Cancer: Cell Structures, Carcinogens and Genomic Instability
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Effects of ionizing radiation on cellular structures, induced instability and carcinogenesis

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Abstract. Ionizing radiation is perhaps the most extensively studied human carcinogen. There have been a number of epidemiological studies on human populations exposed to radiation for medical or occupational reasons, as a result of protracted environmental exposures due to radiation accidents, or after atomic bombings. As a result of these studies exposure to ionizing radiation has been unambiguously linked to cancer causation. While cancer induction is the primary concern and the most important somatic effect of exposure to ionizing radiation, potential health risks do not only involve neoplastic diseases but also somatic mutations that might contribute to birth defects and ocular maladies, and heritable mutations that might impact on disease risks in future generations. Consequantly it is important we understand the long-term health risks associated with exposure to ionizing radiation.

Key words: Genomic instability, ionizing radiation, non-targeted effects, radiation carcinogenesis.

Introduction

According to the American Cancer Society, the United States can expect 1368030 new cases of cancer in 2004 [1]. Among the many carcinogens Americans are exposed to, ionizing radiation will contribute to this statistic. Humans live in a radiation environment. Ionizing radiation is in the air we breathe, the earth we live on, and the food we eat. Man-made radiation adds to this naturally occurring radiation level, thereby increasing the chance for human exposure. For many decades the scientific community, governmental regulatory bodies, and concerned citizens have struggled to estimate health risks associated with radiation exposures, particularly at low doses. While cancer induction is the primary concern and the most important somatic effect of exposure to ionizing radiation, potential health risks do not involve neoplastic diseases exclusively, but also include somatic mutations that might contribute to birth defects and ocular maladies, and heritable mutations that might impact on disease risks in future generations. Consequently, it is important we understand the effect of ionizing radiation on cellular structures and the subsequent long-term health risks associated with exposure to ionizing radiation.

Radiation carcinogenesis

Ionizing radiation is perhaps the most extensively studied human carcinogen. There have been a number of epidemiological studies on human populations exposed to radiation for medical or occupational reasons, as a result of protracted environmental exposures due to radiation accidents, or after atomic bombings (reviewed in [2]). As a result of these studies, exposure to ionizing radiation has been unambiguously linked to carcinogenesis. While many types of human cancer have been convincingly linked to radiation, there are a few notable exceptions including chronic lymphocytic leukemia, Hodgkin's disease, cervical cancer, and prostate cancer.

Cancer incidence is modified by the dose rate, the total dose of radiation delivered, and the quality of radiation, with high linear energy transfer radiation, e.g., radon α particles being more biologically effective than low linear energy transfer radiation, e.g., x- or γ-radiation. In general radiation carcinogenesis is a stochastic effect. That is, the probability of an effect increases as the dose increases, with no dose threshold. However, the severity of the effect is not dose related, such that a high dose of radiation does not induce a "worse" cancer than a low dose of radiation. It should be noted that there are also deterministic effects associated with radiation exposure. While these effects are comparatively rare relative to the well-documented stochastic effects, deterministic effects indicate a threshold of dose and the severity of the effect is dose related. Radiation induced cataracts are an example of a deterministic effect.

There are a number of biological modifiers of radiation-induced cancer risk. These include age at time of exposure, sex, and the target organ. In addition, the cancer risk can be modulated by potential genetic susceptibility factors such as polymorphisms in genes involved in cellular responses to DNA damage (reviewed in [3]). So while it is clear that radiation exposure can lead to cancer, what is not clear is how radiation causes cancer. Cancer appears to arise from the accumulation of multiple genetic abnormalities including gene mutations, deletions, rearrangements and/or alterations in gene expression, as well as chromosomal rearrangements and changes in chromosome number. Radiation-induced cancers have a long latency period between exposure and the appearance of the malignancy. The shortest period is for leukemia, with a peak 5–7 years, but solid tumors show a longer latency period, anything from 10 to 50 years and the excess risk appears to be a lifelong elevation of the natural age-specific cancer risk [4].

Unfortunately for those studying the mechanisms of radiation-induced carcinogenesis and attempting to understand radiation-induced cancer risk, there is no unique signature to cancers associated with radiation exposure. Instead, radiation-induced cancers are similar to those occurring spontaneously.

Radiation-induced genetic damage

Conventionally, radiobiologists have assumed radiation damage can only result from energy deposited directly within the cell nucleus. This deposition of energy results in single- and double-strand DNA cleavage, DNA-DNA and DNA-protein cross-links, and DNA base damages [5]. Failure to faithfully repair these induced damages can result in genetic recombination, deletions, mutations, chromosomal rearrangements and/or cell death [6]. There is no question that these forms of directly induced DNA damage contribute to radiation carcinogenesis. It is assumed that surviving cells can pass on this legacy of radiation to their progeny, thus initiating the carcinogenic process. According to this process, mutations activating oncogenes or deletions affecting tumor suppressor gene function are believed to lead to the accumulation of genomic changes associated with carcinogenesis. Cancer is, therefore, dependent upon the probability of an ionizing event occurring in the genome. This stochastic effect implies radiation causes cancer at random and higher doses only increase the chances of a direct DNA traversal. However, the long latency period between radiation-induced DNA damages and subsequent development of cancer begs the question that directly induced genomic damage might not be responsible for initiating the carcinogenic process, unless it can generate cellular processes leading to genomic instability and the subsequent accumulation of genetic abnormalities.

One of the hallmarks of cancer is its inherent genomic instability, e.g., [7, 8]. Because of the long latency period it is difficult to assign a causal relationship for a specific gene mutation to the development of radiation-induced cancer. Indeed, there is intriguing new evidence uncoupling directly induced DNA damages from the detrimental health effects of radiation exposure. Prakash Hande and colleagues [9] recently reported the detection and quantification of stable intra-chromosomal aberrations in lymphocytes of healthy former nuclear weapons workers exposed to plutonium. Even many years after occupational exposure, a high proportion, in some case more than 50%, of the blood cells of these healthy plutonium workers contained large (>6 Mb) intra-chromosomal rearrangements. The yield of these cytogenetic rearrangements was highly correlated with plutonium dose to the bone marrow, and the control, non-exposed group contained very few such intra-chromosomal aberrations. Thus, the radiation workers, despite their healthy and long-lived status, showed a significant chromosomal aberration burden many years after exposure. This indicates that directly induced radiation damage in this instance chromosomal rearrangements are a superb indicator of radiation exposure but do not necessarily initiate cancer risk. Nevertheless, it remains to be seen whether individuals with a high yield of intra-chromosomal rearrangements are more prone to developing cancer as this population continues to age.

At this stage it would be misleading to conclude that cellular responses to radiation-induced DNA damage have no implications for radiation carcinogenesis. Rearrangements involving *RET* are common in radiation-associated

papillary thyroid cancer (*PTC*), e.g., in childhood thyroid cancers associated with the Chernobyl accident [10, 11], and in thyroid cancers from patients with a history of medical external irradiation [12, 13]. The *RET/PTC1* type of rearrangement is an inversion of chromosome 10 mediated by illegitimate recombination between *RET* and the *H4* gene, which is 30 Mb away from *RET*. Spatial contiguity of *RET* and *H4* might provide a structural basis for generation of *RET/PTC1* rearrangement presumably by allowing a singe track to produce a double-strand break in each gene at the same site in the nucleus [14]. Interestingly, such cytogenetic alterations can be detected 48 hours after exposing human fetal thyroid explants exposed to ionizing radiation [15]. It therefore appears reasonable to suggest that the induced *RET – H4* rearrangement facilitates formation of *RET/PTC1* in irradiated thyroid cells.

Radiation-induced genomic instability

Loss of genomic stability is becoming widely accepted as one of the most important processes in the development of cancer [16, 17]. There is now considerable evidence that exposure to ionizing radiation can result in induced genomic instability in the progeny of cells surviving irradiation. Radiation induced instability is a genome wide process, manifesting as the increased acquisition of chromosomal changes, mutation(s), micronuclei, gene amplifications, transformation, alterations in gene expression and/or cytotoxicity in the clonal descendants of an irradiated cell, and has been the subject of a number of recent reviews [18, 19]. The phenotype of radiation-induced instability suggests that genomic changes are not induced directly by the deposition of energy in the cell. Instead, it appears that the instability can manifest in the progeny of an irradiated cell some generations after the initial insult [18, 19]. In addition, recent evidence suggests that induced instability can occur in cells that were not actually irradiated. Instead, they may have been in a radiation environment but not traversed by the radiation [20–22], or have received medium from irradiated cells [23]. Thus, instability can also be a non-targeted or bystander-type consequence of radiation exposure [22, 24].

Mechanisms of radiation-induced genomic instability

Clonal expansion of cells surviving radiation exposure and subsequent cytogenetic analysis of progeny cells indicates chromosomal instability occurs at a very high frequency. For example, in their pioneering study of delayed effects of radiation, Kadhim et al. [20] found that up to 50% of surviving colonies showed chromosomal aberrations in the clonal descendants of an irradiated normal mouse bone marrow cells after exposure to α particles. This high frequency of induction has been confirmed by a number of other laboratories (reviewed in [25, 26]), and pooling the result from a large number of investi-

gations in the Morgan laboratory, a frequency of 3% of surviving colonies exposed to low linear energy transfer x-rays [25] and 4% of surviving colonies exposed to high linear energy transfer radiation [27] displayed chromosomal instability. This high frequency event suggests that it is unlikely that a single mutation can account for the observed instability. Instead, more profound disruption of pathways controlling cellular homeostasis [28], alterations in gene expression [29], and/or modifications of the cell culture environment [30–32] are more likely to account for the observed phenotype.

Once initiated, instability can be perpetuated in clones by recombinational mechanisms involving interstitial repeat sequences within the genome [33], and/or the formation of dicentric chromosomes stimulating bridge breakage fusion cycles, which generate novel chromosomal rearrangements [34]. In many instances genomically unstable clones show persistently elevated levels of reactive oxygen species [35, 36] and a general failure to thrive, as measured by clonogenic survival as a function of time after the initial radiation exposure [37, 38]. This so called delayed reproductive cell death [37], or lethal mutation [38], results in increased numbers of apoptotic cells in unstable clones, which might in turn contribute to the perpetuation of instability by releasing lytic factors into the culture media. These lytic factors may provide a mechanism for DNA cleavage, resulting in DNA repair-mediated mutation induction or the interaction of induced breaks leading to chromosomal rearrangements. Whether or not lytic factors contribute, there is evidence for soluble factors either secreted by unstable cells or produced as byproducts of unstable cells contributing to the instability phenotype [32]. A schematic model for how radiation-induced genomic instability might be perpetuated *in vitro* is presented in Figure 1.

Radiation induced genomic instability and radiation carcinogenesis

Induced instability *in vitro* likely has an extracellular component whereby signal(s) from an unstable cell can elicit responses in non-irradiated cells [24]. These signals might be actively secreted by unstable cells or might be the result of lytic products from dead and dying cells characteristic of unstable clones [31, 39]. How this translates to the *in vivo* situation is not clear. Radiation-induced genomic instability has been described *in vivo*, although this is certainly not as straightforward or as convincing as the *in vitro* model systems (for discussion see [19]). Instability *in vivo* has a significant genetic component (reviewed in [40]) and is likely influenced by the instability endpoint being assayed [41]. A role for a transferable soluble secreted factor(s), so-called "clastogenic factor(s)" produced in blood plasma from irradiated humans and animals, capable of causing chromosomal damage in non-irradiated lymphocytes, has been described after a number of exposure situations (reviewed in [3]). Thus, there is the precedent for secreted factors eliciting a

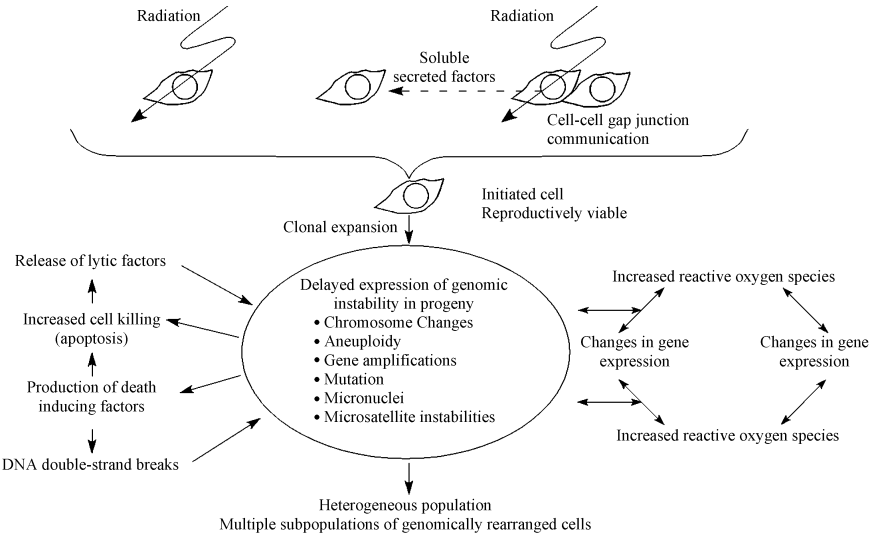

Figure 1. Schematic representation of radiation-induced genomic instability. Ionizing radiation initiates the instability phenotype either directly by hitting the target cell or indirectly via the secretion of soluble factors or cell-to-cell gap junction-mediated communication from an irradiated cell to a non-irradiated cell. Once initiated, instability can manifest in the progeny of that cell during clonal expansion and is measured by multiple endpoints [41]. Cell clones showing induced instability can also exhibit persistently elevated levels of reactive oxygen species [35, 36], which in turn can stimulate changes in gene expression, and/or protein/enzyme levels [50]. The combination of increased reactive oxygen species and subsequent altered cellular homeostasis provide protracted stimuli perpetuating instability over time. Some unstable clones also generate soluble cytotoxic factors, such that media from unstable clones is lethal when transferred to non-irradiated cells [31]. This 'death-inducing effect' results in the induction of DNA double-strand cleavage rapidly after transfer to recipient cells, leading to chromosome changes, micronuclei formation and ultimately cell death [39]. The majority of exposed cells die by apoptosis [39], which might result in lytic products from these dead and dying cells contributing to the 'death-inducing effect' and perpetuating instability over time [24]. The end result is a heterogeneous population of cells containing multiple genomically rearranged subpopulations resulting from clonal expansion of a radiation-initiated cell. The phenotypes of radiation-induced genomic instability are similar to those described for tumor cells.

damage response in undamaged cells, although there is considerable inter-individual variation in both production and response.

Wright and colleagues [42] recently proposed an interesting and plausible mechanism for delayed effects of radiation *in vivo*. They observed that macrophages exhibited the phenotype of activated phagocytes after whole body irradiation of mice. The characteristics of these macrophages are consistent with features of inflammatory responses known to have the potential for both non-targeted bystander type responses and persisting damage, as well as for conferring a predisposition to malignancy. Consequently, radiation-induced instability *in vivo* might reflect inflammatory-type responses to radiation-induced stress and injury. The observations of persistent inflammatory activity in some of the A-bomb survivors [43] lends credence to the hypothe-

sis that radiation injury may predispose exposed individuals to an assortment of detrimental health consequences including malignancy.

Despite the obvious appeal and logic of induced instability providing a mechanism for radiation-induced carcinogenesis, a definitive link has yet to be established. Radiation-induced instability has been observed in the majority of human and rodent primary cells tested, e.g., peripheral blood lymphocytes [44], and bone marrow cells [20, 45]. It appears to be independent of cellular TP53 gene status [46], and the endpoints associated with radiation-induced instability are similar to those observed in tumor samples. Sigurdson and Jones [47] recently reviewed the evidence for a role for induced instability in second cancers observed after radiotherapy. They concluded that they could not confirm or refute that instability induction by radiation is involved. A similar conclusion was reached by Goldberg [48, 49], but both groups of investigators outlined strategies by which prospective clinical trials could be designed to provide unique insights into genome-protective cellular defense responses, radiation carcinogenesis, optimization parameters for radiation therapy and radiation risk assessment for health and regulatory purposes.

Conclusions

That exposure to ionizing radiation can cause cancer is a given fact, but how it does so is not known. In a variety of cells *in vitro* [18] and model systems *in vivo* [18], radiation can induce destabilization of the genome such that surviving cells acquire many of those characteristics associated with tumor cells. As such radiation-induced genomic instability has been proposed as a very early, if not an initiating event in radiation carcinogenesis. However, despite the attraction of such a concept, a definitive link between induced instability and carcinogenesis has yet to be established.

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