ANTIOXIDANTS & REDOX SIGNALING
Volume 27, Number 9, 2017

DOI: 10.1089/ars.2017.7233

Discoveries

NEWS & VIEWS

Radiation Hormesis: The Link to Nanomolar Hydrogen Peroxide

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Abstract

Hydrogen peroxide (H_2O_2) is a stable product of water radiolysis, occurring at nanomolar concentration upon low-dose ionizing radiation (LDIR) (<100 mGy). In view of the recent recognition of H_2O_2 as a central redox signaling molecule that, likewise, is maintained in the nanomolar range in cells, we propose a role for H_2O_2 in radiation hormesis. LDIR is capable of utilizing known molecular redox master switches such as Nrf2/Keap1 or NF-κB/IκB to effect adaptive resistance. This leads to the hypothesis that, as a normal component of the exposome, LDIR mediates hormetic effects by H_2O_2 signaling. *Antioxid. Redox Signal.* 27, 596–598.

Keywords: oxidative stress, exposome, low-dose radiation, linear no-threshold model, oxidative eustress, hydrogen peroxide

Introduction

OXIDATIVE DAMAGE because of endogenous and exogenous oxidants is a major contributor to instability of DNA. Powerful defense systems have evolved to cope with oxidative stress (6). Although endogenous production during normal aerobic metabolism is the major source of oxidants, the exposure to exogenous sources of oxidant challenge is an inevitable attribute of aerobic life. Interest has focused to a large part on the adverse toxicological aspects associated with high exposure. However, in recent time the research focus has shifted toward the more physiological levels of exposure, to low level and to very low level challenges. Gases that are toxic at high concentration, such as nitric oxide, carbon monoxide, and hydrogen sulfide, are now well established as useful regulators of life processes at low concentration. Adaptive stress responses have evolved and the concept of oxidative stress and oxidative stress responses has seen wide acceptance. Interestingly, however, the research arena was resistant to the idea of accepting evidence for beneficial effects of low-dose ionizing radiation (LDIR) and of the concept of radiation hormesis (3); see Figure 1 for schematic presentation. This may not be surprising in view of potentially detrimental metabolic and genetic alterations, which were observed at low dose and low-dose rate irradiation (8). In this article, we are addressing the question of where the range of oxidant production by LDIR (less than ~100 mGy) registers with respect to the range of normal oxygen metabolites, notably the targeted formation of H_2O_2, which occur at low concentration in endogenous cellular processes.

Innovation

A long-standing unresolved controversy in radiation biology concerns the significance of low doses of ionizing radiation (LDIR) in terms of toxic effects and biological responses: can one extrapolate linearly toward zero exposure (linear no-threshold model), or is there a threshold associated with protective responses (radiation hormesis model)? Recent advances in redox biology revealed a central role for hydrogen peroxide (H_2O_2) in redox regulation. LDIR is considered to contribute to oxidative eustress *via* H_2O_2 signaling. To what extent reactive oxygen species other than H_2O_2 play a significant role in positive or negative biological effects of LDIR needs to be ascertained.

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Hydrogen Peroxide

Hydrogen peroxide (H_2O_2) is now recognized as the major redox metabolite operative in redox sensing, signaling, and redox regulation (5). The overall concentration of H_2O_2 in the normal physiological steady state of metabolism is in the range of 1–10 n*M* in mammals. H_2O_2 is being viewed as a major signal molecule not immediately dependent on transcription, together with calcium ions and ATP, capable of initiating instant cellular effects such as initiation of proliferation (2). The impact of oxidants such as H_2O_2 on mammalian cell proliferation has been studied widely, and maintenance of a low steady-state level of H_2O_2 is being viewed as ''oxidative eustress,'' as physiological oxidative stress, a normal attribute of aerobic metabolism (5).

Low Levels of Oxidants

Exogenous H_2O_2 at low concentration (1 μM H_2O_2) was found to stimulate proliferation of cells in culture. Likewise, LDIR, even in the range of background, was found to stimulate growth of cells in culture (1). Thus, the question arises which concentration of H_2O_2 is generated during LDIR and whether this has an impact on cellular redox signaling. This is of interest in view of an ongoing debate about a threshold *vs*. linear dose–response in radiation biology. The threshold encompasses what is known as ''radiation hormesis'' (7). In view of the evidence for effects of low-level ionizing radiation (3, 8), we here consider the potential link of LDIR to normal H_2O_2-dependent redox metabolism.

Ionizing Radiation-Related Oxidant Generation

The primary products of water radiolysis include several chemical species: e_{aq}^-, $HO^\bullet$, $H^\bullet$, $HO_2^\bullet$, H_3O^+, OH^-, H_2, and H_2O_2. H_2O_2 is formed as one of the stable nonradical species, increasing with the absorbed dose of gamma irradiation. In the dose range between 0 and 1 Gy in water, the slope was about 20 n*M* H_2O_2/Gy (9), that is, the H_2O_2 concentration at 100 mGy is around 2 n*M*.

Using HyPer, a genetically encoded fluorescent reporter protein for H_2O_2, in A549 cells or HEK293 cells, irradiation with 1 Gy X-rays caused a small but robust increase in intracellular H_2O_2. This increase was similar to the signal obtained upon addition of 3 μM extracellular H_2O_2, and it was estimated that the intracellular H_2O_2 concentration upon 1 Gy X-ray irradiation is in the low n*M* range (4).

Calculations based on experimental data result in 1 mGy of low linear energy transfer radiation to cause in the exposed mammalian tissue an elevation of the H_2O_2 concentration by about 0.06 n*M* (L. Feinendegen, unpublished).

Radiation Hormesis: Mechanisms

In the terminology of biological stress, the concepts of adaptive responses and preconditioning include the dose–response relationship of hormesis. Low-dose exposure to stressors is generally associated with a beneficial, positive response, *hic* eustress, whereas high dose entails detrimental, negative response, *hic* distress (Fig. 2). This applies to various types of exposure, summarily described as the exposome, and in the present context to ionizing radiation.

What are the mechanisms effecting the eustress response? These can be roughly divided into immediate transcription-independent responses requiring no *de novo* gene activation and/or protein synthesis, and delayed transcriptional/translational responses associated with the processes of gene activation and protein synthesis, processing, and enzyme activation. The predominant transcription-independent agents are Ca^{2+}, ATP, and H_2O_2 (2), as already mentioned, and $NO^\bullet$ that is synthesized by nitric oxide synthases. These orchestrate immediate responses that, by way of controlled signaling processes, activate preexisting molecular switches that, in turn, activate a battery

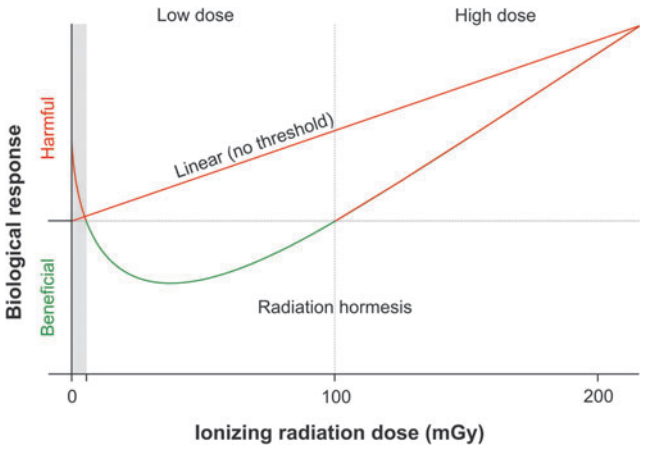

FIG. 1. Schematic presentation of the LNT *versus* hormesis concepts for biological responses upon exposure to ionizing radiation. Transition from high dose to low dose is roughly estimated to occur at ~100 mGy. Beneficial response means protection from potential damage. Ultralow radiation (below background) is indicated by *gray shade* near the origin (drawn not to scale). LNT, linear no-threshold.

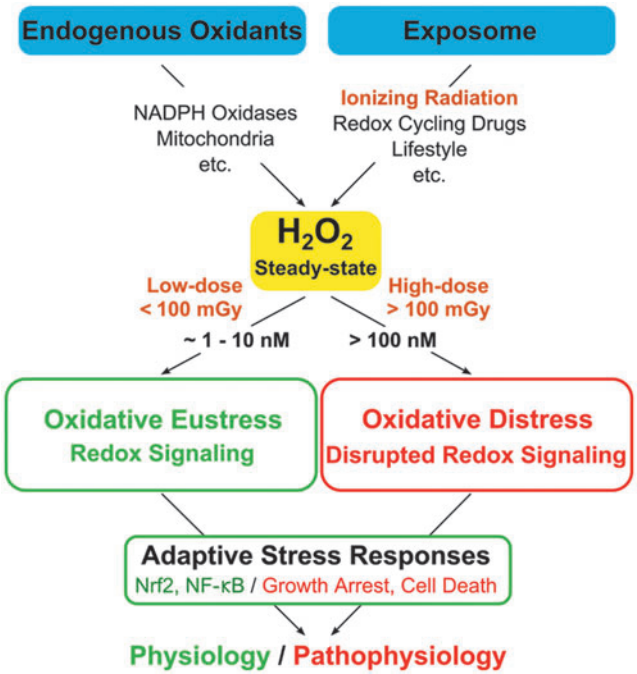

FIG. 2. Contribution of low-dose ionizing radiation to cellular hydrogen peroxide. Up to about 100 mGy, oxidative eustress; higher exposure, oxidative distress. Modified from graphical abstract to Ref. (5), Creative Commons license.

of genes expressing a variety of enzymes useful in the biological response.

Two major such molecular switches in eukaryotes are the Nrf2/Keap1 system and the NF-κB/IκB system (see Fig. 7 in Ref. 6). The master regulator system, Nrf2/Keap1, is activated after exposure to low levels of ionizing radiation. Transcription and translation of heme oxygenase-1, a target gene of Nrf2, were upregulated by a priming dose of radiation. Likewise, NF-κB was shown to mediate adaptive resistance to ionizing radiation.

Ultralow Dose: Below-Background Ionizing Radiation

According to the linear no-threshold (LNT) model, the biological response to ionizing radiation should diminish further when radiation is ultralow, that is, less than background radiation. Interestingly, however, when bacteria were grown at about 400 times less than normal background radiation (gamma dose rate of 0.16 nGy/h), there was a decrease in growth rate, accompanied by upregulation of stress response genes (1). This is contrary to the prediction of the LNT model, suggesting that background ionizing radiation may be used purposefully by biological systems.

Biological Processes and LDIR

The effects of LDIR, observed upon exposure to <100 mGy or to low-dose rate ionizing radiation, vary by animal species, strain, age, sex, organ, cell type, cell metabolism, and cell cycle. Substantial information from cell culture and animal studies has been collected in Refs. (3, 8). In the low-dose rate studies, the accumulated doses were rather high occasionally (8). Classification as ''positive'' or ''negative'' depends on the biological situation and the timeframe considered. Some of the ''positive effects'' after low dose and lose-dose rate exposure are assembled in Refs. (3, 8). The studies include dose-dependent adaptive protection, preconditioning, stress protein induction, diminished chromosome aberrations, diminished incidence of mutations, activation of immune response, suppression of metastasis, prolongation of lifespan, and epigenomic reprogramming. ''Negative effects'' include dose-dependent low dose- and low-dose rate-induced metabolic and gene alterations, which may have the potential of causing or enhancing persistent detrimental processes such as cancer. Also reported were diminished immune response, inhibition of neurogenesis, cataractogenesis, and embryonal malformation (8).

The effects of water radiolysis, which led to n*M* concentration of H_2O_2, entail immediate redox changes and associated oxidative stress responses. To what extent short-lived species, e_{aq}^-, $HO^\bullet$, $H^\bullet$, $HO_2^\bullet$, also contribute to such responses directly or indirectly needs further investigation. It is assumed, however, that because of the stochastic nature at low-dose exposure, such contribution will be minor as compared with the bulk response mounted by H_2O_2-mediated responses. Indeed, at low dose the eustress response tends to be favored over persistent damage (3).

Outlook

Since early evolution, the exposome included cosmic rays, background radiation such as radon, and the products of water radiolysis by ionizing radiation and UV irradiation, notably H_2O_2. DNA and protein damage responses and other oxidative stress responses have, early on, carried the burden of prevention, interception, repair, and damage removal such as by apoptosis and immune stimulation. Importantly, the hormetic nature of the response characteristics calls for increased attention to examine low-dose exposure as a potentially useful means in maintaining life processes over time.

Acknowledgments

H.S. acknowledges support by the National Foundation for Cancer Research (NFCR), Bethesda, MD, USA. Helpful discussion with Wilhelm Stahl is gratefully acknowledged.

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Date of first submission to ARS Central, June 19, 2017; date of final revised submission, July 7, 2017; date of acceptance, July 10, 2017.

Abbreviations Used

IκB = inhibitor of NF-κB
KEAP1 = Kelch-like ECH-associated protein 1
LDIR = low-dose ionizing radiation
LNT = linear no-threshold model
NF-κB = nuclear factor-κB
NRF2 = nuclear factor (erythroid derived 2)-like 2