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REGULAR ARTICLE

The potential use of biogas producing microorganisms in radiation protection

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Abstract Radiation induced injury is a limiting factor in radiation related approaches from earth to space. Inductions of a wide spectrum of damages in radiotherapy patients due to unwanted normal tissues irradiation and space radiation related diseases in astronauts have been caused many limitations in cancer treatment and space missions. There are many radiation protection/mitigation approaches including: physical, chemical, biological and physiological methods. Radiation protection using these methods is expensive and also has many problems including acute toxicities and difficulties in their targeting to normal tissues. Based on experimental and hypothetical data, showing that medical/biological gases have many protective effects such as antioxidant, anti-inflammatory, anti-apoptotic, and induction of radioresistance, we hypothesize that similar gases which have been produced by microorganisms (biogases) have those properties and may be used as radiation mitigators/protectors in radiation related approaches such as radiotherapy, radiation accidents and in space missions. Isolation microorganism in safe laboratory conditions in enough amounts, finding non-toxic dose of microorganisms that provide highest radioprotection percent, dose reduction factor (DRF) calculation to compare the radioprotective efficacy of the microorganisms, finding the best targeting techniques to deliver those microorganisms into normal tissues, genetically manipulations of microorganism to achieve the highest amount of biogases with lowest side effects can be done for testing the hypothesis.

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Introduction

Radiation injuries and radioprotectors

Radiation induced injury is a limiting factor in radiation related approaches from earth to space. Inductions of a wide spectrum of damages in radiotherapy patients due to unwanted normal tissues irradiation and space radiation related diseases in astronauts have been caused many limitations in cancer treatment and space missions [1–4]. Developments of radiation related damages have led to the conclusion that radiation can result in diminished quality of life and carries the potential for severe debilitating disease.

In radiotherapy, the mechanism of normal tissues injury is very complex and based on dose, manifestation time, volume of irradiated tissue and radiosensitivity can be categorized as acute and late injuries. Speaking generally, interaction of low LET ionizing radiation with normal tissues results in formation of free radicals such as reactive oxygen/nitrogen species (ROS/RNS) that cause oxidative stress and activation of some transcription factors, pro-inflammatory molecules and cytotoxicity by inducing DNA damage, alteration of cell function/phenotype, resulting in chronic inflammation, organ dysfunction, and ultimate fibrosis and/or necrosis [5,6] (Fig. 1).

In the other hand, radiation environment in space is very unique and complex and has three components including: galactic cosmic radiation (GCR), solar particle events (SPE) and trapped energetic particles (TEP). The high LET/charge/energy particles such as protons and Helium from GCR can cause more complex biological effects. In addition to cardiovascular, CNS, hematopoietic and many other diseases, recent evidence show, GCR leads to cognitive impairment and increased Aβ plaque accumulation and so Alzheimer's disease [7–9].

There are different radiation protection/mitigation approaches including: physical, chemical, biological and physiological based methods. The physical approaches such as shielding and technological enhanced radiation delivery is more prominent and new radiotherapy devices and techniques have been developed to have less normal tissue injuries, but those techniques are expensive and have their own problems. In space also, GCR and SPE can penetrate into the shielding material of planet and produce secondary radiation, including neutrons, gamma rays and other radiations. So, additional shielding is required.

In the other hand, many biological and chemical radiation protection/mitigation were suggested. Radioadaptive response by ionizing and non-ionizing radiofrequency radiation [10–12], natural radioprotector agents [13,14], antioxidants materials [15,16], immunomodulatory agents [17,18] and many others were tested and hypothesized as useful radiation counterbalancing tricks [19–23].

In recent years, there has been a hypothetical focus on medical gases as radiation protection agents. In an interesting paper, Schoenfeld et al hypothesized that "hydrogen administration to the astronauts by either inhalation or drinking hydrogen-rich water may potentially yield a novel and feasible preventative/therapeutic strategy to prevent radiation-induced adverse events" [24]. Liu et al also hypothesized that hydrogen therapy may be an effective and specific novel treatment for acute radiation syndrome [25]. The main proposed mechanisms of hydrogen are increase in antioxidant enzymes and reducing free radicals.

In continuing to their hypothetical works, Schoenfeld et al, by reviewing the radiolysis properties of water, biological effects of gas, and radiobiological mechanisms, suggested a systems biology approach that proposed medical gases including CO, H_2, NO, and H_2S as chemical radioprotectors for radical scavenging and as biological signaling molecules for management of the body's response to exposure [26]. According to this paper, medical gases have many beneficial properties such as: radical scavenging, anti-apoptotic, anti-inflammatory and they also can decrease radiosensitivity. We showed the main radiation protection mechanisms of these gases in Fig. 2 briefly.

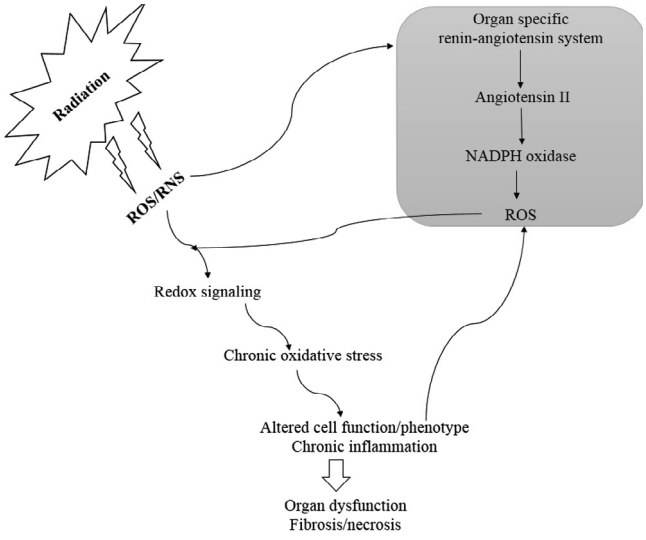

Fig. 1 Putative pathways of chronic oxidative stress resulting in the radiation-induced late effects. Adapted from Zhao et al. with permission (Ref [5]).

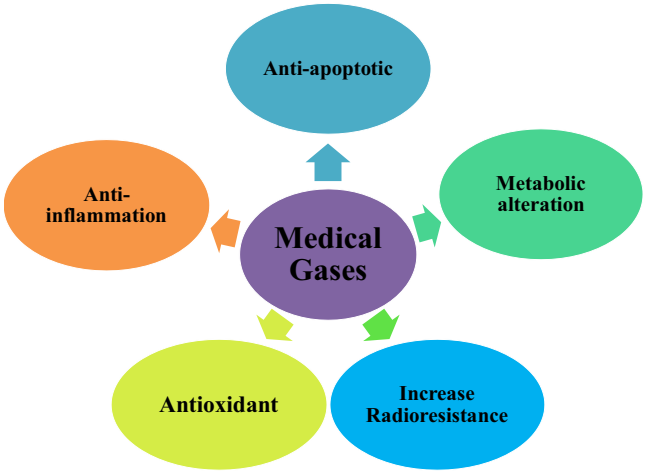

Fig. 2 The main radiation protection mechanisms of medical gases.

Biological gases (Biogases)

It is well established that many microorganisms such as bacteria and archaea produce various gases (biogases) by different mechanisms [27–30]. There are different biogases including: Oxygen (O_2), hydrogen (H_2), nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H_2S). Biogases have complex roles in signal transduction and modulating physiological function based on their rate of production, concentration, chemical reactivity, and availability of target proteins [31].

Biological mechanisms of biogases (here we called them BIONO, $BIOH_2$, BIOCO & $BIOH_2S$) production are not yet fully understood but they occur via a variety of microbial metabolisms, reductive and oxidative processes, biophotolysis, photofermentation, dark fermentation and different unproved mechanisms.

The hypothesis

Based on experimental and hypothetical data, showing that medical/biological gases have many protective effects such as antioxidant, anti-inflammatory, anti-apoptotic, and induction of radioresistance, we hypothesize that similar gases which have been produced by microorganisms (biogases) have those properties and may be used as radiation mitigators/protectors in radiation related approaches such as radiotherapy, radiation accidents and in space missions.

This hypothesis is based on the following items: 1) finding the main microorganisms that produce biogas, 2) production of biogas in well enough amounts, 3) biosafety of microorganisms and their products, 4) finding the best route of administration 5) targeting the microorganisms in normal tissues in radiotherapy and 6) genetic manipulation of those microorganisms for high efficiency.

In regard to item four, route of administration is dependent on sites that biogas should be used. For example, if the treatment site is GI tract, oral, buccal, and rectal administration may be feasible approaches. Also for other sites, targeting microorganisms can be done. The other remedial approach is to earn and separate bacteria from different sites of human body and do an individualized care. For example, we can separate a specific bacteria from a person GI tract and did any required modification on bacteria and again sent into the GI tract.

Also we suggest the following methods to deliver and administrate of bacteria into human body with low immunogenicity:

- Bioengineered bacterial outer membrane vesicles (OMVs) with low immunogenicity [32] that can produce biogas and also deliver biogas to the target. In regard to OMVs, the size of biogas producing bacteria should be smaller than OMVs.
- PEGylation: PEGylation defines the modification of a molecule by the linking of one or more polyethylene glycol (PEG) chains [33]. By PEGylation, we can delivered many biogas producing bacteria via IV route.
- Transdermal delivery using laser, ultrasound, radiofrequency radiation and electroporation [34]. Bacteria can be delivered via these approaches by loading them in a coating material.
- Exosomes: Exosomes are a class of secreted membrane vesicles that carry proteins and RNAs for intercellular communication [35]. They are increasingly seen as drug delivery vehicles that deliver their cargo across the plasma membrane and provide a barrier against premature transformation and elimination. For example human mesenchymal stem cells as the ideal and immunologically inert source of exosomes for drug delivery.

Evaluation of the hypothesis

We recommend the following research directions to test the hypothesis:

1. Isolation and preparation of microorganism in safe laboratory conditions in enough amounts. Irradiation of microorganisms can be used as a powerful approach for enriching biogas-producing bacteria.
2. Performing different invivo and animal studies for finding non-toxic dose of microorganisms that provide highest radioprotection.
3. Injection and targeting of microorganisms into animal bodies, then irradiation of animals by a lethal dose (e.g. LD50/30; the dose of radiation expected to cause death to 50% of an exposed population within 30 days), comparing survival fraction (%) of irradiated groups to control groups. Dose reduction factor (DRF) can be calculated to compare the radioprotective efficacy of the microorganisms.
4. Performing further molecular and cellular investigations to find the best pathways and mechanisms of radiation protection of biogases.
5. Finding the best targeting techniques to deliver those microorganisms into normal tissues. Nanotechnology or cell based drug delivery may be applied.
6. Genetically manipulations of microorganism to achieve the highest amount of biogases with lowest side effects.

Discussion

Radiation protection using different radioprotectors has several problems such as toxicity and targeting. Also, development of new radioprotectors is dependent on enhanced understanding of the molecular mechanisms associated with the development of radiation induced injuries. In this paper we introduced new classes of radioprotectors as ''gas producing microorganism''. A complex microbiological process by many different microorganisms can result to production of biogas, so, knowledge of the microbiology behind the biogas process and microorganisms' functions are required. It is indicated that gas producing organisms have to work closely together and disturbances of this teamwork results in reduced production and breakdown of the biogases [36].

The main properties of biogas as radioprotector are: anti-apoptosis, antioxidants, and anti-inflammation and radioresistance reductions. There are several reports indicating gas producing bacteria in human bodies act as anti-cancer agents [37–39]. For example Murata et al. showed H_2S, a common metabolite of anaerobic oral bacteria, is an anticancer compound that may contribute to the low incidence of oral cancer [40]. Therefore these microorganisms can act as radioprotectors and also as primary and secondary cancer prevention agents. Targeting these agents into normal tissues during radiotherapy may enhance the outcome of treatment and lower normal tissue damages.

One of the main issues regarding this hypothesis is the biosafety of gas producing microorganisms. It is should emphasized that there are many microorganisms such that are available in the human body, but it is important to ensure that those microorganisms not contain pathogens that can damage human tissues. Pretreatment of these living systems with technological techniques is required to have lowest pathology during and after consumption or injection of these organisms.

Most of the gas producing bacteria are best fit for anaerobic conditions. But, human body have sufficient amount of oxygen, in this aerobic environment, we recommend to use of aerobic bacteria or bacteria which are live in both environment (presence or absence of oxygen) to produce biogas. There are many aerobic bacteria that are able to produce biogas such as H_2S, NO and CO_2. We can use these bacteria for radiation protection. For example, *Escherichia coli* is a bacterium that can grow in the absence and presence of oxygen [41]. Also reprogramming of anaerobic bacteria to grow, live and do their action in aerobic condition. This can be done by bioengineering and genetically modification.

It should be mentioned that the suggested microorganisms (e.g. bacteria) for biogas production, are in adaptation with immune system and their residence in the body don't threat the human health. But, microorganism's lifetime varies by type and is dependent to many factors such as reproductive capacity, environment, nutrients and conditions they needs. Also, we can do genetically modification of microorganisms to do their acts in a well-established behavior such as the well enough biogas production, suitable residence time and best generation (cell cycle) time. Another way is to use antibiotics.

The interesting part of this therapy is genetically manipulation of those microorganisms. Biotechno-Microbiological (BIOMIC) studies associated to genetic knowledge can help researchers to find best microorganisms with highest gas efficiency and lowest side effects and also their targeting to place of treatment.

Conclusion

In conclusion, biological gases which produced by microorganism can be used as radioprotectors and also anticancer agents. Further invivo studies are warranted to apply this therapy in radiation related approaches.

Overview Box

First Question: What do we already know about the subject?

Radiation exposure can induce wide spectrum of diseases in radiation related approaches from earth to space. Radiation protection using different radioprotectors has many problems including acute toxicities and difficulties in their targeting to normal tissues.

Second Question: What does your proposed theory add to the current knowledge available, and what benefits does it have?

This hypothesis introduces gas producing microorganisms that might be able to improve radiotherapy outcome and also save astronauts in space missions. The biogases can act as antioxidants, anti-inflammation, anti-apoptosis agents. They also can decrease radiosensitivity.

Third Question: Among numerous available studies, what special further study is proposed for testing the idea?

Isolation microorganism in safe laboratory conditions in enough amounts, finding the best non-toxic dose of microorganisms, finding the best targeting techniques to deliver those microorganisms into normal tissues, genetically manipulations of microorganism to achieve the highest amount of biogases with lowest side effects can be done for testing the hypothesis.

Conflict of interest

The authors declare that they have no conflict of interest.

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