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Mini-review

# Non-targeted effects induced by ionizing radiation: Mechanisms and potential impact on radiation induced health effects

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ABSTRACT

Not-targeted effects represent a paradigm shift from the "DNA centric" view that ionizing radiation only elicits biological effects and subsequent health consequences as a result of an energy deposition event in the cell nucleus. While this is likely true at higher radiation doses (>1 Gy), at low doses (<100 mGy) non-targeted effects associated with radiation exposure might play a significant role. Here definitions of non-targeted effects are presented, the potential mechanisms for the communication of signals and signaling networks from irradiated cells/tissues are proposed, and the various effects of this intra- and intercellular signaling are described. We conclude with speculation on how these observations might lead to and impact long-term human health outcomes.



## 0. Definitions

The following definitions of the primary NTE's are adapted from Kadhim et al. [1] and https://ssl.note-ip.org/index.asp.

### 0.1. Non-targeted effects (NTE's)

Effects manifesting in non-irradiated cells that received a signal(s) communicated from an irradiated cell. NTE's include a plethora of cellular responses usually associated with radiation exposure, plus a number of other phenotypic responses. Responses to genotoxic stress in a biological system are variable, and NTE's are not observed in all experimental model systems [2]. The degree of response depends on the time of analysis, radiation dose and dose rate and radiation quality.

### 0.2. Radiation induced bystander effects (RIBE)

Effects observed in non-irradiated cells that responded to signal(s) communicated by an irradiated cell. RIBE induce and/or modulate responses in a non-irradiated cell. These non-irradiated bystander cells may have been in the same physical environment as the irradiated cells using microbeam exposures [3,4], or cultured in medium transferred from cell cultures that had previously been irradiated [5,6]. RIBE have been observed in both *in vitro* cell culture systems [7] and *in vivo* model systems [8], and have been the subject of a recent review [9].

### 0.3. Radiation induced genomic instability (RIGI)

Effects occurring in the progeny of an irradiated cell generations after the parental cell has been irradiated. While the progeny themselves have not been irradiated they are clonally descended from an irradiated cell, e.g., [10,11].

### 0.4. Abscopal effects

Abscopal effects are generally associated with clinical exposures to ionizing radiation in a radiotherapy type situation [12]. It should be noted that "abscopal effects" are often included as a non-targeted effects of exposure to ionizing radiation, e.g., [8], however, according to the definitions above, this is not correct. During radiotherapy the tumor receives a very large dose of radiation, e.g., 60–70 Gy, the normal tissue in the field of the beam receives a much smaller but still significant radiation dose, e.g., 4–6 Gy, and the whole body is exposed to a comparatively low dose of radiation via leakage from the head of the therapy unit, scattering at the beam collimators and the flattening filter resulting in incident scatter within the treatment room, and scattering from the directly irradiated region of the patient, i.e., internal scatter [13]. Because the whole body therefore receives some radiation dose, any "out of field" abscopal effects should be considered "low dose radiation effects". For the purpose of this discussion, abscopal effects are not considered NTE's.

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## 1. Introduction

NTE's are not new and have been the subject of intense research over the last 20 years (http://lowdose.energy.gov and https://ssl.note-ip.org/index.asp). The concept that NTE's might play a role in radiation health effects has been suggested [14,15]. Indeed, many of the phenotypes associated with NTE's have also been associated with cancer and the carcinogenic process and, more recently, with a host of non-cancer effects [16]. Thus, rather than provide a comprehensive review of NTE's research and how they might impact health effects associated with exposure to ionizing radiation, we hypothesize that NTE's do contribute to the health effects caused by exposure to ionizing radiation and focus on the signaling mechanisms that may be involved. This is a hypothesis and hypotheses should be testable. Consequently a challenge for the future is to design testable hypotheses to support or refute the conclusions drawn from observations that suggest a link between observed NTE's and radiation-induced health effects.

## 2. What are non-targeted effects and are they interrelated?

NTE's include RIBE and RIGI, and reflect a number of endpoints including, but not limited to, the induction of mutation and chromosome rearrangements, gene expression changes and cell killing [17]. There appears to be a link between RIBE and RIGI [18,19]. The overwhelming consensus is that there is a strong link between these manifestations of NTE's and this has been supported experimentally [20]. Indeed, RIGI might be considered under the rubric of a RIBE. NTE's appear to be largely a low radiation dose phenomenon [21], although this is controversial [22]. At high doses the effects observed will likely be largely overwhelmed by direct damage to cells. We should mention that as the dose is decreased, the energy deposition will be heterogeneous on the spatial scale of the cell or tissue [23] and not all cells may have a direct interaction, and non-targeted effects are likely contributors to the observed response. This is particularly the case for low dose exposures of high LET radiation, e.g., iron ions, for discussion see [24].

## 3. Health effects associated with exposure to ionizing radiation

Ionizing radiation is a carcinogen, albeit at low doses a relatively poor one. The role of radiation in non-cancer effects, i.e., cardiovascular effects, hypertension, stroke and opacities in the lens of the eye [25] as well as central nervous system effects [26], is evolving and subject to intense investigation. At higher doses, radiation induced carcinogenesis is less controversial and estimates of cancer risk suggest a 5% increase in risk per Sv of radiation exposure. The risk for radiation-induced cancer varies as a function of sex, age at exposure, radiation dose and dose rate, the quality of radiation, and a host of genetic, epigenetic and lifestyle factors that characterize the exposed individual [27].

Epidemiological studies suggest a latency period of 4–8 years for leukemia and 15+ years for solid cancers [28]. Obviously many molecular, biochemical, and cellular events occur between the initial radiation exposure and the manifestation of the cancer phenotype. However, much of experimental radiation research has focused on events occurring at much shorter times after exposure; days and weeks, and occasionally months rather than years. These studies include analysis of alterations in gene, protein and metabolome expression, induction of mutations, chromosomal rearrangements, cell cycle alterations, and apoptosis, predominantly in *in vitro* model systems, although there are studies in small and large animal models [29]. Many of these studies have utilized radiation doses greater than 100 mGy. The goals of this review are to discuss how NTE's might impact these well-described initial events associated with radiation exposure and speculate on how they might contribute to long-term health effects.

A central premise is that both targeted and NTE's lead to the activation of inflammatory cytokines [30]. An excellent review on inflammatory cytokines was recently published by Schaue et al. [31]. We hypothesize these cytokines stimulate the innate immune system within the organ/organism, i.e., elicit a stress response, and over time disrupt tissue homeostasis and elicit a plethora of down stream effects, some of which can ultimately result in detrimental health effects. For example, the radiation induced release of cytokines may be the result of the direct action of radiation, or the result of a cascade of reactive radical species induced in targeted and non-targeted cells [32]. Cell populations showing RIGI show persistently elevated levels of reactive oxygen species (ROS) [33,34]. Furthermore, RIGI can be attenuated by ROS scavengers [35]. The persistent elevation in ROS observed in unstable clones appears in part to be mediated by dysfunctional mitochondria [36,37]. Likewise, dysfunctional mitochondria have been implicated in the RIBE [38,39]. This central premise is summarized in Fig. 1.

## 4. What factors might be involved in communicating non-targeted effects?

As expected from a biological process, there are likely to be multiple pathways to a particular endpoint associated with NTE's. These presumably reflect the experimental system interrogated, the endpoint analyzed and dose and dose rate effects of the radiation exposure. A number of factors are likely to be involved including connexin mediated cell-to-cell gap junction communication [40]; reactive oxygen/nitrogen species [41]; iNOS [42]; and cytokines/chemokines [43]. There are results that suggest that the RIBE and RIGI are at least in part mediated by exosomes, implicating a role for RNA in the propagation of NTE's [44]. Other studies suggest that effects in non-targeted cells might well be modulated by DNA repair capacity [45]; epigenetic factors [46]; and/or mitochondrial dysfunction [36]. All candidate processes have scientific merit and

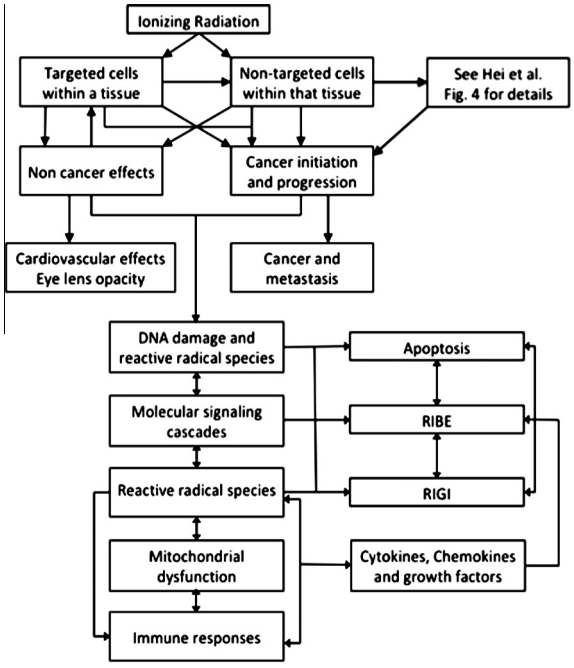


**Fig. 1.** Schematic proposing the relationship between targeted and NTE's, their potential impact on health outcomes, and the inter- and intra-cellular processes that may drive the manifestation of NTE's in the target tissue.

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indicate the plethora of cellular and tissue responses that can respond to exposure to ionizing radiation. While it is likely many of these pathways are redundant [47], the wide assortment of candidate signaling pathways referred to above indicate the complexity of tissue responses to irradiation.

## 5. Potential mechanisms of radiation induced non-targeted effects – a stress response?

NTE's represents a paradigm shift in our understanding of the mechanism(s) of how radiation might exert its effects. It is likely that multiple pathways are involved in signaling the response from an irradiated cell to a non-irradiated cell, and that different cell types will respond differently to the signaling pathways stimulated. A unifying model has been proposed by Hei et al. [38] that paints in broad strokes the potential signaling pathways that may be involved in communicating NTE's (see Hei et al. Fig. 4). Following irradiation, multiple signaling cascades initiate the downstream signaling processes necessary to mediate the non-targeted response. This model proposes that the binding of cytokines/chemokines and growth factors mediates the response. In general, cytokines and growth factors cause a large range of tissue-specific effects. They can impact the micro-environment in the region of the damaged cell or tissues by affecting the stroma, the epithelial cell composition and growth factor stimulation. They can upregulate gene expression, and ultimately result in the observed biological response. These stress response signaling pathways can be initiated in the cell membrane by the rapid activation of cytokine and growth factor receptors [48–50]. Such signaling cascades in turn can contribute to the signals transmitted to the non-targeted cells.

A number of intracellular transducers and signaling pathways have been proposed but transforming growth factor β (TGFβ) appears to be particularly important following radiation exposure [51]. TGFβ signaling is activated after irradiation and orchestrates a complex network of cellular responses. TGFβ acts via autocrine, paracrine and endocrine mechanisms and depending upon the cellular microenvironment can exert both tumor promoter and tumor suppressor effects [52].

Inflammation is a significant endpoint of the activation of stress response signaling [53]. Inflammation can lead to the generation of reactive radical species and feedback can occur when radiation activates ROS/RNS leading to downstream effectors that further activate ROS/RNS. This positive feedback loop likely targets the mitochondria [36] and other membranous structures to perpetuate the induction of reactive radical species [54].

## 6. Bridging the gap between radiation exposure and radiation health effects: a role for NTE's?

Thus far, most of the available data on NTE's have been largely phenomenological. While future mechanistic studies are likely to identify signaling pathways and the molecules involved, the relevance of NTE's to human health remains unclear. A key question in this discussion is whether NTE's are limited to a specific cell type within an organ, to the whole organ or to the whole organism. The answer to this is not immediately obvious. But the fact that NTE's occur indicates that the communication of a radiation response from an irradiated tissue area to a non-irradiated tissue volume, be it by factors passed via cell-to-cell communication, or by factors released, shed or secreted by irradiated cells has significant implications for the long term consequences of exposure to ionizing radiation. This in turn suggests that radiation effects might well manifest outside the region actually irradiated. The impact of this for radiation protection has previously been addressed [55].

## 7. Is there a role for inflammatory responses cancer and non-cancer effects?

Physiological levels of reactive oxygen and nitrogen species play critical roles in numerous cellular functions. In irradiated and NTE cells and tissues the levels of reactive radical species may be increased due to perturbations in oxidative metabolism and chronic inflammatory response [56], both of which impact the carcinogenic processes [57,58]. For example, a study from Gollapalle et al. [59] showed that several weeks after irradiation non-exposed tissues had high levels of presumably oxidative stress induced clustered DNA lesions. Likewise defects in mitochondrial functions lead to a host of pathological conditions including cancer [60,61]. A persistent inflammatory response has been described in animals following irradiation [62] and in the atomic bomb survivors [63,64].

That ionizing radiation is a carcinogen is well established. What is most interesting are the recent reports demonstrating a role for radiation as a risk factor for non-cancer effects [65] including the lens of the eye [66] and non-cancer brain effects [67] and cardiovascular disease [68]. Radiation exposure and circulatory disease has been described in the atomic bomb survivors [69], and in a cohort study based on the Canadian national dose registry of radiation workers [70]. In a comprehensive review Little and colleagues [71] summarized the epidemiological associations between radiation and late cardiovascular effects and speculate on potential mechanisms for these observations. It is tempting to speculate that these non-cancer pathologies are the result of inflammatory processes and the subsequent sequelae of tissue reactions [72,73].

## 8. Relationship of NTE's to radiation induced health effects

The connections between the manifestations of NTE's and the hallmarks of carcinogenesis are obvious. Both are complex processes modulated by a number of factors including genetics, epigenetics, environment, and target organ (tissue). Following irradiation, cancer process may be initiated, but a sequelae of factors must come into play to promote this process and override the innate host immune system. NTE's may well play a role in upsetting tissue homeostasic regulation [54]. The persistence of increased reactive radicals, mitochondrial dysfunction, etc., may drive RIGI thereby providing a dynamic for the carcinogenic process, and an environment conducive to other detrimental effects associated with radiation exposure. We have attempted to summarize this schematically in Fig. 1. While radiation biology has traditionally focused on many of the initial events associated with radiation exposure, DNA damage and repair, mutation induction, chromosomal rearrangements, etc., until recently comparatively little attention has been paid to the long term delayed consequences of irradiation, particularly at low doses (<100 mGy; Morgan and Bair [74]). Our challenge for the future is to link responses that occur on multiple spatial and temporal scales, and to pursue predictive computational approaches to refine and guide experimental design and hypothesis generation. Such integrated approaches will allow us to identify the signaling networks involved in communicating signal(s) from an irradiated cell to a non-irradiated cell, understand their evolutionary significance, and their role, if any, in the detrimental health effects linked to exposure to radiation.

## Conflict of Interest

The authors declare that there are no conflicts of interest.

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