ROS

REVIEW ARTICLES

Oxidative Stress, a Bridge that Links Radioadaptive Responses Induced by Ionizing Radiation to Those Induced by Non-Ionizing Radiation

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ABSTRACT | The disturbance in the balance between production of reactive oxygen species (ROS) and antioxidant defense mechanisms may cause oxidative stress. Some environmental stimuli such as exposure to ionizing radiation or non-ionizing radiations (e.g., radiofrequency electromagnetic fields emitted from mobile phones and other wireless technologies) can severely disturb this balance. Substantial evidence now indicates that not only exposure to ionizing radiation can start oxidizing events which change the atomic structure by direct interactions of radiation with target macromolecules or via water radiolysis-induced products, non-ionizing radiations may trigger the same events. Radioadaptive response or radiation-induced adaptive response can be defined as the acquisition of radiation resistance against exposure to high levels of radiation in cultured cells or organisms that had been pre-exposed to a priming low dose radiation. The induction of adaptive responses by pre-exposure to ionizing and non-ionizing radiations is well documented by different researchers as well as our team. The induction of adaptive response by non-ionizing radiations, like ionizing radiations, requires a minimum level of damage to trigger this phenomenon. Therefore, ROS play a key role in producing the minimum level of damage that is required for triggering the induction of adaptive response. Current data support this hypothesis that there are similar patterns for induction of adaptive response by ionizing and non-ionizing radiations, and oxidative stress is a bridge that links radioadaptive responses induced by ionizing radiation to those induced by non-ionizing radiation.

KEYWORDS | Adaptive response; Electromagnetic fields; Ionizing radiation; Non-ionizing radiation; Oxidative stress; Reactive oxygen species

ABBREVIATIONS | AR, adaptive response; DOX, doxorubicin; EMFs, electromagnetic fields; HBRAs, high background radiation areas; RF-EMFs, radiofrequency electromagnetic fields; ROS, reactive oxygen species

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CONTENTS

1. INTRODUCTION

The so-called "imbalance" between the production of reactive oxygen species (ROS) and antioxidant defense mechanisms can lead to oxidative stress. This imbalance can be due to environmental stimuli such as exposure to ionizing radiation (e.g., cosmic rays, gamma radiation and medical x-rays) or non-ionizing radiations such as exposure to radiofrequency electromagnetic fields (RF-EMFs) emitted from mobile phones and other wireless technologies [1]. Under normal physiological conditions, the reduction of molecular oxygen in mitochondria can lead to production of ROS, and the excessive ROS production is known to be associated with oxidative damage to proteins, lipids, and DNA [2]. Ionizing radiation, due to production of free radicals, can be hazardous to living organisms [3]. Exposure to ionizing radiation may change the atomic structure by starting oxidizing events either through direct interactions of radiation with target macromolecules or via water radiolysis-induced products. On the other hand, substantial evidence now shows that the imbalance between the production of ROS and the antioxidant defense mechanisms in the tissues can be linked to exposure to non-ionizing RF-EMFs emitted from mobile phones [4–10], Wi-Fi [11–13], radars [14], and other wireless communication tools.

2. IONIZING RADIATION

Currently, there is a controversy over the cellular responses following exposure to low doses of ionizing radiation [15]. Substantial data indicate that exposure to ionizing radiation can lead to the induction of oxidative stress in plants [16], animals [17, 18], and humans [19]. On the other hand, it has been shown that low doses of ionizing radiation may cause some bio-positive effects through preventing oxidative stress [20–22]. As an example, it is believed that oxidative stress has a key role in the pathogenesis of diabetic nephropathy [23]. Some animal studies show that exposure to low dose ionizing radiation can protect kidneys from diabetic nephropathy [23, 24]. Moreover, a study conducted in 2012 demonstrated that occupational exposure of radiology workers to chronic low doses of ionizing radiation could lead to enhanced resistance to oxidative stress [25]. Phan et al. also investigated whether repeated exposures to low dose radiation (computed radiography) could protect animals from the acute effects of a subsequent high dose radiation. Their study showed that repeated computed radiographies had made the animals resistant to high doses of radiation, while a single computed radiography had led to transient genotoxicity, enhanced apoptosis, and features of radiation sensitization [26]. Another study confirming the duality of the effects of ionizing radiation on oxidative stress, is a survey conducted by Pramojanee et al. in 2012. These researchers showed that low doses of radiation (e.g., one periapical radiography) in dental radiography could benefit osteoblastic cells by decreasing ROS formation while high doses of radiation in dental radiographies (e.g., 10 periapical radiographies) impaired the osteoblastic proliferation through a rise in ROS production [15].

Mortazavi et al. have previously published reports on the health effects of exposure to elevated levels of natural ionizing radiation in high background radiation areas (HBRAs) of Ramsar [27–32], including the first report on the induction of adaptive response (AR) in the residents of these areas [33]. Adaptive response can be defined as increased resistance to high doses/levels of either ionizing/non-ionizing radiation or other DNA-damaging agents (e.g., ultraviolet, alkylating agents, oxidants, and heat) after preexposure to low doses of the same agent or other agents mentioned above [34]. It is worth mentioning that Ramsar, a city in northern Iran, has inhabited areas of the highest recorded levels of natural radiation (up to 196 times higher than the normal background) on Earth [35]. The extraordinary levels of natural radiation in HBRAs of Ramsar are due to the

presence of high levels of radium in rocks, soils, and groundwater. The people who live in Ramsar are also exposed to high concentrations of radon in their dwellings (radon levels are up to 31 kBq/m^3 [36] compared to the action level of 148 Bq/m^3 that is suggested by the United States Environmental Protection Agency).

In spite of this challenging finding, Mortazavi et al. have shown that in contrast to life-long exposures, short-term exposure to extremely high levels of natural radiation induces neither survival adaptive response [27] nor oxidative stress [35]. Therefore, Mortazavi and colleagues concluded that the induction of adaptive response as discussed by Dimova et al. may be associated with transcription of numerous genes and activation of different signaling pathways which trigger specific cell defense mechanisms [37].

Adaptive response phenomena may have different applications in various fields. In an early report entitled "Adaptive response studies may help choose astronauts for long-term space travel", that was published in 2003 in "Advances in Space Research", we discussed that the candidates of deep space missions (e.g., manned missions to Mars) can be selected through screening by ground-based in vitro tests before any mission. These tests can identify the individuals who better respond to low doses of ionizing radiation and exhibit the highest levels of adaptive response. In these missions, chronic exposure to space radiation would increase the radiation resistance in astronauts who exhibit high adaptive response to low doses of ionizing radiation and protect them against any solar activities which are unpredictable [38, 39].

3. NON-IONIZING RADIATION

The induction of adaptive response by low levels of non-ionizing radiation is now well documented. Sannino et al. for the first time in 2009 found that when cultured cells were pre-exposed to radiofrequency radiation, an adaptive response which increased the resistance of these cells to mitomycin C could be observed [40]. Later, Mortazavi et al. also found that pre-irradiation of laboratory animals with radiofrequency radiation made them less susceptible to lethal effects of a subsequent high dose ionizing radiation [41, 42]. These findings were further confirmed by reports that were focused on the induction of adaptive response after pre-treatment with microwave radiofrequency radiation [43–47].

Cao and Tong have reported alterations in survival, genetic damage, oxidative stress, and changes in several cellular processes in animals pre-exposed to radiofrequency radiation before exposure to sub-lethal or lethal doses of gamma radiation [48]. The findings led the authors to conclude that the induction of adaptive response could make the animals resistant to subsequent damages [48]. Jin et al. have shown that pre-exposure of laboratory animals to radiofrequency radiation with the frequency of 900 MHz at the power density of 120 μW/cm^2 for 1 hour per day for 14 days had a protective effect in hematopoietic tissues damaged by subsequent high dose gamma irradiation [49]. Based on the findings of Jin et al. [49] as well as the findings obtained in his own studies [42], Mortazavi demonstrated that the "dose window theory" that is well discussed for adaptive responses induced by ionizing radiation, is also valid for non-ionizing radiation. In the experiment performed by Jin et al., the viability of the cells exposed to doxorubicin (DOX) alone was 70.2 ± 0.2% whereas when cells were exposed to 900 MHz RF radiation at 12 μW/cm^2 before treatment with DOX, the viability was 82.8 ± 2.1% ($P < 0.01$). Radiofrequency exposure at higher power densities significantly decreased the viability (60.7 ± 0.5% and 58.6 ± 0.5% for 120 μW/cm^2 and 1200 μW/cm^2, respectively) [50]. It is worth noting that Mitchel has previously discussed the critical role of the window theory in induction of adaptive response—"the adaptive response in mammalian cells and mammals operates within a certain window that can be defined by upper and lower dose thresholds, typically between about 1 and 100 mGy for a single low dose rate exposure" [51].

Adaptive responses induced by non-ionizing radiations also may have important applications in different fields. A recent study performed by our team indicates that when laboratory animals are exposed to radiofrequency radiation emitted from a common mobile phone, a survival adaptive response as indicated by increased survival rate after exposure to pathogenic bacteria can be observed. In this regard, pre-exposure of laboratory animals to radiofrequency radiations emitted from mobile phones makes these animals resistant to a subsequent infection caused by *Escherichia coli*. Collectively, the above findings show that adaptive mechanism could be potentially utilized for decreasing the risk of infection during

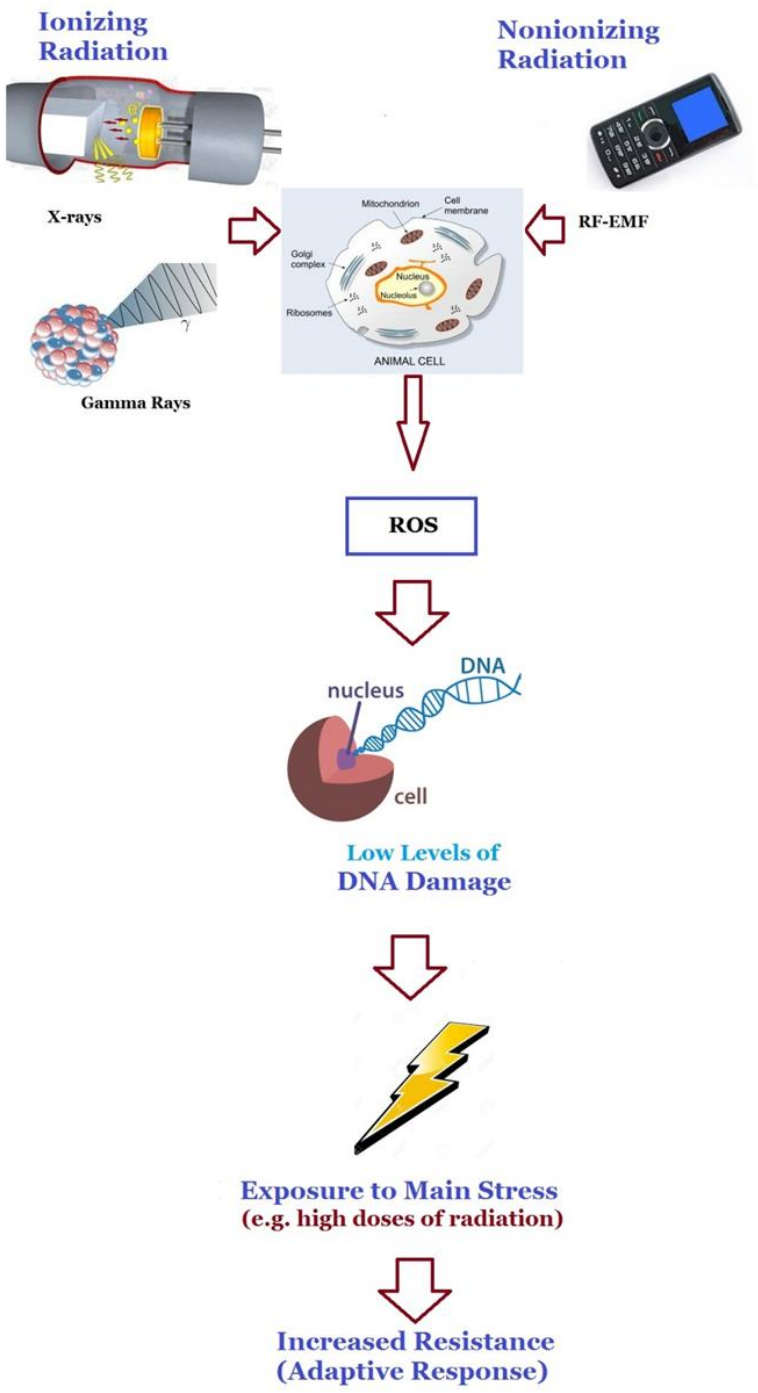

FIGURE 1. Oxidative stress as a key mechanism in the induction of adaptive response by both ionizing radiation and non-ionizing radiation. As discussed in the text, such an adaptive mechanism affords protection and offers survival advantages upon subsequent exposure to high doses of radiation.

deep space missions [34, 52]. It is worth noting that space radiation is among the key environmental factors that increase the risk of bacterial infections during long-term space missions [53].

4. CONCLUDING REMARKS

As discussed before, the induction of adaptive response by ionizing radiation needs a minimum level of damage (i.e., the dose and dose rate should be within a specific window). In a similar pattern, Mortazavi has concluded that the induction of adaptive response by non-ionizing radiation also requires a minimum level of damage to trigger this phenomenon. It can be hypothesized that ROS play a key role in producing the minimum level of damage that is required for the induction of an adaptive response (**Figure 1**). In this context, it seems that there are similar patterns for induction of adaptive response by ionizing and non-ionizing radiations. Hence, we believe that oxidative stress is a bridge that links radioadaptive responses induced by ionizing radiation to those induced by non-ionizing radiation.

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