Review

Dose-Response:
An International Journal
Vol. 23(3): 1-18

DOI: 10.1177/15593258251360051
journals.sagepub.com/home/dos
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Adaptive Response: A Scoping Review of Its Implications in Medicine, Space Exploration, and Beyond

Abolfazl Kanani[1,2,*], Julianna Krasowska[3,*], Krzysztof W. Fornalski[3], Joseph John Bevelacqua[4], James Welsh[5,6], and SMJ Mortazavi[2,7]

Abstract

Objectives: Radiation Adaptive Response (AR) is a biological phenomenon in which exposure to low-dose radiation (LDR) enhances an organism's ability to withstand subsequent higher doses. This scoping review explores AR across multiple disciplines, summarizing evidence, identifying research gaps, and evaluating potential applications in cancer therapy, neurodegenerative disease management, space medicine, and pandemic response.

Methods: A comprehensive review of experimental/clinical studies on AR was conducted, focusing on molecular mechanisms, biological implications, biophysical modeling, and translational applications.

Results: In oncology, AR has shown promise in selectively protecting normal tissues during radiotherapy while sensitizing tumor cells, yet its effects remain cell-type dependent. LDR may manage neurodegenerative diseases by modulating oxidative stress and inflammation. In space medicine, AR-based astronaut selection has been proposed as a novel strategy to mitigate radiation risks during long-term space missions, although empirical validation is lacking. LDR therapy for managing COVID-19 pneumonia has been explored, but ethical concerns and long-term safety risks require further investigation.

Conclusion: Despite AR's potential, its clinical and spaceflight implementation requires mechanistic elucidation, standardized protocols, and rigorous studies. The risks of tumorigenesis, individual variability in AR, and potential immunomodulatory effects must be evaluated before widespread application. Moreover, inconsistent AR appearance complicates its study and clinical use.

Keywords

adaptive response, low-dose, space, cancer therapy, COVID-19

Received: March 18, 2025; accepted: July 1, 2025

[1] Pardis Cancer Research Center, Pardis Cancer Institute, Shiraz, Iran
[2] Ionizing and Non-Ionizing Radiation Protection Research Center (INIRPRC), Shiraz University of Medical Sciences, Shiraz, Iran
[3] Faculty of Physics, Warsaw University of Technology, Poland
[4] Bevelacqua Resources, Richland, WA, USA
[5] Department of Radiation Oncology, Edward Hines Jr VA Hospital, Hines, IL, USA
[6] Department of Radiation Oncology, Loyola University Stritch School of Medicine, Chicago, USA
[7] Department of Medical Physics and Engineering, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

*Abolfazl Kanani, and Julianna Krasowska have equally contributed to this work

Corresponding Authors:
James Welsh, Department of Radiation Oncology, Edward Hines Jr VA Hospital, Hines, IL, United States; Department of Radiation Oncology, Loyola University Stritch School of Medicine, Chicago, United States.
Email: shermanwelsh@gmail.com

SMJ Mortazavi, Ionizing and Non-Ionizing Radiation Protection Research Center (INIRPRC), Shiraz University of Medical Sciences, Shiraz 7134845794, Iran.
Email: mortazavismj@gmail.com

Introduction

All living things are susceptible to various chemical and physical factors that can damage their deoxyribonucleic acid (DNA). These agents can be either natural or human-made. Some examples of these factors are solar ultraviolet light, ionizing and non-ionizing radiation, and chemicals. However, organisms have developed a range of defensive mechanisms to reduce or cancel these harmful damages. The phenomenon known as adaptive response (AR), represents a specific mechanism of protection.[1] This effect is seen in numerous (though not all) radiobiological experiments that demonstrate a decrease in the frequency of lesions, mutations, or even mortality in the irradiated exposed cells or species.[2,3] AR is viewed as a particular instance of the broader phenomenon known as hormesis, which involves a biphasic dose–response pattern where low levels of stressors elicit beneficial effects, whereas higher levels cause harm.[4,5] While AR specifically emphasizes the protective effect of a low initial exposure, preparing the system for a later challenge, hormesis encompasses a broader range of positive low-dose responses across diverse biological contexts. Thus, AR can be understood as a distinct subset within the wider concept of hormesis.

A specific type of AR is a radiation adaptive response (RAR), which describes a biological process that occurs when an organism is exposed to low doses of ionizing[6] or non-ionizing radiation.[7] In this process, the organism activates a defense mechanism that enables it to enhance its ability to repair DNA damage, reduce DNA mutation, and tolerate it for higher doses in the future.[2,8,9] RAR can be manifested in different experimental scenarios, but the most popular and the easiest one is the so-called priming dose effect (called Raper-Yonezawa effect). In this scenario, the first small dose (called adapting, priming or conditioning[10,11] dose (AR, PD or CD)) activates the RAR mechanisms, which are active when the potential high dose would appear (called challenge dose (CD)). RAR usually occurs after a specific time interval between PD and CD,[12] so this is generally a time and dose-dependent effect. Another possible RAR manifestation is the constant dose-rate irradiation where adaptive signals saturate after a certain period of time.[13]

It has been reported that different physical and chemical substances can induce RAR in a variety of organisms, from bacteria[14] to human cells.[15-18] To precisely measure this response, different biological indicators (end-points) were assessed, including DNA damage, chromosomal abnormalities, cell viability, survival rates, and mutation rates. It is now being investigated whether AR could be used for radiation protection and cancer treatment, especially in radiotherapy.[19] This investigation is of crucial importance because it was estimated that RAR is manifested in approximately 50–78% cases of priming-challenging dose scenario[18] and only in 45% of constant dose-rate populational studies of RAR.[13] Therefore, the RAR phenomenon is still not fully understood because we do not know when exactly it is manifested and under what circumstances. If we learned how to trigger and control adaptation precisely, AR could fundamentally transform our interaction with the world around us.[20] Therefore, the presented paper attempts to explore the potential horizons of AR mechanisms within several fields of modern-day life.

Methods

Study Design

This scoping review has been conducted in line with the framework established by Arksey and O'Malley.[21]This study aims to explore the concept of RAR and its implications across various fields, including oncology, neurodegenerative disease management, space medicine, and pandemic response. The review seeks to map existing literature, summarize key findings, and identify gaps in current research rather than conducting a systematic risk-of-bias assessment or meta-analysis. Furthermore, the discussion on RAR modeling is informed by several newly published theoretical descriptions of RAR.

Search Strategy

A structured literature search was conducted using PubMed, Scopus, Web of Science, and Google Scholar to retrieve peer-reviewed articles, conference proceedings, and relevant reports published up to [September 2024]. The search terms included a combination of:

- General Terms: "adaptive response," "radioadaptive response," "low-dose radiation"
- Oncology & Radiotherapy: "low-dose radiation therapy," "cancer radiotherapy," "tumor radioresistance"
- Space Medicine: "adaptive response in space," "radiation protection in astronauts," "cosmic radiation"
- Neurodegeneration: "radiation and Alzheimer's disease," "low-dose radiation neuroprotection"
- Pandemic & Infectious Diseases: "low-dose radiation therapy COVID-19," "adaptive response and immunity"

Additional articles were identified through manual searches of reference lists from key papers and consultation with experts in radiobiology and space medicine.

Inclusion and Exclusion Criteria

Inclusion criteria:

- Studies investigating the biological mechanisms of AR
- Experimental, clinical, and epidemiological studies on AR in oncology, space medicine, neurodegeneration, and infectious diseases
- Theoretical models of AR
- Peer-reviewed articles and authoritative reports in English

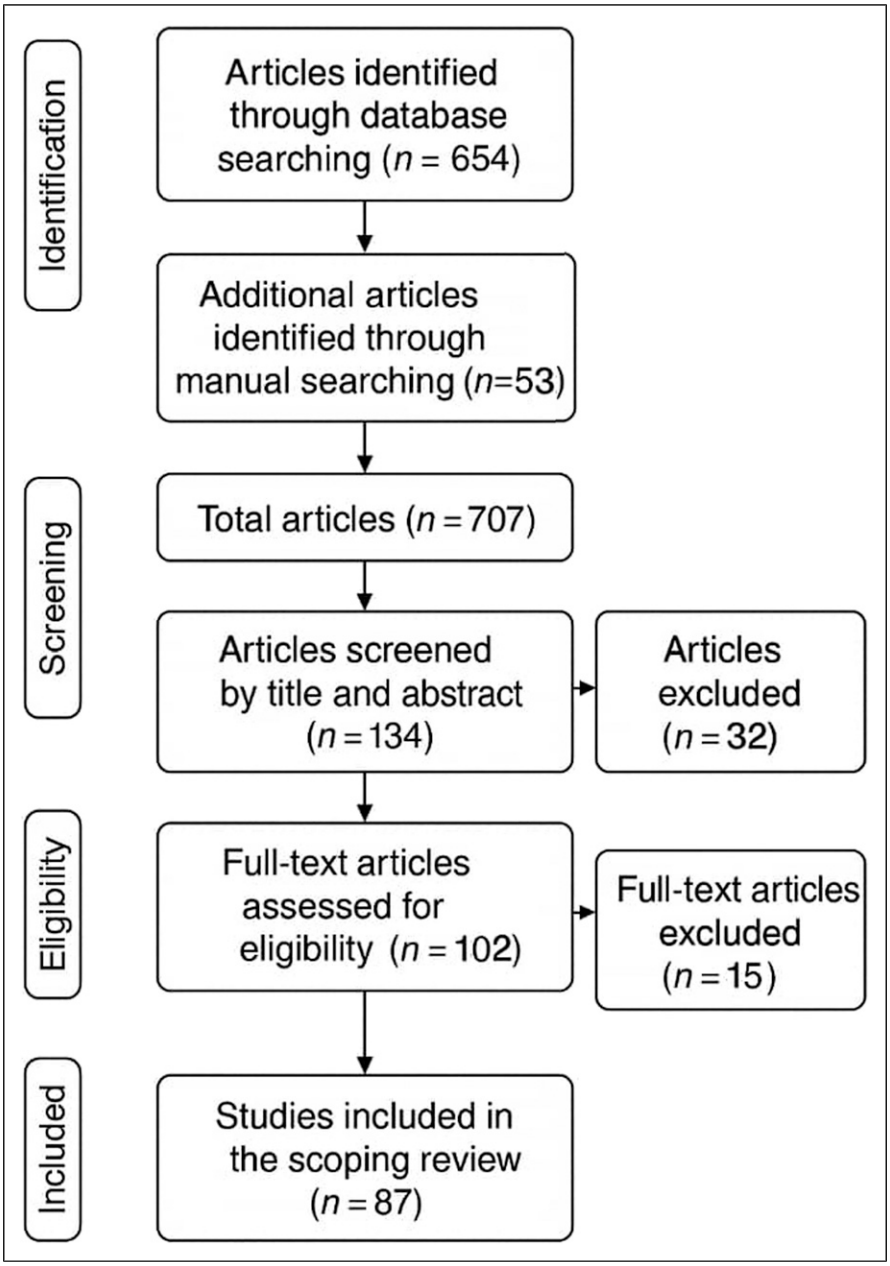

Figure 1. Flow Chart of Article Selection for Scoping Review

Exclusion criteria:

- Studies focusing solely on high-dose radiation effects without discussing AR
- Non-peer-reviewed sources (eg, opinion pieces, blogs)
- Studies with irrelevant exposure conditions (eg, radiotherapy doses exceeding standard AR-inducing levels)

The titles and abstracts of all retrieved records were independently reviewed by two authors to determine their eligibility according to the predefined inclusion and exclusion criteria. Subsequently, the full texts of studies deemed potentially relevant were obtained and thoroughly assessed for final inclusion. Discrepancies between authors were resolved through discussion (Figure 1).

Data Extraction and Synthesis

Key information from each study was extracted by two authors. Extracted data included:

- Study Type: Experimental, clinical, epidemiological, or theoretical modeling
- Exposure Parameters: Radiation dose, dose rate, fractionation scheme

- Biological Effects: DNA repair mechanisms, immune modulation, oxidative stress, cancer progression
- Context of Application: Oncology, space medicine, neurodegenerative disorders, pandemic response
- Study Limitations: Confounding factors, small sample sizes, or contradictory findings

A qualitative synthesis was performed to categorize the findings across different disciplines and highlight key knowledge gaps requiring further investigation.

Limitations of the Review

As a scoping review, this study does not perform a meta-analysis or statistical synthesis of results. The aim is to map the existing evidence without quantitative pooling. Moreover, a formal critical appraisal of the included studies was not conducted, in accordance with the objectives of scoping reviews to map the breadth of evidence rather than evaluate study quality.

Results

An initial search of electronic databases yielded 654 records, with an additional 53 identified through manual searching and reference screening. Following the removal of duplicates, 456 unique records were screened by title and abstract. Of these, 134 full-text articles were reviewed for eligibility, resulting in the inclusion of 87 studies in the final scoping review. A detailed summary of the selection process is presented in the PRISMA flow diagram (Figure 1). Most of the included studies were published in English and came from diverse global regions.

RAR in the Treatment of Cancer Patients

Differential RAR in Normal and Tumor Cells. The application of RAR in radiation risk analysis gradually opens up new horizons and possibilities for treating cancer patients. Several studies have been conducted on healthy and tumoral cells in recent years. A majority of these investigations have shown that cancer cells and healthy tissues respond differently to low-dose radiation (LDR).[22-26] The occurrence or absence of the AR phenomenon has been investigated for various types of healthy and tumor cell lines. Zhao et al[22] demonstrated that a 75 mGy of X-ray irradiation of the LDR cannot induce AR in colon cancer cells or stem cells for a CD of 4 Gy or 10 Gy. Wang et al showed that LDR cannot induce AR in human gastric SGC7901 cells. They concluded that 75 mGy X-ray radiation did not affect ATM mRNA expression.[27] Jiang et al revealed that exposure to 75 mGy of X-ray does not induce AR in four cancer cell lines (two human leukemia cells and two human tumor cell lines) for a CD of 4 Gy. In contrast, AR was detected in the normal cells (human fibroblast cells).[23] Li et al found that a 150 mGy LDR stimulated the proliferation of MDA-MB-231 breast cancer cells without affecting the normal breast cells Hs 578Bst. They also suggested that the p53 status could be the most probable cause of the different responses of LDR on breast tumor cells and normal breast cells.[26] Farhadi et al[28] reported a noticeable difference in AR induction and repair of DNA double-strand break between normal and human lung carcinoma cell lines following 75 mGy LDR irradiation. LDR appears to stimulate the immune system and promote the proliferation of healthy cells,[29] although the same effects disappear in some cancer cell types.[30]

Nevertheless, some documentation does not support the distinction between normal and tumor cells. The results of Wang et al prove that LDR at 50 and 200 mGy X-ray can induce AR before 20 Gy in A549 lung cancer cells. Authors identified sixteen differently expressed miRNAs that may be crucial in AR of LDR.[31] They claimed that the different results for normal and tumor cell lines could be due to the other effective CD in the previous experiments (eg, the study by Jiang et al.[23]). Moreover, the LDR is thought to depend on the specific cell type being studied. Abdelrazek et al, conducted a study on healthy rat's livers and found no AR after 100 mGy whole-body LDR irradiation with X-rays before a CD of 2 Gy.[32] In one appealing study, Grdina et al[33] investigated the potential of computerized tomography in image-guided radiotherapy to induce AR in human colorectal carcinoma cells. They reported that cells exposed to a 100 mGy LDR increased cell survival from 5% to 20% compared to cells not exposed to a 100 mGy LDR before a CD of 2 Gy (conventional dose in fractionated radiotherapy (RT)). They claimed the timing of LDR is critical to the induction of AR and recommended imaging procedures as close in time to the 2 Gy dose in a conventional fractionated RT. The authors stated that the number of treatments would magnify such AR and overall tumor cell survival.

RAR and its Implication in Radiotherapy. A dedicated and separate analysis should be devoted to the extensive review on RAR for cancer, which was performed by Thathamangalam Ananthanarayanan et al.[34] The authors discuss that radiotherapy remains a key treatment modality for cancer, utilizing ionizing radiation to induce cell death through mechanisms such as apoptosis, necrosis, mitotic catastrophe, and senescence.[8] All studies reviewed carefully by the authors indicate that RAR can contribute to increased tumor cell survival, potentially reducing the efficacy of radiotherapy. This effect is particularly relevant in fractionated radiotherapy, where repeated radiation doses may induce adaptive responses and enhance radioresistance.[35,36]

For example, experiments with lung cancer H460 cells demonstrated that exposure to a low priming dose of 0.05 Gy followed by a therapeutic dose of 2 Gy led to a 12.6% increase in cell survival, suggesting the activation of repair and proliferative mechanisms that may compromise treatment efficacy.[37] Conversely, studies on prostate cancer (DU-145) and

leukemia (H-460) cells have shown no significant alteration in survival after similar pre-exposure, highlighting variability across different tumor types.[38]

Thathamangalam Ananthanarayanan et al[34] mentioned that RAR in tumor cells is driven by intricate interactions between DNA repair pathways, cell cycle regulation, and oxidative stress responses. A key factor is the reduction in reactive oxygen species (ROS) production, leading to enhanced DNA repair and increased cellular survival.[9,30] Moreover, activation of hypoxia-related pathways and differential gene expression further contribute to tumor radioresistance.[39]

To counteract the negative effects of RAR in cancer therapy, several strategies have been proposed:

- Enhancing radiation-induced stress to overwhelm adaptive mechanisms in tumor cells[40];
- Targeting key signaling pathways involved in DNA repair and survival, such as ATM/ATR, PARP, and PI3K[41];
- Personalized therapy approaches, including monitoring biomarkers in liquid biopsies before, during, and after treatment to assess RIAR dynamics and optimize therapeutic strategies.[42]

Thathamangalam Ananthanarayanan et al,[34] concluded that RAR has significant implications for radiotherapy, both in protecting normal tissues and potentially fostering tumor radioresistance. While it may help mitigate radiation damage in healthy cells, it can also enhance the survival of malignant cells. Current research focuses on identifying molecular targets and therapeutic strategies to modulate RAR in a way that improves cancer treatment efficacy. A deeper understanding of RAR mechanisms and their modulation may contribute to more effective and personalized cancer radiotherapy protocols.[43,44]

Therapeutic Strategies. In addition to the role of AR in RT, recent experimental and epidemiological data have suggested that AR caused by whole- or half-body exposure to LDR can be used as an immunotherapeutic option for patients with systemic cancers.[45] Interestingly, LDR before chemotherapy could properly prevents chemotherapy-induced cardiotoxicity by enhancing adaptive immune response and other mechanisms.[46] In a new perspective, Welsh et al[47] introduced the "abscopal effect" induced by LDR as a critical factor in boosting the immune system and inducing anticancer response in metastatic malignant lesions. A combination of mild dietary restriction, AR, and other cancer treatments (eg, chemotherapy) have been suggested as a novel strategy to enhance the treatment efficacy and reduce side effects from cancer radiotherapy.[48]

LDR-induced AR involves activating multiple signaling pathways that require further investigation.[49] Some studies indicate that the cells respond to ionizing radiation by activating genes involved in DNA repair, stress response, cell cycle regulation, and apoptosis. LDR can stimulate antioxidative functions, activate DNA repair systems, and alter metabolic processes in normal cells.[50] Future research will be crucial to identify factors contributing to this subject. There still needs to be a consensus guide on this matter, and inconsistent results remain. However, LDR can potentially enhance the effects of cancer therapeutics.[50] Finding a way to stimulate and activate AR in normal cells while inhibiting or blocking any AR induction in cancer cells is vital. This approach could improve or complement conventional cancer treatments for patients. Additionally, we need to consider other effects induced by LDR, such as bystander effects, hyperradiosensitivity, induced radioresistance, and other inherent repair mechanisms.[47,50] Fortunately, many radiation oncology centers can administer LDR treatment. Therefore, it should be considered for future exploration in clinical settings. Different ARs for each cell type, organ, and each individual should be considered for the appropriate clinical setting.[26,48,51]

Attempts to account for the occurrence of RAR in radiotherapy will require careful analysis of patient cells. In their work, Schaffer et al[52] conducted a study on bladder epithelial cells, and their results demonstrated that the same doses can induce radioresistance for a healthy cell line and radiosensitivity for cancer cells. Careful analysis of the cells' characteristics may make it possible not only to determine the indication, or lack thereof, for radiotherapy treatment but also to determine an irradiation scheme that better protects healthy tissues and, at the same time, increases the radiosensitivity of the cancerous cells.

Imprint of AR in the Management of Coronavirus Pneumonia

The first use of low-dose radiation therapy (LDRT) for the management of the COVID-19 pandemic was Ghadimi-Moghadam et al.[53] The suggested recommendation entails a modified approach that involves administering a single dose of 100, 180, or 250 mGy X-ray, either delivered locally to the chest or the whole-body. The key advantage of this approach is that it induces an AR mechanism that augments various repair mechanisms. Compared to other treatment protocols utilizing antiviral drugs, the LDR approach does not apply considerable selective pressure on the virus, thus inhibiting virus evolution. This advantage is particularly crucial for RNA viruses, like the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), which has a moderate to high mutation rate, and any antiviral drug treatment would be subjected to a greater degree of selective pressure on the virus.[54] The LDR approach can also effectively modulate excessive inflammatory responses, regulate lymphocyte counts, control bacterial coinfections, and reduce death rates in COVID-19 patients.[53,55]

Several clinical studies were conducted to assess the potential of LDRT as an alternative care for managing various coronavirus patients. Sharma et al carried out a pilot trial to

study the potential clinical efficacy of LDR (700 mGy) in both lungs of ten patients suffering from disease with moderate to severe risk. Nine patients showed complete clinical recovery within 3 to 7 days. There was also no evidence of acute radiation toxicity in patients.[56] In an Indian trial, 25 patients diagnosed with COVID-19 pneumonia were treated with LDRT of 0.5 Gy to the lungs within 10 days of symptom onset and five days of hospitalization. The results revealed that oxygenation improved significantly, along with a reduction in the demand for supplementary oxygen following LDRT. Furthermore, 88% of patients recovered clinically within 10 days after LDRT.[57] A case report has demonstrated promising outcomes with LDRT of 1 Gy to the whole lung, leading to improved ventilatory function and decreased need for oxygen support.[58] The ULTRA-COVID study investigated the LDRT approach in COVID-19 patients who did not show improvement with their standard medical care. Preliminary results for two patients treated with LDRT of 0.8 Gy showed significant clinical and radiological improvement after a single radiation session.[59] According to the Phase I-II Spain trial, the $SatO_2/F_2$ index can significantly improve following LDRT of 1 Gy to the entire lungs.[60] The first experience with LDRT use in Africa also demonstrated promising outcomes in managing severe COVID-19 pneumonia.[61] Mortazavi et al[62] have pointed out the benefits of LDRT in elderly COVID-19 patients and those with genetic risk factors.

Numerous dose ranges and delivery approaches have been investigated. The radiation can be administered in a single dose of between 0.1 to 1 Gy[54,63] or in two doses of between 0.1 to 0.25 Gy or 1 to 1.5 Gy given in two fractions separated by two or three days.[53] The Researchers also explored different LDRT approaches by administering doses to the chest, lungs, and entire body.[62,64] For SARS-COV-2 patients, combining the benefits of LDRT, plasma exchange therapy, and strong antiviral medication was proposed as a more successful treatment approach.[65] Ganesan et al[66] also suggested a combination of LDRT with standard pharmacologic treatments for added clinical benefit. Interestingly, one hypothesis suggests that administering LDRT to the whole body can decrease or inhibit blood clotting by reducing oxidative stress.[67] Heavy-charged particles like C-12 and Fe-56 with optimal energy have also been suggested for developing vaccines for SARS-COV-2.[68] Recently, Reun and Fray proposed an integrated mechanistic model that relies on the radiation-induced nucleoshuttling of the ATM kinase to explain LDRT in medical applications.[69] It is important to note that the single-dose protocols used in many studies differ from the classical AR model, which involves a PD followed by a CD. Moreover, Calabrese et al showed that low-dose radiotherapy effectively relieved inflammation, supporting the hormesis concept. This effect is partly explained by RT-induced polarization of macrophages to an anti-inflammatory M2 phenotype. This framework helps contextualize low-dose radiation's potential in treating inflammatory conditions like COVID-19 pneumonia.

Some conflicting and controversial studies discussed the LDRT for COVID patients. In a systematic review, Kolahdouzan et al reported no discernible impact on the overall survival of COVID-19 patients following whole lung irradiation. Nevertheless, they found a modest improvement in days without intubation.[70] Another study failed to prove any benefit of a whole-lung LDRT in patients with COVID-19.[71] Additionally, some researchers have discussed the potential risks associated with LDRT for lung, breast, and breast cancer as well as circulatory disease following LDRT.[64,72] In management of COVID-19, the rapid progression of COVID-19 restricts the possibility of applying sequential priming and challenge doses, potentially affecting the engagement of traditional AR pathways. The ability of RT machine systems to deliver LDRT, its low cost, wider availability compared to other approaches, and reduced burden on the health care system, encourage scientists to use LDRT as a smart option for treating this pneumonia.[73] Further investigations should be designed to reduce uncertainties in related clinical trials and improve the selection of dose range and delivering schema.

The Role of AR in Deep Space Missions

A variety of challenges await astronauts during their exploration of space. Sometimes, the exploration is long-term and takes several months. These challenges include exposure to different types of space radiation, including protons, neutrons, and heavy ions from galactic cosmic rays (GCR) and solar energetic particles. Additional challenges include experiencing microgravity, substantial environmental changes, situational stress, and dietary adjustments.[73-75] One of the most serious risks for astronauts is exposure to space radiation. This radiation has the potential to increase the risk of cancer, cardiovascular disease, and damage to the central nervous system.[76] Thus, astronauts require robust radiation protection during deep space missions. A physical shielding system has traditionally been considered one of the most critical protections against space radiation. However, even with an efficient mission strategy and passive shielding, astronauts would receive 0.7 ± 0.1 Sv from GCR for even the shortest round-trip.[77] Therefore, we are confronted with insufficient shielding.

The use of radioprotectors was the next appealing option to protect astronauts.[76,78,79] It has been shown that a single dose of vitamin C can act as an antioxidant and a free-radical scavenger after exposure to radiation when administered within 24 hours after exposure.[80] NASA has recently achieved the successful cultivation of vegetables on the International Space Station with the use of the Veggie system.[81] This innovative approach aims to offer astronauts fresh food options and a wider range of diet choices. Therefore, Mortazavi and his colleagues have recommended employing all possible strategies to invigorate astronauts with a vitamin C-rich diet.[75]

In addition, vitamin E has also shown a notable impact in reducing chromosomal aberrations in bone marrow following exposure to gamma radiation.[79]

But again, the AR concept has introduced a new perspective on this issue of modern life that was ignored in some studies.[82] Researchers tried to optimize deep space missions using two approaches based on the AR. The first possible approach is to employ LDR to stimulate AR and subsequently establish a level of protection for future exposure in the space.[83] Some studies provide evidence supporting this idea.[84-86] Buonanno et al[85] confirmed that when normal human fibroblasts were exposed to 200 mGy of 0.05 or 1-GeV protons, it protected the cells against chromosomal damage caused by a subsequent CD of 500 mGy from 1 GeV/u iron ions. Aghajari et al[87] examined the impact of radiofrequency electromagnetic field (RF-EMF) to induce AR on immunomodulation in a mouse model of hindlimb unloading (HU) as a microgravity condition in space. Their research revealed that RF-EMF modulated HU mice by enhancing IL-6 and reducing IL-9.

But the most interesting idea for protecting astronauts comes from the second approach to AR concept, which was first introduced by Mortazavi et al[51] in 2003. They suggested that astronauts with the highest AR levels should be selected to reduce the risk of exposure to space radiation and minimize the requirement for shielding. Their method for screening selected astronauts was based on the following steps[88,89]: (a) Exposing blood samples of each candidate to a PD and then CD; (b) Measuring the level of radioadaptation (eg, chromosome aberration) for each candidate; (c) Determining the magnitude of radioadaptation based on equations by Sihver and Mortazavi[88]; (d) Selecting candidates with a magnitude of radioadaptation; (e) Activating AR due to the GCR during a space mission. Consequently, the selected astronauts will have an increased tolerance to subsequent higher radiation levels in the future.

In addition to astronauts, activation of AR in microbiomes may also play a key role in deep space missions.[90,91] Also, the human microbiome plays an important role in several physiological changes that astronauts undergo during their daily activities.[92] The AR can potentially enhance the microbiome's resistance to several factors, including heat and ultraviolet rays. In the battle of adaptation in space between astronauts and microbiomes, the microbiomes may emerge as the winner.[93] It can result in life-threatening situations due to deadly infections.[94] Therefore, it may be necessary to modify the previous protection strategies. On the other hand, LDR may decrease the likelihood of infection caused by immunosuppression during deep space missions.[95,96] Also, different bacteria can respond differently to LDR.[14] Therefore, we appear to be confronted with a complex problem that requires further investigation to design optimized plans for deep space missions.

In a recent publication, Fornalski[97] has presented a promising approach for modern radiation protection during deep space missions that could enhance astronauts' health following chronic exposure to relatively low dose rates of ionizing radiation. He has examined the relationship between the appearance of adaptive responses and radiosensitivity (or radioresistance), along with their potential practical applications through a recent straightforward biophysical model of AR[97] (which will be described later).

Moreover, astronauts have exhibited notable telomere length changes during space missions—for example, Scott Kelly experienced telomere elongation while in space, followed by rapid shortening after returning to Earth.[98] These effects may result from unique space-related conditions such as microgravity, oxidative stress, and elevated radiation exposure, particularly during spacewalks where radiation dose and quality differ significantly. Such findings imply that space-specific environmental factors, including radiation characteristics and dose rate, may influence the activation or limitation of adaptive responses.[99]

Due to the easy access to the sources and the frequent use in medicine, most studies are conducted for photon radiation. However, in the work of Vares et al, it was shown that in vitro AR induced by X-rays. A priming dose can also protect against heavy ion radiation. A decreasing AR mutation frequency was observed for carbon and neon ions for different LET values of challenging doses.[100] Moreover, AR may not only protect against heavy ion radiation but can also be induced by it. In the case of heavy-ion PD, the difference in mutation frequency between primed and unprimed cells was smaller for heavy ions than for X-rays, but it was still observable in some cases.[101] These observations may be particularly relevant for space missions.

Practical Guidelines for Implementing AR in Space

Phase I: In Vitro Testing Prior to Launch. Based on a detailed preflight protocol, blood samples from astronaut candidates are exposed to low-dose radiation (LDR) (eg, a few centigrays) followed by high-dose radiation (HDR) (eg, 1-2 Gy). This is done to measure chromosomal aberrations or DNA damage levels and assess the magnitude of the induced adaptive response in each individual.[51,91] The astronauts showing the strongest AR (ie, the least chromosomal damage or DNA damage after HDR) would be selected for missions (Figure 2).

Phase II: Adaptive Response in Space. After selection, the astronauts would be exposed to chronic galactic cosmic rays (GCR) during space missions, which would further enhance their AR. If a solar particle event (SPE) occurs—a sudden and significant radiation event—the astronauts with the highest AR would theoretically be more resilient and better able to tolerate the effects with minimal health impact.[51,94,102]

Justification for High-Cost Missions: The paper emphasizes that this strategy is crucial for ensuring the success of extremely expensive space missions (eg, deep space exploration) that may cost trillions of dollars. By selecting

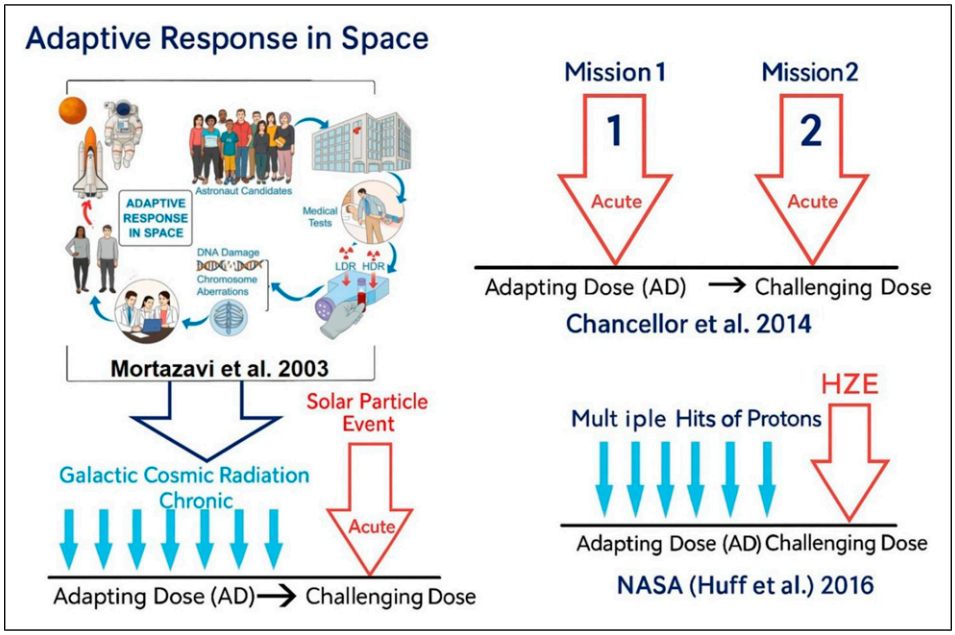

Figure 2. Based on the Model Developed by Mortazavi et al, Astronaut Candidates' Blood Samples are Exposed to Low-Dose (LDR) and High-Dose Radiation (HDR) to Assess Chromosomal or DNA Damage and Measure Adaptive Response (AR). Candidates With the Strongest AR (Least Damage) are Selected. Selected Astronauts Exposed to Galactic Cosmic Rays (GCR) During Missions Enhance Their AR. During Solar Particle Events (SPEs), Those With the Highest AR are Expected to Better Withstand Radiation With Minimal Health Impacts. NASA and Chancellor Have Developed Alternative Models[51,94,102] (Adapted From References[51,88,89])

astronauts with higher AR, the risk of adverse health effects from radiation exposure is minimized, maximizing the chances of mission success and astronaut survival.[51,94,102] Please note that up to the recent biophysical models, the strength of AR is strictly correlated with individual radiosensitivity.[13,103]

The Indispensable Impact of AR on Residents of High Background Radiation Areas

The world's population receives an average annual effective dose of about 3 mSv. Over 80% (2.4 mSv) of the radiation exposure originates from natural sources, while about 20% (0.8 mSv) is attributed to human-made sources.[104] However, some high background natural radiation areas (HBNRAs) are distributed across our planet, where residents are exposed to radiation levels up to 200 times higher than those in normal background radiation areas (NBRAs).[105] Some of the HBNRAs include Ramsar (Iran),[106-108] Guarapari (Brazil),[109] Kerela and Orissa (India),[110] Yangjiang (China),[111] and Mamuju (Indonesia).[112] For instance, the natural radiation levels in Ramsar can reach up to 260 mGy y^{-1}[113].

At first glance, we anticipate observing the indisputable effects of exposure to high levels of ionizing radiation. However, HBNRAs provide intriguing clinical and laboratory findings for radiation scientists.

Mortazavi et al conducted a small-scale study on lung cancer mortality in Ramsar, focusing on both HBNRA and NBRA. They proved that the NBRA had the highest mortality rate for lung cancer, whereas the HBNRA had the lowest rate of mortality.[114] Also, most local physicians in Ramsar did not report any increase in cancer incidence rate for HBNRA inhabitants.[113] Taeb et al[106] performed a study that demonstrated the substantial alteration in Cyfra21, CEA, and Tag72 tumor marker levels due to chronic exposure to high background radiation. Residents of the HBRA, despite being exposed to elevated radiation levels, generally exhibited good health and notable alterations in molecular processes, particularly in the expression levels of HIF-1a and NF-KB. Whether these changes represent a beneficial adaptive response remains unclear, warranting further investigation.[115] Bakhtiari et al[116] observed a remarkable increase in the expression of MLH1 among individuals residing in HBNRA in Ramsar. Furthermore, they reported an association between the expression of MLH1 and MSH2 genes in both males and females. The presence of the MLH1 and MSH2 genes in the repairing complexes of the mismatch repair system proves the activation of the mismatch repair system as a reaction to high background radiation. This activation may explain the occurrence of AR and reduced incidence of cancer in the residents of HBNRA. Talebian et al[115] investigated the HIF-1a and NF-KB expression in residents of HBNRA for different genders and residency duration. The study found that both genes exhibited different expression levels in the HBNRA than the NBRA. Specifically, HIF-a was down-regulated and NF-kB was over-expressed among residents of HBNRA. These findings provide further evidence for the involvement of

the AR phenomenon in the inhabitants of HBNRA. The presence of a link between chromosomal abnormalities in HBNRAs and NBRAs can also support the AR mechanism in HBNRA's inhabitants.[6,107,117,118]

In addition to Ramsar, comparable outcomes were documented for other HBRNAs. In a study conducted in China, Zhang et al[119] found that the reduced receptor expression for advanced glycation end products and S100A6 might be linked with AR and lower cancer mortality in an HNBRA. Hayata et al[120] did not report a statistically significant increase in the occurrence of chromosome aberration among the HBNRA residents. Zou et al[111] did not report any significant difference in cancer mortality rates between the residents of HBNRA and NBRA. Das and Karuppasamy[121] found no notable difference in the frequency of chromosome aberration in the blood samples of infants from HBNRAs of the Kerala coast in India and NBRAs. In another study, Das et al,[122] conducted a study on the telomere length (a cancer biomarker) of the residents of Kerala. They found no remarkable effect on the telomere length of the HBNRA's residents. However, there is limited research to support the evidence for increasing the frequency of chromosome aberration.[123] It is interesting to note that Berkely findings appear to assist us in explaining the rate of cancer mortality in HNBRAs.[124] Their findings showed that most mice exposed to LDR did not show an increased risk of cancer.[125]

Recently, Bugała and Fornalski have used their existing biophysical model for the radiation adaptive response to HNBRAs, specifically calibrated for scenarios involving constant dose-rate irradiation. This calibration utilized data from residents in various high-background radiation areas, including Ramsar in Iran, Kerala in India, and Yangjiang in China.[13] The research focused on specific outcomes such as chromosomal aberrations, cancer incidence, and cancer mortality. Among the publications examined, approximately 45% indicated the presence of an adaptive response in relation to chromosomal aberrations. On the contrary, 55% of studies exhibit no AR. But, the average reduction of chromosomal aberration observed in these 45% AR studies was about 10%. In terms of cancer incidence, the reduction was approximately 15%, while cancer mortality showed a reduction of around 17%, with these figures reflecting only those results that demonstrated an adaptive response. For the remaining 55% of studies on chromosomal aberrations, the results were evaluated against the linear no-threshold (LNT) hypothesis, but findings were found to be inconsistent with the linear model.[13] Jaworowski[126] (2010) provides a historical account of the adoption of the LNT model and the exclusion of radiation hormesis from risk assessment frameworks.

Further epidemiological and radiobiological investigations are vital to provide a more comprehensive understanding of the association between sex, age, and residency duration with AR phenomenon in the residents of HBNRAs. Moreover, generalizing animal studies to human situations necessitates implementing some studies that consider all potential confounding factors.

The Potential Function of AR in the Management of Neurodegenerative Diseases

Recently, Cuttler et al reported a notable improvement in the condition of an 81-year-old patient with the final stages of advanced Alzheimer's disease (AD).[127,128] This improvement occurred after the patient received five computed tomography brain scans, each with a dose of about 40 mGy, over three months. Based on this case, they carried out a pilot clinical trial to explore the advantages of LDR in four patients with severe AD.[129] They recorded impressive progress in cognitive function and behavior for three patients. In addition, they documented a small improvement in the patient's visual and hearing capability.[130] This treatment seems to be caused by the AR induced by X-ray radiation. Kim et al[131] examined the effect of LDRT on five patients with mild to moderate AD in the same pilot trial. The LDRT was administered six times at 0.5 Gy each. One patient was found with a temporary improvement. Yang et al[132] conducted an animal study demonstrating that LDRT can relieve cognitive deficits and inhibit the buildup of amyloid plaques by controlling neuroinflammation in the late AD stage. Some studies currently support the potential use of LDRT as a therapeutic approach for AD patients.[133] Two interesting investigations have demonstrated the protective role of non-ionizing radiofrequency radiation against cognitive impairment associated with AD.[134,135] The mechanism behind these improvements is not fully understood. However, Bevelacqua and Mortazavi[136] attempted to discuss the mechanisms of this phenomenon in an article. They believed that the repair mechanisms activated by AR battle the biological damage caused by AD. This opens up novel treatment options for other neurodegenerative disorders, such as Parkinson's disease. In a mouse model, the LDRT was administered in a total dose of 1.5 Gy in 0.25 Gy fractions once a week before inducing Parkinsonism.[137] The outcomes showed that LDRT can reduce induced oxidative stress while enhancing glutathione levels and quinone oxidoreductase activity.

Despite the promising outcomes of the LDRT for managing neurodegenerative disorders, various complex issues must be addressed.[138] Before converting it to a standard strategy, we should explore an appropriate dose administration protocol and patient eligibility criteria. Furthermore, several comprehensive and long-term studies should be designed to determine potential side effects.

Modeling of the Radiation Adaptive Response

The last 20 years is a period of great development of mathematical and physical methods in AR studies. First comprehensive biomathematical model was created by prof. Ludwig Feinendegen.[139-142] Feinendegen's model of the adaptive response to radiation incorporates the concept of radiation hormesis, which suggests that low

doses of radiation can have beneficial effects, whereas higher doses are harmful. According to his model, the body's response to low-dose radiation exhibits a threshold-like behavior—below a certain dose, radiation can stimulate protective mechanisms at both the cellular and organismal levels. Once this threshold is exceeded, the dose-response relationship becomes linear, as described by the LNT model.

Feinendegen emphasizes the role of biological defense mechanisms triggered by low doses of radiation, including enhanced DNA repair, apoptosis of damaged cells, and other cellular processes that promote genomic stability. A key aspect of his model is the dose-response function, which results from the simultaneous influence of both beneficial and detrimental factors. To illustrate this, Feinendegen uses a hump-shaped curve to describe the adaptive response as a function of radiation dose. Additionally, the time factor is incorporated, with radiation-induced effects considered as a consequence of prior exposure.

Feinendegen also defined cancer risk (R), which represents the probability function of radiation-induced cancer for an individual exposed to ionizing radiation (D)[143,144]:

$$R = P_{ind}D - p_{AR}(D,t)\cdot\left(R_{spo} + P_{ind}D\right) \approx P_{ind}D - p_{AR}\,R_{spo} \quad (1)$$

where $P_{ind}D$ is the linear term (radiation-induced lethal cancer risk), p_{AR} is the dose- and time-dependent probability function of the adaptive response, and R_{spo} represents the spontaneous lifetime cancer risk of the exposed individual.

In this context, one shall mention phenomenological models of cancer risk related to adaptive response by Kino,[145] who introduced several solutions based on purely biomathematical approach.

The first mathematical model describing the effects of the radiation adaptive response in a priming dose scheme (known as the Yonezawa effect or Raper-Yonezawa effect) is the multiparameter, phenomenological model developed by M. Yonezawa and O. Smirnova.[146,147] This model focuses on the impact of ionizing radiation on hematopoiesis—a system essential for the proper functioning of the body. The model categorizes cells based on their developmental stage and the extent of damage they have sustained. It employs a system of multiple differential equations with numerous free parameters derived from experimental data. This approach enables the simulation of both radiation pulses (including exposure following the Raper-Yonezawa scheme) and chronic irradiation at a specific dose rate.

Another model describing the radiation adaptive response in the priming dose (Raper-Yonezawa) approach was developed by G. Esposito and colleagues.[148] This model is based on the Lethal-Potentially Lethal model, a widely used framework in radiation biophysics for describing cellular survival curves. The model evaluates the protective effect of the priming dose depending on the time elapsed since exposure to a low dose while also considering both the dose magnitude and dose rate. It introduces multiple variables, formulated through a system of differential equations, to describe key factors such as the rate of cell repair, the production of free radicals induced by ionizing radiation, and the activity of antioxidant enzymes. To explain the radiation adaptive response, the authors emphasize the enhanced efficiency of DNA repair and the increased production of antioxidant enzymes following exposure to a priming dose.

Professor Nicolas Foray and his team have also researched modeling adaptive response and radiosensitivity, publishing their findings in several scientific papers.[149-152] One of their approaches is based on the radiobiological linear-quadratic (LQ) model, which is commonly used to describe the survival fraction of cell colonies. Foray's model allows for the assessment of the occurrence and extent of the radiation adaptive response by analyzing the number of double-strand DNA breaks and the involvement of ATM (Ataxia-Telangiectasia Mutated) monomers in DNA repair processes. This analysis depends on both the radiation dose received and the time elapsed since exposure. A key premise of the model is its biological interpretability, particularly in explaining:

- The effects of ionizing radiation across a wide dose range,
- The increased radiosensitivity of certain genes due to mutations in cytoplasmic proteins, and
- The phenomenon of hyper-radiosensitivity to low doses of radiation.

The authors propose that ionizing radiation induces oxidation of ATM dimers, which subsequently leads to ATM monomerization at a rate proportional to the absorbed radiation dose. These monomers then diffuse into the cell nucleus, facilitating the recognition of double-strand DNA breaks by phosphorylating histone H2AX (γH2AX) and ultimately enabling DNA repair. Among the double-strand breaks that remain unrepaired, only a fraction contribute to cell death, while the rest are tolerated by the cells. This hypothesis provides a consistent biomathematical and molecular interpretation of the LQ model, considering both recognized but unrepaired breaks and unrecognized breaks as lethal cellular events.

A particularly interesting model, with significant implications for both medicine and the space industry, was recently introduced by Dr Yehoshua Socol and his collaborators.[153] Their primary goal is to describe the time-evolution of an organism's response to radiation using the analogy of a damped oscillator operating in the critical damping regime. The model suggests that an organism's resistance to radiation-induced stress can be significantly enhanced through "radiation training"—a series of short, multiple-dose pulses that help the organism adapt. This approach has the potential to greatly improve the effectiveness of radiation therapy by allowing for higher therapeutic doses, a possibility extensively discussed by the authors.

Several interesting biophysical models, which are strictly related to medical and clinical applications, were published by prof. Bobby Scott. In one of his papers,[154] Scott introduces the HRR (Hormetic Relative Risk) model, which suggests that low doses of radiation can stimulate the body's natural defense mechanisms, leading to a reduced risk of lung cancers, including those associated with smoking. In another paper[155] Scott proposes a new model where the body's protective system is regulated, at least partially, through the epigenetic reprogramming of adaptive-response genes triggered by radiation stress. In other study,[156] Scott explores how small doses of radiation can enhance the body's natural cancer barriers, suggesting that low doses of radiation may lead to the epigenetic activation of adaptive-response genes, resulting in a reduced frequency of mutations below the spontaneous level. These studies highlight the potential health benefits of low-dose radiation, suggesting that such exposure could activate the body's natural defense mechanisms, leading to a reduced risk of cancer and other diseases.

Finally, one shall discuss here the model by Fornalski and Collaborators,[157,158] which has been already mentioned within this article. The model is based on the Feinendegen's approach, where the probability density function of AR appearance is a time- and dose-dependent hunchbacked curve. Here, the authors proposed the form of:

$$p_{AR}(D,t) = \alpha_0 D^2 t^2 \exp(-\alpha_1 D - \alpha_2 t) \tag{2}$$

where D represents the absorbed dose received t time ago, and *"α"* are free parameters. In general, in a situation where multiple doses can be delivered, the total probability function is given by a sum of equation (2) as: $P_{AR} = \sum p_{AR}$. Assuming, that P_{AR} is responsible for DNA lesions (N) repair, and therefore their decrease over time, $dN = - N P_{AR}\, dt$.

In the special case of irradiation scheme with low (LD), priming dose D_1 followed by high (HD), challenging dose D_2 (so called Raper-Yonezawa scheme), we can use the dedicated biological endpoints ($Y_{HD|LD}$), such as eg, mutation frequency, and compare them with endpoints for single high dose scenario (Y_{HD}) using the delta parameter defined as[2]:

$$\delta = 1 - \frac{Y_{HD|LD}}{Y_{HD}} \tag{3}$$

which is a very practical quantity to describe the existence (for $\delta > 0$) of AR and its experimental output. In other words, equation (3) shows that two doses, low + high (priming + challenging), give smaller biological endpoint ($Y_{HD|LD}$) than a single high one (Y_{HD}). The mentioned general end-point, designed here as Y, can be mutation frequency, chromosomal aberrations, cell mortality, comet assay, etc. Of course, in that situation, the low dose of D_1 generates the repair enhancement signal, which decreases N value of lesions over time (T) as:

$$N(T) = N_0\, e^{-\int_0^T P_{AR}\, dt} \tag{4}$$

which can be calculated directly into equation (3).[2] In the case of mutation frequency, $Y \equiv \lim_{T\to\infty} N(T)$, which is the most common biological endpoint in AR analysis.

Analogically, the model can be applied to low constant dose-rate ($\dot{D}$) scenarios, eg, for HNBRAs[13] or cosmic rays,[97] where

$$P_{AR} = \lim_{t\to\infty} \int_0^t p_{AR}(\dot{D},t)\, dt = \alpha_3' \dot{D}^2 \exp(-\alpha_1' \dot{D}) \tag{5}$$

This approach seems to be quite universal because the presented model can be applied to every possible experimental scenario exhibiting AR effect, including several multi-dose irradiation, modular dose-rate, etc.[157]

To conclude, medical and radiobiological experiments of AR are crucial to collect real data and understand the essence of AR effect. However, the last 20 years have shown us that mathematics and physics should join AR research to improve its effects, especially to understand the universality of AR mechanisms and its limitations.

Discussion

It is worth noting that the concept of AR was first proposed initially in the context of chemical exposures.[8] Today, the concept of AR is widely recognized in the radiation field: hundreds of different AR studies have been published so far; many of them were summarized by UNSCEAR.[17,159] However, the significance of its involvement in some domains has been disregarded or has not yet been implemented in practical or clinical settings for various reasons: AR effect is not always presented in dedicated experimental settings,[18] they can be too weak to be significant,[35] or results are inconclusive.[160]

Therefore, this paper aims to review how AR can open up new horizons for addressing the human challenges in modern life while also considering the limitations, requirements, and obstacles ahead.

Mathematical and biophysical modeling seems to be more and more important in AR studies. Especially, the last described model can be used for at least two irradiation schemes. For two doses in the PD - CD scheme, in which the important parameters are the values of the two doses, and the time that will pass between them. The value of the probability of AR occurring, after time t after receiving dose D, is expressed by the equation $p_{AR} \propto D^2 t^2 e^{-\alpha_1 D - \alpha_2 t}$, from which, based on experimental data, the most optimal irradiation schemes for obtaining AR can be determined. The model can also be used for the case of continuous irradiation with a constant dose-rate $\dot{D}$, according to the equation $p_{AR} \propto \dot{D}^2 e^{-\alpha_1' \dot{D}}$. In the case for a constant dose-rate, the AR probability saturates after some time, reaching a maximum value. The model was also analyzed taking into account other intracellular processes and the authors showed that in the section of cases where the adaptive response occurred, it was negligibly small, compared to other processes involved.[35]

Despite numerous studies attempting to clarify the mechanism of AR in different situations, one significant hurdle in the practical use of AR is the need for more understanding of its exact mechanisms, which are under scientific investigation for years.[3] One study reported the active role of base excision repair genes and proteins in AR.[161] Also, the differential activation of Ca^{2+} and NO signaling pathways along mitogen activated protein kinase as well as detoxification response and DNA repair pathways might significantly contribute to the development of AR.[109,162,163] Other researchers have proposed the impact of the immune system and intrinsic radiosensitivity.[164,165] Finally, improving our knowledge of the cellular and molecular mechanisms of AR would enable us to anticipate the individual responses in a specific radiation scenario.

The variability in AR expression across different biological systems suggests the need for personalized radiation treatment approaches. Individual genetic and epigenetic factors likely influence AR induction, and further research should focus on identifying biomarkers that predict AR susceptibility. This could lead to more effective patient stratification in radiotherapy, allowing clinicians to tailor radiation doses to maximize therapeutic benefits while minimizing risks. However, assessing endpoints like chromosomal aberrations or micronuclei which occur at low frequencies, detecting AR or hormetic effects can be challenging. However, experimental designs employing a PD followed by a CD (PD–CD), or leveraging the Raper–Yonezawa effect, enhance the ability to detect such responses. These approaches provide more sensitive and time-efficient alternatives compared to long-term animal studies, making them valuable tools in AR and hormesis research.

Additionally, the impact of AR on non-cancerous diseases remains an underexplored area. Studies have hinted at the potential of AR in mitigating oxidative stress-related diseases, including neurodegenerative disorders such as Alzheimer's and Parkinson's. Investigating the long-term effects of chronic low-dose radiation exposure on the central nervous system could provide valuable insights into novel therapeutic strategies.

In space medicine, while AR-based astronaut selection presents a compelling strategy for radiation risk mitigation, its practical implementation requires further empirical validation. Standardized testing protocols to assess AR levels in prospective astronauts should be developed and integrated into spaceflight health assessments. Moreover, the interactions between space radiation, microgravity, and AR mechanisms need further exploration to understand their combined effects on astronaut physiology.

Moreover, epidemiological data from long-term studies of atomic bomb survivors in Hiroshima and Nagasaki, particularly those exposed to doses between 100 and 200 mGy, reveal no significant increase in health risks. This evidence aligns with the priming dose ranges used in RAR research and provides a valuable historical context supporting the safety and potential clinical relevance of low-dose radiation.[11,166,167]

Finally, ethical considerations surrounding AR application in clinical and environmental settings should not be overlooked. The use of low-dose radiation therapy for disease management must be carefully evaluated to ensure that potential benefits outweigh risks. Regulatory frameworks should be updated to reflect the evolving understanding of AR, providing guidelines for safe and effective implementation in both medical and occupational radiation exposure scenarios.

By addressing these gaps, the field of AR research can move toward practical applications that improve human health and safety in both terrestrial and extraterrestrial environments.

On the other hand, AR is recognized as a specific form of hormesis, which broadly refers to beneficial effects triggered by low levels of various stressors. Whereas AR focuses on the protective outcomes from low-dose radiation preconditioning, hormesis covers a broader spectrum of adaptive reactions seen in diverse biological contexts. Framing AR within hormesis aids in better understanding the mechanisms and importance of low-dose radiation effects on living systems.

This review has several limitations that should be acknowledged. The absence of a meta-analysis or statistical synthesis limits the ability to draw definitive conclusions about effect sizes. Potential publication bias and heterogeneity in experimental protocols across studies may further impact the generalizability and applicability of the findings. Future studies should consider conducting quantitative syntheses and addressing these methodological variations to strengthen the evidence base. The second potential limitation of this review is that the keyword 'hormesis' was not included in the search strategy. Although the review focused specifically on AR, which is generally considered a subset of hormesis, this exclusion may have led to the omission of studies that discuss related low-dose biological effects within the broader hormetic context.

Conclusion

Radiation Adaptive Response as a specific subset of hormesis represents a transformative mechanism with significant potential across various domains, including cancer treatment, neurodegenerative disease management, space exploration, and pandemic response. By leveraging the body's natural ability to enhance resilience through exposure to low-dose radiation, AR opens new possibilities for improving outcomes in radiation therapy, where it can protect healthy cells while selectively targeting cancer cells. The reason for this conclusion is simple: if the adaptive response is strictly dependent on individual radiosensitivity, and cancer cells and healthy cells differ in their radiosensitivity, both will manifest their AR in a completely different way. Furthermore, AR could play a key role in managing neurodegenerative diseases like Alzheimer's and Parkinson's, as early research shows promising results in using LDR to modulate disease progression.

In the context of space exploration, AR offers a novel approach to protecting astronauts from the harmful effects of

space radiation, such as galactic cosmic rays and solar particle events. By screening and selecting astronauts based on their natural AR levels, we can improve radiation tolerance and mission success, significantly reducing health risks during long-term space missions. The application of AR in managing COVID-19 pneumonia demonstrates its broader relevance, particularly in reducing inflammation and complications from viral infections. Finally, the last 20 years showed significant development of AR modeling: its numerical methods, theoretical explanations, and mathematical descriptions. Overall, AR – when well understood and controlled – can offer an innovative and multidisciplinary solution to radiation-related challenges, but further research is needed to fully understand its mechanisms and to optimize its clinical and practical applications in various fields.

ORCID iDs

Abolfazl Kanani https://orcid.org/0000-0003-2002-3587
SMJ Mortazavi https://orcid.org/0000-0003-0139-2774

Author Contributions

S.M.J.M., J.S.W., and K.W.F. conceived the idea and designed the study. A.K. and J.K. conducted the primary analysis. A.K., J.K., K.W.F., J.J.B., and S.M.J.M. contributed to the literature review and the writing and editing of the article. S.M.J.M., K.W.F., and J.S.W. finalized the review. All authors have read and agreed to the published version of the manuscript.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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