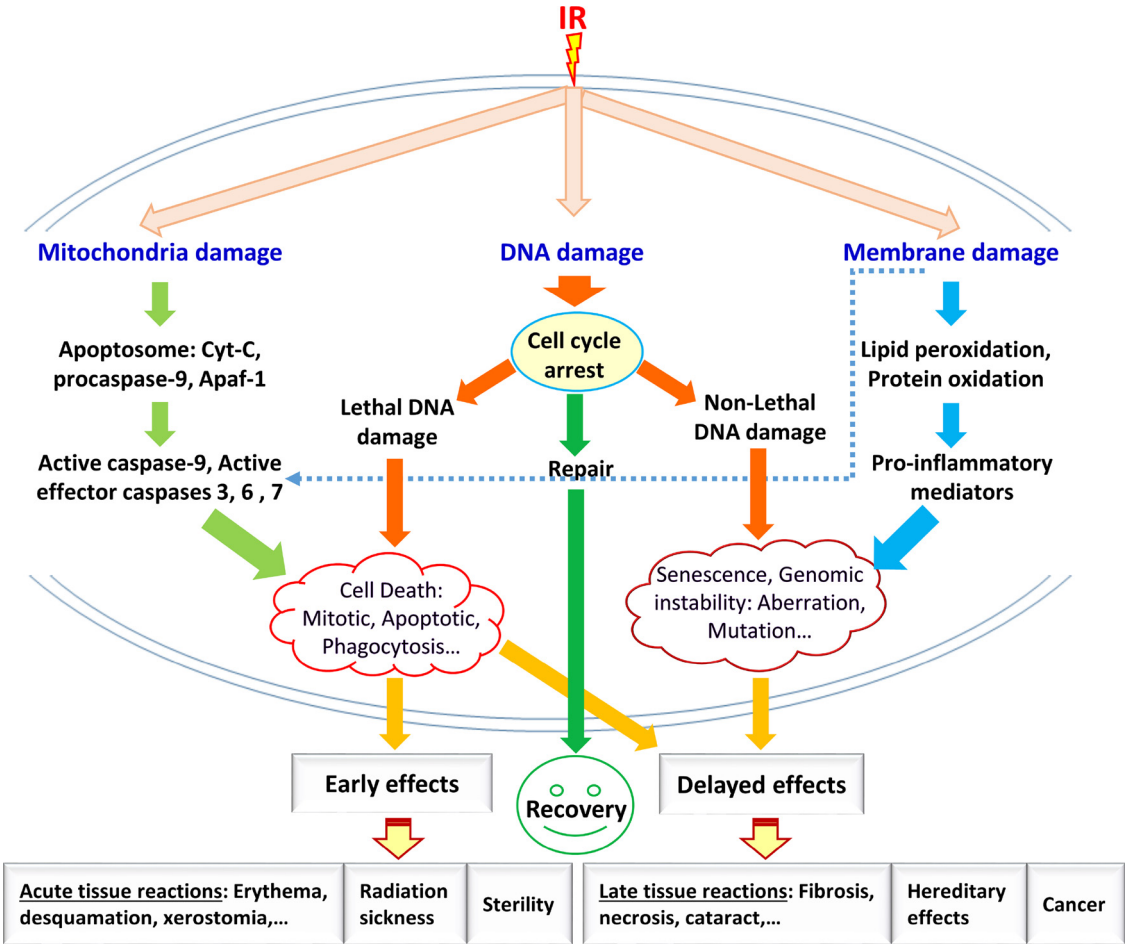

Fig. 1. Schematic overview of the main known pathways of radiation-induced damages that take place in cells and tissues with their potential biological consequences. Exposure of ionizing radiation produces oxidative stress and causes damage to biomolecules (DNA, lipid, protein). Damage to DNA can be lethal or non-lethal depending upon the radiation dose. Non-lethal damage (mis/unrepaired) may leads to genomic instability such as chromosomal aberrations, DNA mutations and cell senescence. Lethal damage can cause cell cycle arrest and cell death (mitotic, apoptosis, phagocytosis). Further, membrane damage and lipid peroxidation initiates inflammatory response that may lead to cell senescence or death. In addition, radiation-induced oxidative stress may also damage different cellular organelles including mitochondria, the powerhouse of the cell. The release of cytochrome C from mitochondria initiates the process of cell death through different effectors proteins including caspases. Cells may recover from DNA damage (error free repair). Persistent lethal or non-lethal damages may manifest as cell death or genomic instability. While the latter can lead to delayed consequences of radiation-induced cancer in somatic cells or hereditary effects in germinal cells (non-proven in human), cell death can result in acute (erythema, radiation sickness, sterility, etc.) or late (fibrosis, necrosis, cataract, etc.) tissue reactions. Acute effects are manageable using radioprotectors but how much late effects can be minimized using radioprotectors is still debatable.

modern life style require effective radioprotectors to safeguard human when needed from hazardous potential.

Understanding the main pathways of radiation induced injuries and the counteracting mechanisms of radioprotection are important steps in developing more efficient radiation countermeasures. Therefore, the aim of this review was to put together and discuss the various known and emerging mechanisms of radioprotectors. It is evident that radioprotective mechanisms are multidimensional in nature and vary from simple scavenging of free radicals to complex repair and regeneration of tissues. These mechanisms can also be applied to screen natural or synthetic compounds and unravel new classes of radioprotective agents, eventually with better tolerance and wider applications.

Exposure to ionizing radiation causes damages to various cellular organelles and components in particular DNA, mitochondria and cellular membrane (Fig. 1). This produces sequential molecular events that culminate either in the repair of the damage or sustaining genomic instability or cell death. At the level of tissues, organs and the total body, the consequence of radiation exposure may be recovery or the manifestation of early and delayed injuries such as acute and late tissues reactions, radiation sickness, sterility, hereditary effects and cancer. From a radiation protection point of view, the effects are classified as either deterministic (tissue reactions) requiring a threshold dose to manifest, or stochastic, not depending on such a threshold but its probability increases with increasing radiation doses. While deterministic effects results from cell killing or the loss of cellular function, stochastic effects are random, and caused by genetic aberrations and mutations which may trigger long term hereditary effects and cancer.

Ionizing radiation interacts with biological targets either through direct effects on cellular molecules or indirectly via the free radicals generated from the radiolysis of water (Fig. 2) [7]. The latter produces different harmful free radicals and compounds such as hydroxyl radical (·OH), H·, H_2 and H_2O_2. The hydroxyl radical (·OH) is the most notorious and causes the utmost damage to the cell. One of the primary events during radiation exposure is activation of antioxidant enzymes. The superoxide dismutase (I/II) converts superoxide (O_2^-) produced during irradiation and metabolic activity of cells to hydrogen peroxides (H_2O_2) and later to water and oxygen by catalase and glutathione peroxidase. The hydrogen peroxides produced in the nucleus and mitochondria are released to cytoplasm [8]. In biological system, oxidation of biomolecules produces alkyl (R·), peroxyl (ROO·) and peroxynitrite anion ($ONOO^-$) radicals. Further hydrogen peroxides are

Download English Version:

https://daneshyari.com/en/article/8524582

Download Persian Version:

https://daneshyari.com/article/8524582

Daneshyari.com