Review of the effect of reduced levels of background radiation on living organisms

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Abstract

It is well understood that all life is subject to continuous low levels of ionizing radiation, most prominently from the natural background of the biosphere, differing appreciably in particular situations across the surface of the globe. Added to this, albeit in much more isolated situations inclusive of particular workplaces and different environments, are exposures from ionizing radiations traced to human activities. Accordingly, studies of the effects of background-level radiations are subject to complex multifactorial influences. The radiation safety regulations and limits for lower levels of exposure are based on extrapolation from more elevated doses and dose rates, embodied in the linear no-threshold (LNT) model. The LNT model assumes the relationship between biological effects and radiation dose at low levels to be linear, all doses in excess of normal background carrying risk. Substantiated for high dose exposures, the validity of the model is unknown for low doses, the elucidation of possible beneficial hormetic and adaptive effects remaining a challenge. Herein, an overview of the effect on organisms of reduced low-levels of radiations is presented using available evidence and discussion of theoretical possibilities.

Keywords: low dose radiation; background radiation; reduced background radiation; biological benefits; health risks.

Highlights

- Earth's low natural background radiation and cosmic rays are relevant during the evolution of living organisms.

- Effects of background-level radiations are subject to complex multifactorial influences.
- Low-level background radiations could be beneficial to organisms.
- Possibilities of harnessing the benefits of low-level background radiations

1. Introduction

Ionizing radiation (IR) is part of nature and all living organisms since conception and birth have been and are still being exposed to natural background IR. Life has evolved in the presence of environment background radiation. Living organisms cannot escape from these background IR; cosmic, terrestrial γ, natural background (including naturally occurring radon, thorium, uranium, ^{40}K are present in rock, soil and water, with plants absorbing activity from the soil and passing to the food chain). UNSCEAR has estimated the global average radiation dose due to natural background radiation sources is approximately 2.4 mSv (UNSCEAR 2008) (extra-terrestrial as well as in soil and water). Globally, there is a wide range of naturally occurring IR, averaging from 2.36 mSv/y in India (Mohanty et al. 2004) to 260 mSv/y in Iran (Ghiassi-nejad et al. 2002).

Natural environmental IR is believed to have played a relevant role during the evolution of living organisms, and has contributed to the development of defense mechanisms to minimize oxidative stress and the ability to repair radiation induced DNA damage, and life has adapted well to low doses of IR. Human bodies are also naturally radioactive as we eat, drink and breath radioactive substances that are present in the environment. Our bodies are constantly replenished with these radioactive substances through ingestion and inhalation.

For radiological protection, the International Commission on Radiological Protection (ICRP) has adopted the Linear No-Threshold (LNT) model, to estimate stochastic health effects of IR (radiation induced cancer, genetic mutations and teratogenic effect). Although, the LNT model was intended for radiation protection uses, it has been widely used as the standard for radiation safety. The LNT model extrapolates stochastic risk of low dose/low dose-rate from the high doses, therefore, implying that any radiation dose is harmful[1]. This has inferred that even the smallest amount of radiation increases cancer risk and it has led to the fear of even the lowest level of radiation. While there is significant epidemiological evidence for enhanced

[1] ICRP include a Dose and Dose-Eate Effectiveness Factor (DDREF) of 2 for risk estimates, which is a judged factor that generalises the usually lower biological effectiveness (per unit of dose) of radiation exposures at low doses and dose rates compared with exposures at high doses and dose rates.

cancer risk around 100 mGy and above for low-LET radiation, the evidence below 100 mGy is limited, although recent studies indicating sufficient statistical information to estimate risks down to around 20 mGy (refs). However, this is still an order of magnitude higher than doses associated with typical the average natural background exposure, which is greater than the majority of occupational exposures. Here, we seek to assess the validity of the LNT model by determining the effect of very low radiation level (which are much lower than the normal background radiation level) on organisms by reviewing published studies.

Since, the LNT model predicts all IR exposure has an increased risk of deleterious effects, then, it is implied cells grown in less than background IR should see benefit. Therefore, below-background IR dose studies could provide insights and information on the biological role of low-dose IR. These below natural background IR studies could provide evidence on the potential value, or otherwise, of very low-dose radiation for living organism. Moreover, the mechanisms of low-dose sensitivity, biological evolution and adaptation could be determined.

It has been established that reactive oxygen species (ROS) are induced by IR in most cells, initiating oxidative damage by these ROS, with effects lasting for minutes, hours, or days; contributing to the activation of protective or damaging processes that could influence the damaging effects of IR (Spitz et al. 2004). Spitz et al. (2004) provided evidence that this physiological manifestation of IR-induced alteration in redox sensitive processes are linked to deleterious effects of radiation, and radiation induced signalling, such as, adaptive responses, by-stander effects, cell cycle perturbation, cytotoxicity, heat-induced radiosensitization, genomic instability, inflammation and fibrosis (Spitz et al. 2004). To combat ROS, cells are equipped with antioxidant enzymes to process the accumulated ROS with enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase, reducing cellular damage induced by IR (Scandalios 2005). Moreover, endogenous antioxidants, such as cellular non-protein thiols and antioxidant enzymes also contribute to the protection (Weiss and Landauer 2003). Adaptive response is potentially one of the benefits of low doses of IR; describing the ability of cells that were pre-exposed to low doses of radiation (or chemical mutagenic agent), to acquire resistance to moderate or higher doses of the same or a different agent as observed by Olivieri et al (1984) on human lymphocytes cultures with low, chronic doses of IR (Olivieri, Bodycote, and Wolff 1984; Wolff et al. 1988), and as described by Wolff (1992) (Wolff 1992). de Toledo (2006) reported that fibroblasts exposed to acute 10 cGy (100 mSv) ^{137}Cs γ IR, when protracted to more than 48 hours had a reduced micronuclei frequency level similar to or lower than those which occur spontaneously (de Toledo et al. 2006), indicating an adaptive response. They showed that there was an upregulated cellular content of the antioxidant glutathione, and postulated that there is a significant role of oxidative metabolism in mediating low-dose radiation effects. Similarly, Carbone et al. (2009) demonstrated that TK6 cells maintained in different level of environmental radiation for 6 months, when subsequently exposed to 2 Gy X-ray, those cells grown in environmental background radiation yielded a lower level of micronuclei formation when compared to those cultured in a low background radiation environment; indicating background radiation could act as a conditioning agent in the radiation-induced adaptive response (Carbone et al. 2009). They also measured the antioxidant enzymatic activity of the post X-ray irradiated cells, and observed the irradiated cells grown in the background IR exhibit an increase of ROS-scavenging efficiency (CAT/SOD and GPx/SOD ratios) with respect to the lower background IR.

2. Methods and Materials

2.1 Deep Underground Laboratory (DUL)

There are 14 Deep Underground Laboratories (DULs) that were mainly constructed for astroparticle physics and neutrino physics (Smith 2012;Best et al. 2016), but offer a novel opportunity to perform experiments in astrobiology and biology in extreme environments, and to study radiation effects on life (Ianni 2021). These DULs are found mainly in USA, Canada, UK, Italy, France, Spain, Finland, Russia, Japan, China, India, and several that are under construction, such as, in Australia, South Korea and the Andes in South America (Ianni 2021). DULs are novel environments for biological experiments with much reduced cosmic radiation flux. Organisms growing in this type of laboratory will have received minimal background radiation dose.

2.2 Methods

The strategy in such experiments is to study two groups of identical model organisms simultaneously placed in DUL and a normal background radiation laboratory (BRL), and the following are determined.

i. Differences in responses are observed and results compared.
ii. Post conditioning of cell grown in DUL and BRL are challenged with different stressors (such as, radiations and chemicals) and responses are observed and compared.

The exposure time is dependent on research purposes, from several days to approximately a year (Fratini et al. 2015; Castillo et al. 2018; Morciano et al. 2018). The common endpoints studied are development, life cycle duration, growth rate, fertility, gene or protein expression and lifespan of microorganisms (Planel et al. 1987; Satta et al. 1995; Satta et al. 2002; Castillo et al. 2015; Carbone et al. 2010; Fratini et al. 2015; Castillo and Smith 2017; Castillo et al. 2018; Castillo, Winder, and Smith 2021), cell signalling, DNA repair and antioxidant regulation to low-dose radiation (Lampe et al. 2017). Recently, Zarubin et al. demonstrated the first transcriptome profiling of Drosophila melanogaster, response of a species of fly (fruit fly) to DUL in Russia (Zarubin et al. 2021).

2.3 Materials

Organisms that are commonly found living in deep sub-surfaces and extreme environment are unicellular bacteria (Castillo et al. 2015; Castillo and Smith 2017; Wadsworth et al. 2020), protozoa (Planel et al. 1987), archaea, and yeast (Satta et al. 1995). However, multicellular organisms (small animal) such as, flies (Morciano et al. 2018; Zarubin et al. 2021), nematodes (Van Voorhies et al. 2020), fishes (Pirkkanen et al. 2020), and mammalian cells (Satta et al. 2002; Fratini et al. 2015; Castillo, Winder, and Smith 2021; Carbone et al. 2010) were also experimented and studied. Liu et al. (2020) were the first to investigate the biological effects of cancer cells cultured in DUL environment, to provide novel insights to cancer, using well-differentiated laryngeal squamous cell carcinoma (FD-LSC-1) (Liu, et al. 2020a).

3. Results

3.1 Different types of organisms grown in DUL

Table 1 shows the effects of below background IR on organisms. Although, most of the organisms were shown to suffer some kind of detrimental effects, there were no reported effects on bacteria such as Bacillus subtilis and Escherichia coli (Wadsworth et al. 2020).

Table 1 Effects of reduced background IR on organisms

Species	**Response compared to background radiation**	**Authors**
Paramecium tetraurelia, *Synechococcus lividus*	Sharp decrease in the number, growth was slowed down in (protozoa and cyanobacteria)	(Planel et al. 1987)
Saccharomyces cerevisiae	Impaired biological defence to chemical radiomimetic agent methyl methane sulfonate, decreased protection	(Satta et al. 1995)
V79 (hamster lung fibroblast)	i) increase in oxidative stress, ii) higher hprt mutation frequency, iii) decrease in resistance to gamma radiation	(Satta et al. 2002)
Human lymphoblastoid TK6 cells	DNA damage repaired inefficiently, unable to react to the imbalance of ROS post 1 Gy, increased micronuclei frequency, indicating chromosome damage	(Carbone et al. 2010)
Paramecium tetraurelia & mouse lymphoma L5178Y & M10, mouse deficient XRCC4-deficient cells.	Inhibitory effects on cell growth for Paramecium tetraurelia growth after 40-50 days, and for L5178Y grown for 7 days in reduced IR background; no growth retardation observed in XRCC4-deficient mouse M10 cells, but displayed impaired DNA double strand break repair.	(Kawanishi et al. 2012)
Chinese hamster V79 lung fibroblast cells	Lower capacity to reduce oxidative stress accompanied by an increase in mutation frequency. Cells kept in lower IR background kept memory of this state for at least six months, hence, reduced efficiency when returned to normal IR background.	(Fratini et al. 2015)
Shewanella oneidensis & *Deinococcus radiodurans*	Stress response is triggered by absence of normal levels of IR - S. Oneidensis (sensitive to radiation) and D. radiodurans (> 143 times resistant to radiation)	(Castillo and Smith 2017)
Shewanella oneidensis	Sensitive to withdrawal of background levels of IR, wide metabolic response, marked decrease in protein translation	(Castillo et al. 2018)
Chinese hamster V79 lung fibroblast cells	Heterogeneous cell populations (transcriptional response – gene regulation). Re-exposed to background radiation, the variation in number decreased, a higher radiation status - for a tighter cell reproduction control. Depended on background radiation for optimal growth.	(Castillo, Winder, and Smith 2021)

Embryo lake whitefish (Coregonus clupeaformis)	Embryogenesis of lake whitefish study showed no significant differences to timing of hatch or percent survival between DUL and reference background, however, a 10% increase in body length and body weight was observed in embryos reared underground (mitigated by higher radon levels and air pressure (25% higher) in underground, as these were not factored in).	(Pirkkanen et al. 2020)
Drosophila melanogaster	Depending on their genetic background, reduced IR background affected viability for several generations when flies are moved back to normal IR background. Lower IR background showed reduced ~30% fertility for both sexes. Flies maintained memory of positive selection.	(Morciano et al. 2018)
Bacillus subtilis & Escherichia coli	Extreme low radiation did not alter growth parameters of these two organisms	(Wadsworth et al. 2020)
Well-differentiated laryngeal squamous cell carcinoma cells (FD-LSC-1)	FD-LSC-1 cells proliferation were inhibited when grown in DUL, and also induced changes in protein expression associated with ribosomes, gene spliceosome, RNA transport, energy metabolism and others. The changes in protein expression is related to proliferation inhibition and enhanced survivability of cells adapting to the DUL background.	(Liu, et al. 2020a)
Caenorhabditis elegans (nematode)	Exposure to below IR background rapidly induces phenotypic and transcriptomic changes within 72 hours.	(Van Voorhies et al. 2020)
Chinese hamster V79lung fibroblast cells	V79 cells proliferation rate was inhibited within a short time of DUL condition. There is a change in the proteomic profile, that could be related to the delayed proliferation, however, there was enhanced survival, indicating cells could adapt to the changing environment.	(Liu, , et al. 2020b)
Drosophila melanogaster	Observed gene expression changes as an adaptive response to underground IR, lack of some physical stimuli on the surface background affecting organisms could not be ruled out. Overall, cellular metabolism was down-regulated, immune system process and response to biotic stimuli are up-regulated, that are similar to some kind of stress response affecting the flies.	(Zarubin et al. 2021)

3.2 Impact of reduction of background radiation on organisms

Table 1 describes the stresses organisms suffer from below background radiation. One obvious negative effect is the reduction in growth rate/proliferations (Planel et al. 1987; Kawanishi et al. 2012; Castillo et al. 2015; Liu, et al. 2020b) and reduced resistance to further DNA damaging agent (Satta et al. 1995). Cancer cell line are also reported to be affected by reduced background IR (Liu et al. 2020a). There is also a reduction in their oxidative resistance, higher mutation frequency and decreased resistance to γ IR (Carbone et al. 2009; Satta et al. 2002; Fratini et al. 2015), and genetic adaptations. From these evidences, it could be inferred that organisms could adapt to environmental background IR and this adaptation could trigger their ability to respond to harmful effects of IR, with a retained memory of this response. Some of these benefits are similar to radiation hormesis.

4. Discussion and Conclusions

4.1 Limitations of DULs experiments

Although, cosmic rays could be reduced, when performing experiments in these DULs, there are many inherent highly unique technical and logistical challenges to overcome, and these are not trivial, such as, accessibility, efforts required to reach to hundreds and thousands of metres below ground level; ability to maintain experimental control of deep-underground environment constant including reduced natural radon gases, temperature, air-pressure and electricity supply (Pirkkanen et al. 2020). Others issues include timely access to DULs, with personnel access limitation due to ventilation restrictions due to radiation contamination events, mine equipment failures, above and below background safety drills (Van Voorhies et al. 2020). All these challenges may impact on the data collected. Moreover, organisms studied must be able to survive in these background conditions; and the biology of living systems and organisms is very complex (Morciano et al. 2018). The organisms chosen for investigation have to be easy to grow in culture, have a rapid life cycle, with extensive knowledge being available of its genetics and gene function, developmental biology and physiology; and with predictable adverse effects (Van Voorhies et al. 2020). The organisms mentioned/studied above are therefore not comprehensive.

4.2 Discussions All organisms evolve in the presence of natural background of environmental IR and below background IR dose studies have provided insight and information on the biological role of radiation. Studies of exposure to low environmental radiation level have demonstrated the potential benefits of background IR. Compiled results have shown the opposite of the LNT model prediction, i.e., with very low background radiation levels, the organisms are worst off, contradicting the expectations from the LNT model, inferring the invalidity of the LNT model (for low-level of radiation). The response of cell population to IR are more complex than predicted by the LNT model, a linear relationship with dose may not be applicable to phenomena, such as, adaptive response, genomic instability, bystander effects and others (Huang et al. 2007). The reported negative impacts on organisms due to very low background radiation infer that the environmental background IR play roles in the maintenance or induction of cell mechanism that contribute to protection against cell damage from reactive oxygen species or repair damaged DNA. It is arguable that background IR has a "conditioning agent" for the cellular response to DNA damage (Carbone et al. 2009; Lampe et al. 2016). Moreover, these data would support the existence of hormetic effects of low-dose radiation in these natural background radiation conditions (Parsons, 1990; Luckey 1991; Luckey, 2006).

The results of DULs experiments indirectly provide some evidence that environmental background IR is essential for the survival of living organisms and its absence may be seen as a stress. Environmental background IR may therefore play an important role in contributing to the development of an organism's defense mechanism at cellular level, even possibly genetically, with organisms being able to adapt to environmental background IR and this adaptation enabling their ability to respond to harmful effects of IR. Human body has the adaptive protective mechanism at the cellular and sub-organs levels, to process the initial radiation damages induce by low-doses and low dose rates at cellular level, that could protect against cancer induction through DNA repair, antioxidant production, apoptosis, bystander effects, and, immune system response by removing of surviving DNA damaged cells (Löbrich et al. 2005; Feinendegen et al. 2012) defending the organism against all DNA damage, enhance both survival and maintain the genomic stability (Pollycove and Feinendegen 2003). Additionally, there are literatures that have critically assessed and reported that low-dose radiation support radiation hormesis (Doss, 2018), and the LNT model's validity and applicability for risk assessment and radiation protection may need to be re-considered (Siegel et al. 2019). Conversely, there are those that support the LNT model application for the radiation protection purposes (Shore et al. 2018;Shore et al. 2019).

4.3 Conclusion

In summary, evidence has shown that background radiation has some potential benefits to organisms and have genetic memory (Fratini et al. 2015; Morciano et al. 2018). Moreover, organisms could undergo adaptive response to stress (Olivieri, Bodycote, and Wolff 1984; Wolff et al. 1988; de Toledo et al. 2006; Carbone et al. 2009; Zarubin et al. 2021) and to chronic stress environments, such as the pacific white shrimps (Litopenaeus vannamei) response to acute cold stress (Wang et al. 2020). Below-background radiation doses studies has provided insight and information on the biological role of background radiation. However, the results thus far are applicable to the organisms and end-points studied (except the well-differentiated laryngeal squamous cell carcinoma cells), and it would require some assumptions to claim that the results would be applicable to humans.

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V79 (hamster lung fibroblast)	i) increase in oxidative stress, ii) higher hprt mutation frequency, iii) decrease in resistance to gamma radiation	(Satta et al. 2002)
Human lymphoblastoid TK6 cells	More sensitive to acute exposures to X-ray radiation in term of DNA damage and oxidative metabolism (decrease of ROS-scavenging efficiency). Higher yield of micronuclei indicating environmental radiation act as a conditioning agent in radiation-induced adaptive response.	(Carbone et al. 2009)
Human lymphoblastoid TK6 cells	DNA damage repaired inefficiently, unable to react to the imbalance of ROS post 1 Gy, increased micronuclei frequency, indicating chromosome damage. Background radiation environment supports the maintenance of protective responses of TK6 cells.	(Carbone et al. 2010)
Paramecium tetraurelia &mouse lymphoma L5178Y & M10, mouse deficient XRCC4-deficient cells.	Inhibitory effects on cell growth for Paramecium tetraurelia growth after 40-50 days, and for L5178Y grown for 7 days in reduced IR background; no growth retardation observed in XRCC4-deficient mouse M10 cells, but displayed impaired DNA double strand break repair.	(Kawanishi et al. 2012)
Chinese hamster V79 lung fibroblast cells	Lower capacity to reduce oxidative stress accompanied by an increase in mutation frequency, indicating environmental radiation contributes to the development of defence mechanism in living organisms. Cells kept in lower IR background kept memory of this state for at least six months, hence, reduced efficiency when returned to normal IR background.	(Fratini et al. 2015)

Shewanella oneidensis & Deinococcus radiodurans	Both showed growth is inhibited and stress response is triggered by absence of normal levels of IR - S. Oneidensis (sensitive to radiation) and D. radiodurans (> 143 times resistant to radiation).	(Castillo et al. 2015; Castillo and Smith 2017)
Shewanella oneidensis	Transcriptome analysis revealed bacteria is sensitive to withdrawal of background levels of IR, and demonstrated wide metabolic response, with marked decrease in protein translation, suggesting a transcriptional response is required to maintain homeostasis and normal growth.	(Castillo et al. 2018)
Drosophila melanogaster	Depending on their genetic background, reduced IR background affected viability for several generations when flies are moved back to normal IR background. Lower IR background showed reduced ~30% fertility for both sexes. Flies maintained memory of positive selection. Environmental radiation contributes to the development of defence mechanisms at cellular level.	(Morciano et al. 2018)
Embryo lake whitefish (Coregonus clupeaformis)	Embryogenesis of lake whitefish study showed no significant differences in timing of hatch or percent survival between DUL and reference background, however, a 10% increase in body length and body weight was observed in embryos reared underground (mitigated by higher radon levels and air pressure (25% higher) in underground, as these were not factored in).	(Pirkkanen et al. 2020)
Bacillus subtilis & Escherichia coli	Extreme low radiation did not alter growth parameters of these two organisms.	(Wadsworth et al. 2020)
Caenorhabditis elegans (nematode)	Exposure to below IR background rapidly induces phenotypic and transcriptomic changes within 72 hours.	(Van Voorhies et al. 2020)
Well-differentiated laryngeal squamous cell carcinoma cells (FD-LSC-1)	FD-LSC-1 cells proliferation were inhibited when grown in DUL, and also induced changes in protein expression associated with ribosomes, gene spliceosome, RNA transport, energy metabolism and others. The changes in protein expression is related to proliferation inhibition and enhanced survivability of cells adapting to the DUL background.	(Liu, et al. 2020a)
Chinese hamster V79lung fibroblast cells	V79 cells proliferation rate was inhibited within a short time (several days to two weeks) of DUL condition. There is a change in the proteomic profile, that may induce the delayed proliferation, however, there was enhanced survival, indicating cells could adapt to the changing environment.	(Liu, , et al. 2020b)

Chinese hamster V79 lung fibroblast cells	Heterogeneous cell populations (transcriptional response – gene regulation). Re-exposed to background radiation, the variation in number decreased, a higher radiation status - for a tighter cell reproduction control. Depended on background radiation for optimal growth.	(Castillo, Winder, and Smith 2021)
Drosophila melanogaster	Observed gene expression changes as an adaptive response to underground IR, lack of some physical stimuli on the surface background affecting organisms could not be ruled out. Overall, cellular metabolism was down-regulated, immune system process and response to biotic stimuli are up-regulated, that are similar to some kind of stress response affecting the flies.	(Zarubin et al. 2021)

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