Paper

Factors Influencing Effects of Low-dose Radiation Exposure

Carmel Mothersill,[1] Colin Seymour,[1] Alan Cocchetto,[2] and David Williams[3]

Abstract—**It is now well accepted that the mechanisms induced by low-dose exposures to ionizing radiation (LDR) are different from those occurring after high-dose exposures. However, the downstream *effects* of these mechanisms are unclear as are the quantitative relationships between exposure, effect, harm, and risk. In this paper, we will discuss the mechanisms known to be important with an overall emphasis on how so-called "non-targeted effects" (NTE) communicate and coordinate responses to LDR. Targeted deposition of ionizing radiation energy in cells causing DNA damage is still regarded as the dominant trigger leading to all downstream events whether targeted or non-targeted. We regard this as an over-simplification dating back to formal target theory. It ignores that last 100 y of biological research into stress responses and signaling mechanisms in organisms exposed to toxic substances, including ionizing radiation. We will provide evidence for situations where energy deposition in cellular targets alone cannot be plausible as a mechanism for LDR effects. An example is where the energy deposition takes place in an organism not receiving the radiation dose. We will also discuss how effects after LDR depend more on dose rate and radiation quality rather than actual dose, which appears rather irrelevant. Finally, we will use recent evidence from studies of cataract and melanoma induction to suggest that after LDR, post-translational effects, such as protein misfolding or defects in energy metabolism or mitochondrial function, may dominate the etiology and progression of the disease. A focus on such novel pathways may open the way to successful prophylaxis and development of new biomarkers for better risk assessment after low dose exposures.**
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Key words: biological indicators; health effects; radiation, biology; radiation, low-level

INTRODUCTION

SEVERAL RECENT reviews have highlighted the difference in mechanisms underlying low-dose radiation effects when compared with high dose mechanisms (Khan and Wang 2022; Mothersill and Seymour 2022a and b; Narasimhamurthy et al. 2022). Low dose is defined here using the ICRP Publication 103 recommendations (2007) as <100 mGy dose or < 6 mGy h^{-1} dose rate. Low-dose mechanisms involve non-linear responses described later, with clear transition points where mechanisms shift abruptly (Scott et al. 2003; Mothersill and Seymour 2013; Desai et al. 2022). These patterns are usually associated with active and programmed responses to stimuli that are sensed rather than passive responses to damage (Mothersill and Seymour 1997; Azzam et al. 2001, 2012; Singh et al. 2011a; Le et al. 2017; Khan and Wang 2022). They are energy-dependent requiring functioning energy production systems and are accompanied by high levels of "oxidative stress" (Chen et al. 2009; Shimura and Kunugita 2016; Le et al. 2018a)[5], which may be a consequence of the responses rather than, as is commonly assumed, a generator of low-dose radiation damage (LDRD). High dose mechanisms (>0.1 Gy) largely involved targeted DNA damage, in which the dose increases as the amount of damage increases in a proportional manner (Teoule 1987; Lomax et al. 2013; Desouky et al. 2015; Lad et al. 2019). However, the idea that the low-dose sparing, which leads to the appearance of a "shoulder" on classical semi-log survival curves, was due to accumulation of damage or repair capacity is not now supported by the facts (Mothersill and Seymour 2019; Mukherjee et al. 2022; Csordás et al. 2023).

Crucial to the acceptance of the "separate mechanisms" argument was the discovery and mechanistic characterization of non-targeted effects (NTE). These are seen in cells, tissues, and organisms that were never exposed to radiation and thus never actually received an energy deposition from ionizing radiation in a target (for recent reviews and keystone papers see Mothersill and Seymour 1997, 1998, 2022b, 2022a; Azzam et al. 2001; Maguire et al. 2005; Murphy et al. 2005; Shao et al. 2006; Lyng et al. 2006b; Chen et al. 2008; Nugent et al. 2010; Mothersill et al. 2010, 2012, 2022c; Le et al. 2017, 2018b; Gonon et al. 2022; Jokar et al. 2022; Smolarz et al. 2022; Verma and Tiku 2022; Buonanno

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[5]Li M. Investigation of the effect of yeast NADH dehydrogenase (NDI1) on the radiation-induced bystander response in human colon carcinoma cells. ICRR; 2023. In press.

et al. 2023; Tang et al. 2023). The recent UNSCEAR report (Annex C 2021) discusses the biological mechanisms and processes with could impact inference of cancer risk. Among the processes are low-dose phenomena, such as genomic instability, bystander effects, adaptive responses and low-dose hypersensitivity. In relation to bystander effects the conclusions mainly rely on a review by Tomita and Maeda in 2019, who provide a detailed and extensive review of bystander phenomena and noted the mixed results reported. They conclude by concurring with the position on bystander phenomena stated in the UNSCEAR White Paper (2012) that there is little of the coherence required of robust data among bystander studies that can be used confidently for risk assessment. We would argue, as did Mothersill and Seymour (2022b), that uncertainty of low-dose outcomes is a fact of life and indicates that factors other than radiation influence outcomes such as carcinogenesis. Rather than trying to determine whether bystander effects are relevant to cancer risk assessment, a better question would be "Which of the many competing risk and benefit factors actually wins and why?"

NTE dominance at low doses

Fig. 1 shows the current understanding of NTE mechanisms. Key features are highlighted in this flow chart that traces to the key events in the two major NTE: (1) radiation-induced genomic instability (RIGI), where there is the appearance of radiation damage in cells that are the descendants of irradiated cells whose immediate progeny are normal, often for several generations (Seymour et al. 1986; Seymour and Mothersill 1997; Kadhim et al. 2004; Shimura and Kunugita 2016; Schofield and Kondratowicz 2018); and (2) the radiation-induced bystander effect (RIBE), which refers to the detection of radiation-like damage in the absence of any direct deposition of energy but where there is signaling between the irradiated and the non-irradiated entities (Mothersill and Seymour 1997; Azzam et al. 2001; Klammer et al. 2015). RIBE signal emission once activated in a targeted cell has been shown to persist for multiple generations in the form of persistently elevated and potentially mutagenic oxidative stress (Lorimore et al. 2003a; Tamminga and Kovalchuk 2011; Azzam et al. 2012). This makes RIBE a likely driver of genomic instability through the activation of damage associated molecular patterns (DAMPS) (Mavragani et al. 2016; Mladenov et al. 2018; Hu and Shao 2020; Du et al. 2020; Buonanno et al. 2023). The random appearance and non-clonal nature of the chromosomal aberrations and lethal mutations seen in RIGI supports this view (Mothersill and Seymour 2012) as does the demonstration that RIGI can be induced by RIBE signals alone and does not require direct energy deposition (Lorimore et al. 2003b; Morgan 2003; Buonanno et al. 2023; Gopinathan and Gopinathan 2023; Zhang et al. 2023).

From the perspective of low-dose radiobiology, probably the key research findings in the NTE field relate to the dose-response relationships. Fig. 2 shows the three common ways these experiments are done using cultured cells and one well-established method for assaying effects in whole animals (fish). The experiments done in many different laboratories using many cell types show clearly that NTE are low-dose phenomena (Mothersill and Seymour 1998;

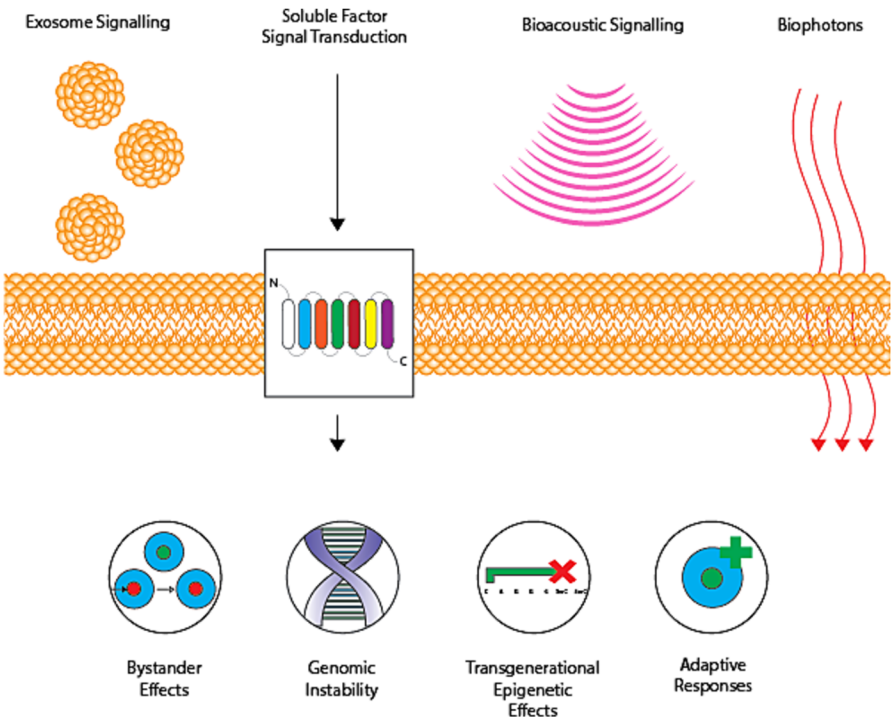

Fig. 1. State-of the-art of current understanding of all the processes that appear to be involved in the bystander signaling and response process.

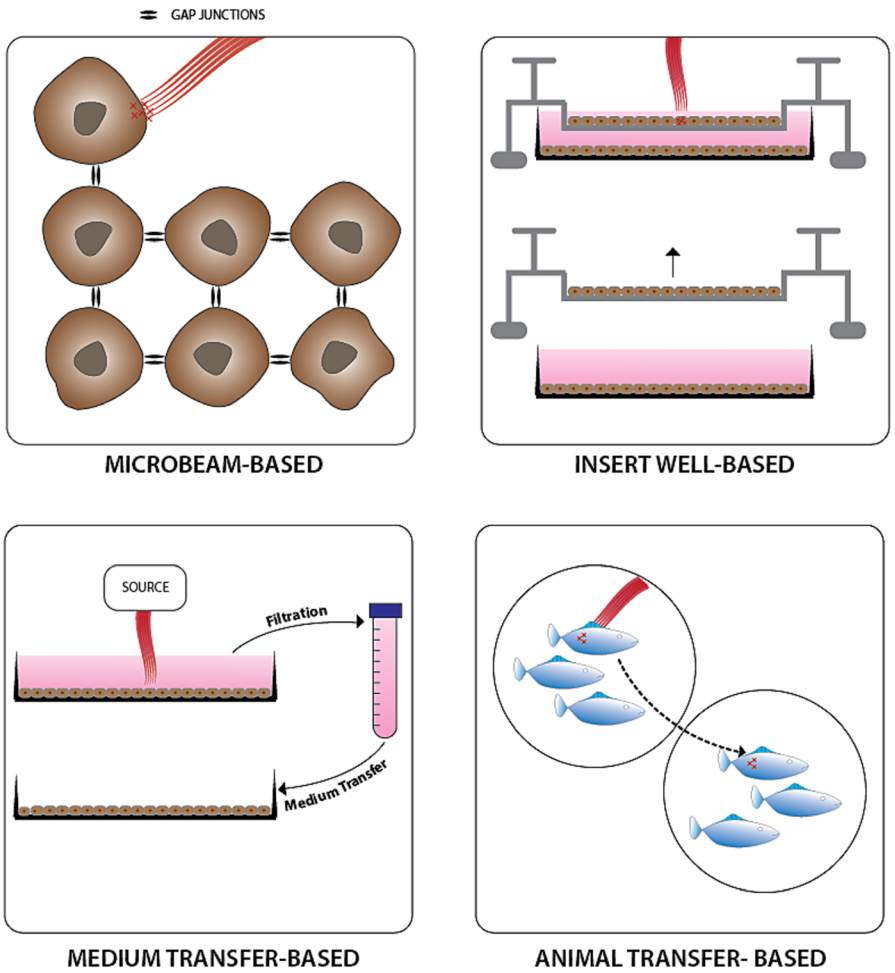

Fig. 2. Techniques commonly used to measure bystander effects in vitro and in vivo.

Belyakov et al. 2001; Matsumoto et al. 2001; Zhou et al. 2005; Liu et al. 2006; Facoetti et al. 2009; Herok et al. 2010; Belloni et al. 2011; Rajendran et al. 2011; Kalanxhi and Dahle 2012; Xu et al. 2015; Miller et al. 2017; Ariyoshi et al. 2019). A classic dose response for human cells exposed to culture medium from irradiated cells over many orders of magnitude of dose (1 μGy to 5 Gy) from the authors' laboratory (Liu et al. 2006) is reproduced here (Fig. 3). The endpoint is clonogenic cell death, meaning that fewer surviving colonies indicates a bigger bystander effect. It shows a clearly non-linear response divided into three distinct phases. Phase 1 occurs at doses below 2 mGy and has a trend suggesting more colonies survive in the RIBE-exposed set than in the directly-irradiated set, although neither set is significantly different from the untreated control set. Phase 2 occurs between 2 mGy and 0.5 Gy, and here culture medium from irradiated cells has the same effect as direct irradiation. A steady reduction in cloning efficiency is seen as the dose increases. Phase 3 occurs at doses greater than 0.5 Gy. Here there is a divergence of response—the directly irradiated cells show a classic exponential decline in cloning efficiency with increasing dose, but the recipients of bystander signals plateau with no further increase in effect with increasing dose to donors of conditioned medium. This means for this example:

- All clonogenic cell death below 0.5 Gy may be due to non-targeted effects as is argued in Seymour and Mothersill (2000); and
- NTE saturate at 0.5Gy.

Similar results were found by Schettino et al (Schettino et al. 2000, 2003, 2005) who suggested that below 2 mGy direct dose to cells, there was a randomness to the data where some cells release signals but others do not, resulting in high variability after very low-dose exposure.

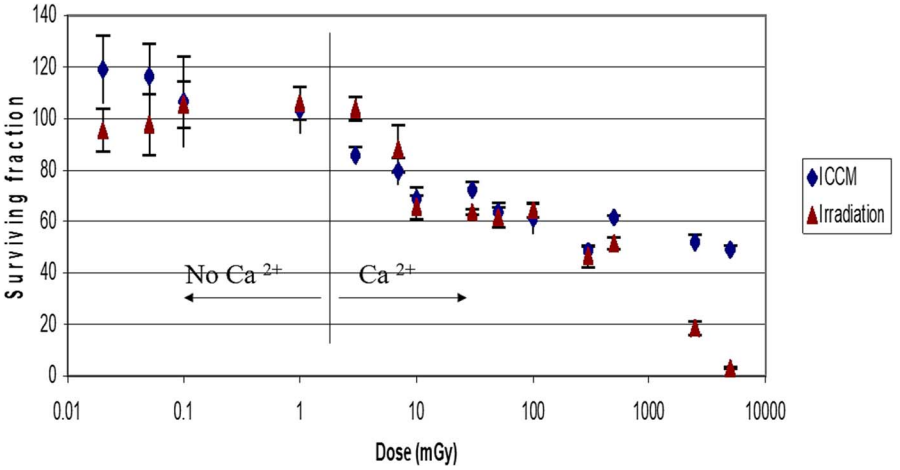

Fig. 3. Dose response (clonogenic survival) for direct and bystander cell killing over 7 orders of magnitude of the dose highlighting the importance of calcium signaling in determining the type of effect seen. Triangle symbols indicate the cells received a direct dose of ionizing radiation; diamond symbols indicate the cells received irradiated cell conditioned medium from irradiated donors. Figure reproduced from data obtained by Liu et al. (2006).

A recent analysis (reproduced here as Fig. 4)[4] shows that while the data may differ considerably between different laboratories using different cells and different dose rates, the pattern of saturation is widespread as there is no indication of an increasing percent change in deleterious effect as the dose (x-axis) increases. In fact, the data suggest a very low threshold for triggering the full effect and that the magnitude of the effect is highly variable and cell-line or laboratory dependent. It is interesting, however, that while there are datasets showing "protective" bystander effects, where the percent change in cloning efficiency is positive, none of these protective effects occur at doses to donor cells above 5 Gy. This may be because laboratories looking for adaptive or protective effects rarely look at high doses.

Non-targeted effects and radiation quality

A question of considerable interest in radiation protection concerns radiation quality or Linear energy transfer (LET) effects in the low-dose region. This is of importance in environmental protection due to concerns about uranium mining and associated radium and radon contamination of ecosystems. Beta radiation from tritium releases around CANDU reactors is also of concern. The literature is limited and contradictory. This is partly because of technical challenges when trying to look at bystander effects using alpha emitters such as radium or beta emitters such as tritium, which are added to culture medium. External alpha sources can be used, but dosimetry is difficult. However, the first report of a bystander effect was by Nagasawa and Little (1992). They used external alpha and calculated that the fluence used meant that only a third of the cells would get a traversal of particles. They measured sister chromatid exchanges and found that more cells had these mutations than could have been traversed. Boyd et al. (2008) looked at radiopharmaceuticals used in alpha-linked immunotherapy for cancer. They concluded that radionuclides emitting high LET radiation may elicit toxic or protective effects on neighboring untargeted cells at low and high dose, respectively. They suggested that radiopharmaceutical-induced bystander effects may depend on LET of the decay particles but are independent of site of intracellular concentration of radionuclide.

Suzuki et al. (2023) looked at bystander effects using heavy ion microbeams and concluded that gap junctions were involved in the mechanism but were not the only factor involved in determining response. They showed that the mutation frequency (MF) in cells irradiated with carbon ions was 8- to 6-fold higher than that in the unirradiated control at 0.5 and 3 h; however, no mutation was observed in cells treated with the gap-junction inhibitor. At 24 h, the MFs induced by each ion source were 3- to 5-fold higher and the same with and without the inhibitor. These findings suggest that the bystander cellular effects depend on the biological endpoints, ion species, and time after microbeam irradiations with different pathways. Buonanno et al. (2011) looked at long-term consequences of bystander treatment of cells over 20 generations after treatment of donor cells with heavy ions and protons. They concluded that, relative to controls, the progeny of bystander cells that were co-cultured with cells irradiated with iron or silicon ions, but not protons, exhibited reduced cloning efficiency and harbored higher levels of chromosomal damage, protein oxidation, and lipid peroxidation. This correlated with decreased activity of antioxidant enzymes, inactivation of the redox-sensitive metabolic enzyme aconitase, and altered translation of proteins encoded by mitochondrial DNA. Together, these results demonstrate that the long-term consequences of the induced nontargeted effects greatly depend on the quality and dose of the radiation and involve persistent oxidative stress due to induced perturbations in oxidative metabolism.

[4]Gresham C. An investigation of various intrinsic and external factors that influence in vitro cell survival outcomes during radiation-induced bystander effect experiments. Hamilton, ON, CA: McMaster University; 2023. Unpublished Master's thesis.

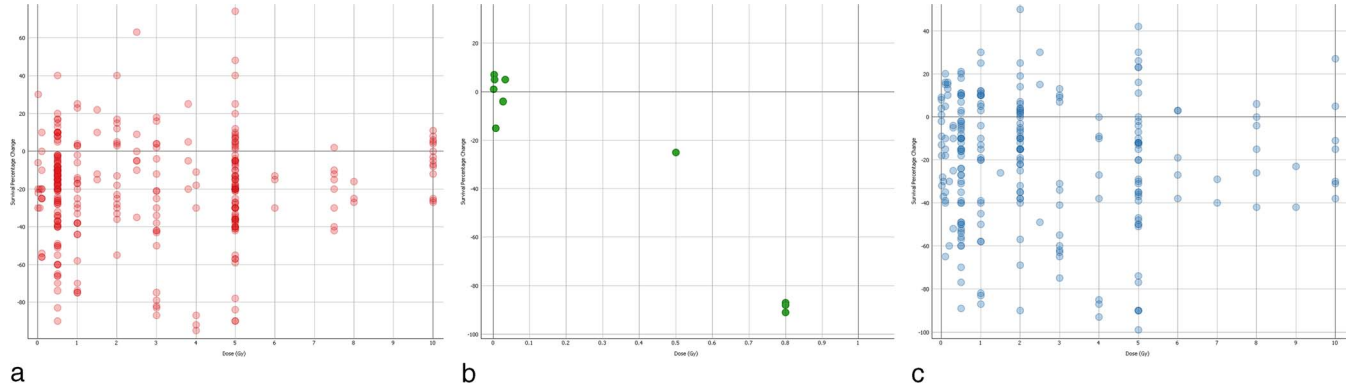

Fig. 4. Plots of pooled data from multiple laboratories which looked at bystander effect in relation to the dose rate used by different studies. The plot looks at the variation in data and at the dose rate used showing relative size of the bystander cell kill or sparing effect. Points above the line show enhanced survival while points below the line show decreased survival relative to the control. 4a: data where a high acute dose rate (>1 Gy min^{-1}) was used 4b: data where a low acute dose rate (<0.02 Gy min^{-1}) was used 4c: data where an intermediate dose rate (0.02–1.0 Gy min^{-1}) was used

Prise et al. (2003) looked at the effects of soft x rays using a microbeam at the Gray Laboratory in the UK. They tracked effects in individual human fibroblast cells and showed evidence of a significant radiation quality-dependent bystander effect, measured as chromosomal damage in the form of micronuclei which were radiation quality dependent. Kadhim et al. (2006) looked at genomic instability following high or low LET radiation exposure. They report that their work using human and mouse primary cell systems has shown LET-dependent differences in the induction and expression of genomic instability. They suggest these differences might be attributed to differences in radiation track structure, dose rate, contribution of bystander cells, and radiation dose but conclude that dose might be the most significant factor in determining induction of GI after low-LET radiation. Cherubini et al. (2015) looked at low-dose hyper-radiosensitivity and induced radioresistance (HRS/IRR) as well as bystander effects in rodent and human cells as a function of radiation quality. Using T98G cells and V79 fibroblasts, they found evidence of HRS/IRR following proton and carbon ion exposure but no bystander effect using protons.

Yokota et al. (2015) used gamma rays and carbon ions and found that the bystander effect in their normal fibroblast system depended on nitric oxide and radiation dose, but there was no radiation quality effect. The most significant radiation quality effect appears to concern neutrons where no bystander effect has been reported if the gamma component of the beam is shielded. Seth et al. (2014) looked at human cells, as did Liu et al. (2006), and neither group found a bystander effect. Wang et al. (2011) looked at zebrafish in vivo and found no inter-animal bystander effect. The latter study concluded that the results confirm in vitro experiments that suggest neutrons do not induce bystander signaling. In fact, they may suppress gamma-induced signaling, suggesting a possible intriguing new and as yet unclear mechanism. Data from our own laboratory are summarized in Table 1.

Role of NTE in communication of stress responses

While the phenomenology of NTE is very well documented and mechanisms are widely understood (see recent reviews listed above), there are questions about the role of these effects, which are very widespread in nature having been documented in a wide range of animals and plants (including yeasts) both in vivo and in vitro (DeVeaux et al. 2006; Mothersill et al. 2006; Yang et al. 2008; Mancuso et al. 2008; Chai and Hei 2009; Singh et al. 2011b; Smith et al. 2013; Rusin et al. 2019; Li et al. 2023). Such evolutionary conservation usually means the process is advantageous or essential. It is becoming increasingly clear that NTE are signaling mechanisms that appear to coordinate responses across hierarchical levels of organization. For example, at the tissue level, an insult to a cell or group of cells results in emission of stress signals, which induce tissue-level responses in other cells either to protect themselves or to aid the stressed cells. Stress signaling and responses are well known in the chemical ecology field, where plants "warn" other plants using chemicals when they are being attacked by insects or grazing animals (Pickett et al. 2003; Baxter et al. 2014).

Cross-kingdom stress signaling has also been documented extensively in forests where trees and mycelium establish subterranean communication networks (Simard 2018; Liang et al. 2020; Fortey 2021; Thomas and Cooper 2022). A possible reason NTE were dismissed for so long as having any relevance in environmental radiobiology may be because the focus was on cell death as an endpoint to demonstrate bystander effects and chromosome damage or lethal mutations to reveal genomic instability (Hei et al. 2011; Mothersill et al. 2017; Schofield and Kondratowicz 2018), none of which would appear to be important to conserve in evolution. The role of low-dose ionizing radiation on clonal development and cellular signaling was also shown by Fernandez-Antoran (2019) for doses as low as 50 mGy where low-dose radiation leads to preferential expansion of p53 mutant cells driven by

Table 1:. Comparison of non-targeted data from our laboratory and collaborators for different radiation qualities.

Radiation quality	RIBE	Genomic instability	Photon emission
Gamma/x-ray	Yes (confirmed above 2 mGy Max effect at 0.5Gy)	Yes (confirmed above 100 mGy Max effect at 0.5Gy)	Yes
Alpha	Yes (Pu acute alpha exposure to 0.5-2 alpha particles per cell approximately 0.5 Gy to hit cell) No (chronic exp to radium – total 0.06-300 mGy)	Yes (Acute exposure Pu source) Yes (Radium chronic exposure)	No
Beta	Yes (tritium chronic dose in vivo) Yes (Yttrium-90 acute dose in vitro) Yes (tritium acute dose in vitro)	TBD[a]	Yes
Neutron	No (essential to shield out gamma component of beam)	TBD (Gamma component of beam was not shielded out)	TBD

[a]TBD = to be determined

changes in the oxidative environment. The consequences of radiation effects on clonal expansion (e.g., triggered by intercellular signaling) on health and on the association between cancer and radiation were recently discussed in Eidemüller et al. (2023). It is a fairly recent realization that looking under the lamppost constrained thinking, limiting researchers in the field to viewing NTE as essentially "bad." Now most researchers in the field view NTE as a communication mechanism, which can transcend traditional organizational levels. This is very exciting and may open the way for development of long sought-after methods of monitoring population level or even ecosystem level impacts of low-dose radiation exposure. Instead of measuring selected biomarkers of harm in individuals, we could measure expression of and response to signals in populations.

Central importance of mitochondria

If we accept that NTE are a low-dose phenomenon and that their existence in cells that did not get a deposition of energy challenges target theory and the central paradigm of targeted DNA damage, then how are low-dose effects caused? Why is there a threshold dose? Why does the response saturate? While we do not know the answers to these questions, we do have information suggesting a central role for mitochondria in these low-dose non-targeted effects. Soon after the medium transfer induced bystander effect was published in 1997 (Mothersill and Seymour 1997). Lyng et al. showed that mitochondrial membrane depolarization due to a rapid calcium flux led to induction of apoptosis in unirradiated cells treated with medium from irradiated cells (Lyng et al. 2002, 2006a). Later studies showed migration of mitochondria towards the nucleus and shape changes associated with cytoskeletal alterations involving G-actin (Lyng et al. 2004; Olwell et al. 2005; Nugent 2008). Later studies (Liu et al. 2007) suggested that the "target size" for bystander effects was similar to the size of a mitochondrion and still later studies (Le et al. 2015a, 2018c) confirmed a role for complex 1 of the mitochondrial electron transport chain (ETC) in the transduction of the biophoton signal emitted by directly irradiated cells. This later effect leads to the release of exosomes, which transmit information to unirradiated cells resulting in the characteristic bystander effects (Le et al. 2017).

Very recently we have shown that if complex 1 in the ETC is circumvented in the directly irradiated cells, using a yeast construct ND11, then no bystander effects occur in cells receiving medium from these cells (Li 2023). The ultimate effect of complex 1 malfunction appears to be ATP depletion (Le et al. 2018c), although elevated oxidative stress could also be implicated (Mazière et al. 2000; Le et al. 2015b, 2015a; Dumbuya et al. 2020). The central role of mitochondria has recently been reviewed by Averbeck (2023). Using all these published data, we can explain the 2 mGy threshold for triggering RIBE as due to the need for a sufficient voltage to open the calcium ion channel and allow calcium to enter the cell. Liu et al. (2006) showed that for the HPV-G cell line used, radiation doses below 2 mGy were not associated with a calcium flux, while those above 2 mGy were (Liu et al. 2006). Similarly, the saturation could perhaps be explained as due to the numbers of mitochondria in cells. It is likely that there is a quantitative relationship between calcium ion increase in the cell, mitochondrial reaction, and downstream depletion of ATP. Further studies could clarify this.

An important caveat to this work is that the mechanistic studies cited above were all done in vitro using mainly human keratinocyte cells lines. While there is an abundance of evidence that bystander effects occur in vivo in multiple species, we cannot say that the mechanisms are the same, only that the phenomena are similar.

Consequences of low-dose NTE for environmental and human health

This brings us to consideration of the environmental protection implications of NTE and the implications for protection of human health. Above, when we analyzed stress signal communication, we discussed the wider relevance in ecology of these NTE mechanisms in facilitating the population level response to stressors. But what does

this mean for radiation protection? Currently radiation is regulated using an assumption of a linear relationship between dose and effect. Dose limits are set to protect humans from cancer and in the natural world to limit consequences of discharges or nuclear activities for 12 reference animals and plants. These are chosen to be representative of species living in different habitats where the exposure can be calculated and the dosimetry can be modeled or where there is sufficient information in various databases to enable decision making using, for example, the ERICA or RadResBiota tools (Doering 2010; Beresford and Copplestone 2022; Beresford et al. 2022; Maystrenko and Rybak 2022). However, NTE complicate this approach because they dissociate *dose* or *exposure* from *effect* both in space (RIBE) and in time (RIGI). This is because the effect is no longer limited to the organism that gets the energy deposition. Not only can intra organism communication of signals occur but intra- and inter-species stress communication has also been documented (Mothersill et al. 2007, 2009, 2014; Reis et al. 2018). We have previously suggested approaches to address this (Mothersill et al. 2019b, 2022a; i Batlle et al. 2022), including the addition of a term to dose effect models, which quantifies the non-targeted component over time or the use of a "variable response model." These approaches are, however, very limited as they ignore knock-on effects in complex population structures. As effect-driven rather than dose-driven models, they do take account of other stressors that can compound effects in populations and ecosystems. One question that could usefully be asked at an early point in the decision tree is whether NTE are likely to be induced by the exposure and, if so, is the outcome likely to provide protection or harm in the system under consideration.

While the ecosystem level considerations of NTE are highly complex, the issue of human protection is more straightforward. Only one species is involved, and the endpoints of harm are well identified although difficult to quantify after low-dose exposure. These include various cancers, cardiovascular disease, cataract, immune compromise, and the state of chronic fatigue and immune dysfunction syndrome (CFIDS), which can manifest actually as most of the other disease states (Lipman et al. 1988; Michael 2000; Worgul et al. 2007; Barjaktarovic et al. 2011; Hanna et al. 2015; Mothersill and Seymour 2016; Liggett and DeGregori 2017; Rusin et al. 2018, 2021, 2022; Sylvester et al. 2018; Calabrese 2019; Mothersill et al. 2022a; Rusin et al. 2021, 2022).

We have decided to use two specific diseases linked to low-dose radiation to highlight the changes in the approach to regulating low-dose exposure because of new information; these are melanoma and cataract formation (Gilchrest et al. 1999; Chumak et al. 2007; Kadhim et al. 2013; Lian

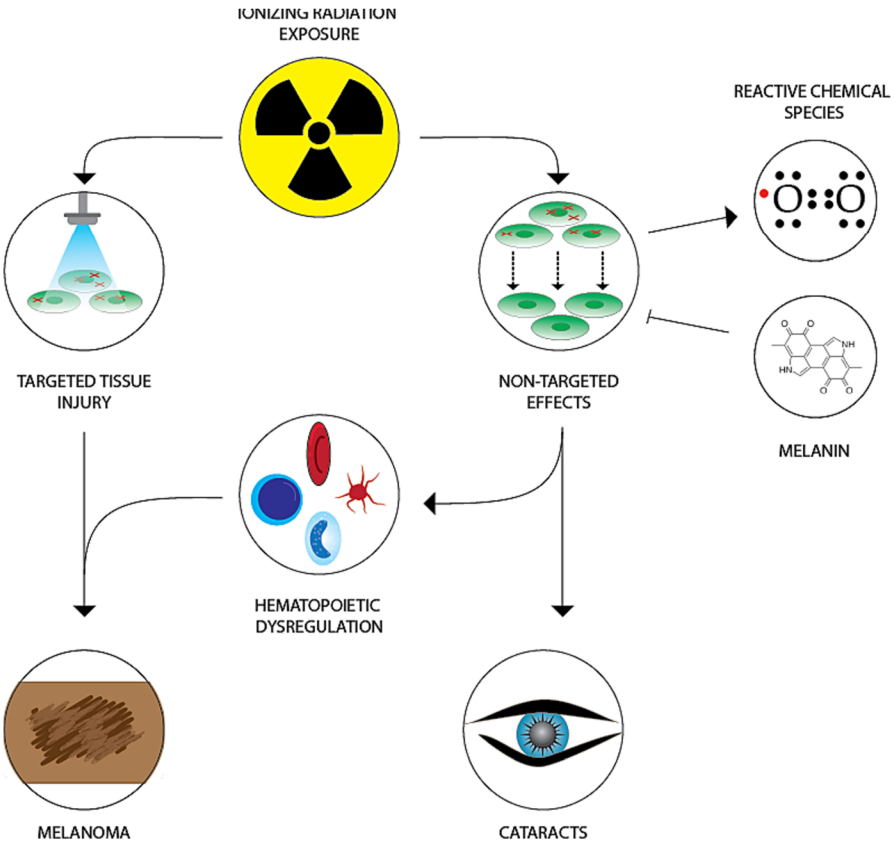

Fig. 5. Proposed model of the mechanisms which could link ionizing radiation and secondary UVA photon emission associated non-targeted effects to disease states such as cataract and melanomas.

et al. 2015; Revenco et al. 2017). They were selected because both are considered to involve UVA exposure (Moan et al. 1999; Zigman 2000; Wang et al. 2001; Francis Simpanya et al. 2008; Khan et al. 2018; Haag et al. 2021) in their etiology. As discussed earlier, UVA photons secondary to low-dose ionizing radiation exposure are an important activator of RIBE (Whiteside and McMillan 2009; Jella et al. 2014; Le et al. 2015a, 2017). Melanin protects against both conditions (Young 1988; Mosse et al. 2006; Mothersill et al. 2022) and has also been shown to prevent RIBE by absorbing the UVA photons (Le et al. 2015a). Fig. 5 shows the interactions between UVA, melanin LDR, and RIBE that can lead to melanoma and to cataracts.

Case study melanoma formation. Malignant melanoma as the most aggressive form of skin cancer (Cabaco et al. 2022), and recent evidence links it to UVA as well as UVB exposure (Moon et al. 2017; Cabaco et al. 2022; Fadadu and Wei 2022). While there is no epidemiological evidence linking radiation with melanoma induction, epidemiology is a blunt tool for low-dose exposure, and it is likely that UV exposure would mask any ionizing radiation-induced melanomas. However, given the fact that ionizing radiation can result in UVA photon production internally as discussed earlier, we thought the concept was worthy of consideration. Studies by Widel et al. (2012) and Krzywon et al. (2018) reveal that coexistence of fibroblasts with melanoma cells may strongly modulate the direct action and may change bystander effects exerted by UVA light. They found that after exposure to a UVA fluence 20 kJ m^{-2}, there was a low toxicity for melanoma cells. However, after irradiation and co-culture with non-irradiated melanoma cells, there was a strong decline in their viability and an increased frequency of apoptosis, whereas co-culture with fibroblast exerted a protective effect on irradiated melanoma cells. This again points to the complexity introduced by consideration of NTE in low-dose radiobiology. Our group recently published a model for how LDR could be implicated in melanoma etiology (Cocchetto et al. 2023). This paper proposes an integrated model with ionizing radiation as a suggested trigger for melanoma and subsequent hematopoietic dysregulation in this underlying process. This is proposed to be mediated through UVA induction and biophoton generation inside the body resulting from radiation-induced bystander effects (RIBE). Evidence in support of this approach has been organized in the model into a systems view linking melanoma markers with the initiating events, in this case, low-dose radiation exposure. This results in the formation of reactive oxygen species (ROS) as well as important immunologic and other downstream effects.

Case study cataract formation. Recent concern about cataract formation following low-dose exposure of medical and nuclear workers stems from the realization that cataract formation is a stochastic rather than deterministic process (Chumak et al. 2007; Worgul et al. 2007; Alhasan and Aalam 2022). Ali and Richardson (Ali and Richardson 2023) developed a stylized, multi-tissue eye model recently by modifying a model by Behrens et al. (2009) to include the retina, uvea, sclera, and lens epithelial cell populations. These tissues are not normally included when calculating dose to lenticular tissues, but their model suggests that in the LDR field, mechanisms targeting other tissues may be highly important. These include oxidative stress due to inflammation of other tissues and also differences in radiosensitivity caused by hypoxia in the lens. It is possible that secondary UVA photons due to NTE will increase the effective "dose" in the lens and that communication of NTE stress signals such as elevated oxidative stress will amplify the damage response (Le et al. 2015a; Mothersill et al. 2019a). Indeed, recent evidence (Ainsbury et al. 2016; Ainsbury and Barnard 2021; Laskowski et al. 2022) could support a role for NTE due to the saturable dose response seen for cataract induction by LDR, which is characteristic of damage responses driven by NTE.

In conclusion, this paper aims to review the role of non-targeted effects underlying low-dose radiation response. The mechanisms are important to consider both in environmental radiation protection where ecosystem protection is the goal and also for human radiation protection, which is concerned with prevention of radiation-associated cancers and non-cancer diseases.

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