4-1-2022

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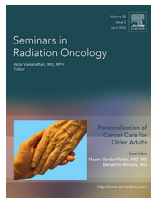
Recommended Citation

Al-Jumayli M, Brown SL, Chetty IJ, Extermann M, and Movsas B. The Biological Process of Aging and the Impact of Ionizing Radiation. Semin Radiat Oncol 2022; 32(2):172-178.



The Biological Process of Aging and the Impact of Ionizing Radiation

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Ionizing radiation is used to create models of accelerated aging because the processes of aging and radiation injury share common elements. In this chapter we review the biological processes of aging and the similarities and impact of ionizing radiation on those processes. The information draws on data from laboratory studies and from epidemiology studies of radiation exposure victims. The chapter reviews the effects of radiation on DNA, cells, and organs systems on aged adults. The science of aging and the effect of radiation on the aging process are areas of active research and our understanding is evolving.

Semin Radiat Oncol 32:172–178

Introduction

Radiation is given to patients of all ages. Cancer is an age-related disease, and the majority of cancer patients receiving radiation therapy are older than 65. With age comes diversity in health. Senescence may occur at different rates in different organs. It can be influenced by comorbidities, medications, and external factors. Radiation itself has been implicated in inducing accelerated aging.[1,2] Older animal models show greater sensitivity to the mutagenic effect of radiation.[3] Furthermore, nowadays, radiation is frequently given with cytotoxic chemotherapies which have their own toxicities and can highten the toxicities and aging effects of radiotherapy.

Aging has been defined as the time-related deterioration of physiological functions necessary for survival.[4] In simple terms, ionizing radiation through molecular and cellular events affects aging in 3 ways. Cell damage causes carcinogenesis. Cell death results in tissue injury. Molecular events lead to nonspecific life-shortening. The molecular and cellular processes affecting the aging of cells, tissue, and individuals are an evolving science.

In the late 1940s, through to the 1960s, the effect of ionizing radiation (IR) on longevity was vigorously pursued and formulated.[5,6] At that time, Upton et al.[7] studied the accelerated aging and shortened life span in mice by a single large, nonlethal dose of gamma-rays from an atomic bomb explosion. The fundamental questions regarding the biological basis governing the effects of radiation on longevity remained virtually unanswered due to uncertainty concerning radiation's ability to accelerate the normal aging process. At the time, the connection between radiation and aging was considered weak because radiation's effects, unlike aging, appeared to mostly cause genetic damage and affect dividing cells (as opposed to postmitotic cells) and radiation's detrimental effects were thought to almost always be confined to causing neoplasms.[8,9]

In general, radiation-mediated aging appears to be more associated with free-radical damage, Double Stranded Breaks (DSBs), apoptosis, and inflammation rather than dysfunctional metabolic processes. The biological mechanisms of aging - including oxidation stress, chromosomal damage, apoptosis, senescence cells, inflammation, telomere shortening, and stem cell exhaustion - are now much better understood and continue to converge with radiation's biological effects. Ironically, radiation hormesis is best demonstrated in its ability to reduce inflammation. Some animal studies suggest radiation, at chronic low levels, increases longevity. However, there is virtually no support for a life span extending hypothesis for A-bomb survivors and other exposed groups[10]; this is well documented for radiation-induced aging at high doses.[11]

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Conflict of interest: Dr Extermann: Aileron, Alnylam (consulting), OncLive (honoraria); Dr Brown: NIH (R01 CA218596), Humanetics (patent royalties). Dr Movsas: Research support to Department from Varian, ViewRay and Philips.

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https://doi.org/10.1016/j.semradonc.2021.11.011
1053-4296/

Recent advances in technology and computing power have opened new avenues of understanding of the relationship between radiation exposure and aging. In addition, epidemiology studies, driven especially by A-bomb survivors, have matured. In the following text, the impact of radiation exposure on the molecular and cellular factors affecting the biological process of aging are reviewed along with a discussion of lifestyle factors (exercise, diet, etc.) that can influence response to radiation and common medications that reduce those effects.

Epidemiology

The historical reasons for rejecting any relationship between radiation and aging have diminished with contemporary epidemiological studies that find radiation health effects are now not limited to an excess risk of cancer. Epidemiological data, especially from A-bomb survivors on cancer and non-cancer diseases, associates radiation exposure with much of the aging health effect spectrum, maybe more than for any other contaminant or progeroid syndrome.[11] Radiation risks now extend to excess heart disease, stroke, digestive diseases, and respiratory diseases. Some of these medical disorders linked to metabolic syndrome (also known as the insulin resistance syndrome) such as diabetes, atherosclerotic diseases, and dementia, appear to be more strongly related to obesity and an overactive TOR nutrient pathway than with radiation-mediated reactive oxygen species (ROS).[12,13]

Cancer and Non-cancer Health Effects

There is a significant rise in the incidence and mortality rates of cancer and non-cancer diseases with age. Epidemiological studies showed an association between ionizing radiation and most forms of cancer and some non-cancer diseases. Cancer, cardiovascular disease, dementia, and type 2 diabetes are elevated in older A bomb survivors (Table 1). The excess incidence rates of most solid cancers induced in A-bomb survivors are mainly dependent on the attained age of the individual, rather than the age at exposure or age since exposure[14] Furthermore, there was strong evidence of a graded dose-response for doses exceeding 500 mSv.

Positive associations between ionizing radiation and cardiovascular disease have been reported for radiotherapy patients and radiation workers, but not at population radiation background levels.[15] Furthermore, radiation-induced cataracts were found to happen with a low or absent dose threshold among Atomic bomb survivors. Evidence is emerging that the immune systems of Atomic bomb survivors were damaged in proportion to the dose of radiation that they were exposed to in 1945.[16] Radiation can enhance the progression of liver disease and liver cancer when hepatitis C is present.[17]

There is a significant evidence of higher incidence of common age-related diseases, such as type 2 diabetes, and cognitive impairment. This result is unexpected especially due to the latter 2 diseases being associated with oxidative stress and inflammation, both characteristics of radiation exposure. Hayashi et al. found that atomic-bomb survivors with specific HLA haplotypes may have an increased risk of diabetes with increased-dose categories.[18] Similarly, intracranial radiotherapy leads to permanent and significant cognitive disability in 50%-90% of patients.[19]

Loss of skin elasticity is another physiological aging factor but also precedes erythema during high dose radiotherapy.[20] Analysis of early A-bomb data by Hollingsworth et al.[21] showed no dose-response for physiological markers of aging such as greying hair and skin elasticity, although these negative associations were contradicted by a later study.[22,23] As some atomic bomb survivors are still living, our understanding of the relationship that radiation exposure has on the aging-associated spectrum of degenerative conditions will evolve.

Oxidative Stress, Antioxidants, and Inflammation

Reactive oxygen species (ROS) can promote many aspects of tumor development and progression at different levels, including cellular proliferation, evasion of apoptosis, tissue metastasis and invasion, as well as angiogenesis.[24] As ROS constitute a persistent source of DNA damage, they are

Table 1 Supporting Evidence of Ionizing Radiation-Induced Pathological Changes and Accelerated Aging Effects

Biological Effect of Aging	Radiation Effects	Reference
Apoptosis	dose response cell death was seen in Atomic bomb survivors	83
Cancers	Excess leukemia and solid cancer in Atomic bomb survivors	84
Cardiovascular disease	Excess heart disease and stroke in Atomic bomb survivors	
Cataracts	More common in Atomic bomb survivors	85
Chronic inflammation	Increase in Atomic bomb survivors	86
Infectious disease	Low prevalence of anti-hepatitis C virus antibody and chronic liver disease among atomic bomb survivors (low prevalence)	17
Cognitive impairment and Dementia	Radiotherapy of the head can cause Dementia or Cognitive Impairment	19
Skin changes	skin elasticity, hair greying	22
Type 2 diabetes	Positive association of type -2 DM of A-bomb survivors	18
Shortened life span	Life spans shortened for Atomic bomb survivors	23

assumed to contribute to the age-related deterioration of functions in the organism. This imbalance may lead to age-dependent oxidative stress that compromises both cellular structures and homeostasis.[25]

Ionizing radiation worsens an already unbalanced oxidant-antioxidant status in aging cells. Radiation results in the high local production of ROS attributable to chemical interactions between high-energy electrons, photons, and the molecular targets of oxygen and water within cells. Radiation can also produce ROS through signaling processes that evolve in their release from mitochondria. Radiotherapy promotes further oxidative shift, which in turn potentiates the already existing chronic oxidative stress linked to breast cancer and aging, resulting in a further increase of mutagenic potential.[26]

Similarly, antioxidant protection against curative and palliative doses of ionizing radiation in human blood was reported to decrease with aging.[26] Adding antioxidant supplements to the diet can minimize the effects of ionizing radiation later on.[27] The opposite approaches were achieved with knocked-down cytoglobin (a vertebrate globin that scavenges ROS), which made glioma cells more sensitive to radiation.[28]

In summary, irradiating aging cells that already display an unbalanced oxidant-antioxidant status would unequivocally contribute to overload the antioxidant systems. In aging cells, when ROS production exceeds the antioxidant defense capacity of the cell, excess oxidative stress occurs and induces damage to the DNA, proteins, and membrane lipids. Radiation further contributes to ROS generation, increasing the possibilities of oncogenic transformation.

Telomere Attrition and Genomic Instability

The length of telomeres in somatic cells shortens over time due to increasing age or pathogenic factors, and a shortening telomere is a trigger for cellular senescence. Both chemotherapy and radiation therapy significantly impair telomere maintenance and function in normal human cells, which may lead to cellular senescence) and ultimately result in tissue/organ damage and secondary malignancies in long-term survivors of cancer.[29]

Cell proliferation beyond replicative senescence leads to uncapped chromosomes that can fuse with each other or with their sister chromatids after DNA replication.[30] Such unstable chromosome configurations can set up fusion −bridge−breakage cycles, which are prone to produce rapid and important changes in gene dosage, thus linking telomere dysfunction and chromosome instability. Carcinogenesis is particularly induced when the cellular response to telomere attrition is reduced due to cell cycle checkpoint defects, as demonstrated by studies carried out in mice with impaired p53 function.[31]

Telomere dysfunction is an important component of the genomic instability observed in human cancer measured using a PCR-based assay designed to detect telomere fusions.[32] Age-dependent telomere attrition in a cell environment with impaired cell cycle checkpoints contributes to human carcinogenesis in older adults. There is limited and equivocal information available on the change in the telomere. Cells with short telomeres are more radiosensitive than their long telomere counterparts.[33] Shortened telomeres provide radiation-induced double-strand breaks (DSBs) with a new joining possibility. Dysfunctional telomeres, DNA damage, and the persistent response to these events eventually trigger cellular senescence, a state of irreversible cell cycle arrest. Cells bearing senescent markers increase with age in a variety of tissues in mice[34] and primates.[35,36]

DNA Damage and Repair, and the Effect of Aging

Mechanisms designed to detect DNA damage and mediate its repair arrest cell's in their replicative cycle to avoid DNA replication or segregation.[37] When DNA damage persists unrepaired, DNA damage response can trigger cell death by apoptosis or halt a cell's proliferation through induction of senescence. Double strand breaks (DSB) can arise from ionizing radiation, oxidative stress, or replication stress, but can also be formed during genetically programmed processes such as meiotic recombination in germ cells and V(D)J recombination in developing lymphocytes.[38] The 2 main pathways responsible for DSB repair are nonhomologous end-joining,[39] an error-prone repair pathway, and homologous recombination.[40]

When analyzing age-related radiosensitivity, DSB repair pathways impairment must be considered. The exact nature of age-related misrepair remains unknown, emerging evidence points to DNA repair proteins recruitment to the damaged DNA at the nucleus. It had been previously suggested that recruitment rates of DNA repair proteins at DSB sites after irradiation might be inversely correlated with donor age.[41] Similarly, it has been reported that age may diminish the effectiveness of the 2 main DSB repair pathways (nonhomologous end-joining and homologous recombination).

Cells respond to foreign DNA introduced in the cytoplasm by triggering innate immune responses, which are not specific to a particular pathogen in the way adaptive immune responses are. Some studies reveal a direct link between innate immune signaling and the response of cells to induced DNA damage; aging could radically affect this process. Dysfunctional telomeres, DNA damage, and the persistent response to these events eventually can trigger cellular senescence. Senescence is a cellular response that has evolved in response to old, stressed and damaged cells. The production of the so-called senescence-associated secretory phenotype (SASP),[41] includes a host of proinflammatory cytokines IL (interleukin)-6 and IL-8 thought to be an evolutionary attempt to elicit an immune response to facilitate the removal of old damaged cells.[42] The system works well in young, healthy individuals promoting wound healing and reducing fibrosis. An accumulation of senescent cells that occurs as an individual ages has been implicated in many age-related deteriorations, dysfunctions and diseases.[42]

As cancers are among the pathologies that are fueled by inflammation,[43] the cytokines that comprise the SASP in aging organisms, together with the innate immune responses triggered by DNA damage, can synergistically contribute to age-related cancers by stimulating inflammation. Although there is evidence that the SASP suppresses tumor formation by reinforcing cellular senescence, it also promotes cancer progression by stimulating the growth of nearby precancerous cells. The most convincing evidence for this activity comes from xenograft studies. Co-injection of senescent fibroblasts significantly stimulated the proliferation of mouse and human epithelial tumor cells, while co-injection of non-senescent fibroblasts did not.[44]

Cellular Senescence, Stem Cells and the Induction of Neoplasms

Senescent cells (SC) represent a relatively stable state of proliferative arrest accompanied by a failure to re-enter the cell division cycle. It is worth noting that ionizing radiation is more damaging to proliferating cells, particularly those in the late G2/M phase of the cell cycle and that the non-proliferating senescent cells are less sensitive to a radiation exposure.

In the early 1960s, investigators noted that normal human fetal cell culture underwent a finite number of divisions before becoming senescent.[45] Although senescence was initially understood as a protective mechanism to suppress the development of cancer and promote tissue repair, this cellular mechanism is now seen as a double-edged sword.[46] SC are characterized by a senescence-associated secretory phenotype (SASP) which includes short-lived chemical moieties such as cytokines, chemokines, and reactive oxygen species (ROS) which cause a number of effects including activating an immune response, aging, and damaging the SC and its neighboring healthy cells.

Ionizing radiation's effect on SC has a dual role in cancer radiotherapy (RT). On the one hand, radiation induces tumor cells into a senescent state, inhibiting their proliferation and activating cancer immune surveillance. Some radiosensitizers under development are aimed at increasing SC when combined with ionizing radiation.[47,48] Although ionizing radiation is more damaging to proliferating cells, ionizing radiation can induce senescence in surrounding and normal cells as well as in cancer cells, which leads to normal tissue fibrosis and organ dysfunction.[49] Moreover, ionizing radiation-induced senescence may emerge as a method for helping cancer cells overcome the damaging effects of radiation and worsen the biological behavior of tumor cells following radiation treatment by multiple mechanisms including impeding both innate and adaptive immune responses.[50,51]

Influence of Radiation on the Senescence Mechanisms

Radiation has pluripotent effects that contribute to SC, including its effect on DNA repair, cell cycle arrest, and SASPs. The accuracy of DNA damage repair by related downstream signaling pathways determines cell fate, including senescence and apoptosis.[52] DNA double-stranded breaks are a potent stimulus for inducing senescence.[53] Ionizing radiation-induced senescence is also a form of the more general stress-induced premature senescence.[54]

Radiation has a direct effect on cellular senescence in the tumor microenvironment. Senescence-like growth arrest (SLGA) in response to radiation may reflect a key mechanism of residual-cell survival, ultimately resulting in radio-resistance, tumor regrowth, and dormant tumor recurrence.[55] Recently, the phenomenon that SC can regrow after exposure to radiation has attracted increasing attention, which reflects that SC plays 'opposing roles' in RT and other genotoxic therapies.[56-58] SC appearing in the context of neoadjuvant chemoradiotherapy for rectal cancer can promote epithelial-mesenchymal transition (EMT) and further affect the residual tumor microenvironment.[59]

Finally, the radiation dose plays a crucial role in inducing senescence or apoptosis upon cell exposure; a low dose (0.5 −10 Gy) of radiation induces senescence, while a high dose (>10 Gy) typically induces apoptosis.[60]

Normal cells that undergo radiation-induced senescence leads to tissue fibrosis and organ dysfunction and increases the risk of secondary neoplasms in almost all bodily systems.[61,62] As a result, decreasing these side effects induced by senescence has been a direction for improving the therapeutic radiation ratio (see parallel article:**Predictors of Toxicity Among Older Adults with Cancer, section** Mitigators of radiation injury among older patients, sub-section: Anti-senolytics).

Cell Division Cycle Arrest

The first step in a senescence phenotype following a radiation exposure sufficient to produce consequential DNA damage, is that cell progression is arrested at the G2/M boundary. This is accompanied by mitotic bypass into the G1 phase.[63] Ataxia telangiectasia-mutated protein (ATM), p53, p21, p16-Rb, p38-mitogen-activated protein kinase (p38-MAPK), NF-κB signaling pathway factors, reactive oxygen species (ROS), senescence-associated secretory phenotype (SASP) factors, and cyclin-CDK complexes are all involved in this process.[49,63,64]

p53 and Other Proteins/Factors Related to p53

The function of the tumor suppressor protein p53 is related to cell cycle control, DNA repair, and apoptosis.[65] p53 and phosphorylated retinoblastoma protein (pRB) are the main proteins involved in establishing and maintaining the state of irreversible growth arrest in replicative senescence in normal human cells; p53 inactivation could reverse SC phenotype in cells with a low level of p16.[66]

There is increasing evidence supporting that insulin-like growth factor-binding protein 5 (IGFBP-5) plays a crucial

role in SC phenotype via a p53-dependent pathway. IGFBP-5 especially functions in the coagulation factor Xa- or interleukin-6 (IL-6)-induced premature senescence of endothelial cells, smooth muscle cells, and fibroblasts.[66-68]

Long noncoding RNAs (lncRNA) and microRNAs (miRNA) also contribute to SC induced by radiation.[56,69] Ionizing radiation-induced senescence is modulated by miR-155 via the p53 and p38-MAPK pathways and partially regulates tumor protein 53-induced nuclear protein 1 (TP53INP1) expression in human WI-38 lung fibroblasts.[56]

Cancer Stem Cells and Radiosensitivity

Surviving nontumorigenic cells were shown to have a tendency to exhibit senescence, while breast cancer-initiating cells (CICs) could be mobilized from the quiescent/G0 phase of the cell cycle to actively cycling cells after sublethal doses of radiation.[70] Ionizing radiation-induced senescence is the result of the inaccurate repair of damaged DNA after radiation. Targeting accelerated and increased ionizing radiation-induced senescence has been an important method for increasing the effectiveness of RT [129].

Mitochondrial Dysfunction

Mitochondria play an important role in radiation-induced cellular damage, a major contributor to the aging process, and different qualities of radiation affect the changes in mitochondrial dynamics.[71] Cells exposed to low-dose X-rays and replicative senescent cells exhibit a residual capacity to use fatty acids and glutamine as alternative fuels, respectively.[72] Several mitochondrial signaling pathways have been revealed to induce cellular senescence[73]; cellular senescence, as mentioned, is a process that contributes to cellular dysfunction associated with aging.

Ferritinophagy

Ferroptosis is a form of regulated necrotic cell death controlled by glutathione peroxidase 4. Ferritinophagy is a lysosomal process that promotes ferritin degradation and ferroptosis. Increased dysfunctional iron metabolism is thought to lead to increased levels of iron and ferroptosis, which in turn leads to cell death; inhibition of ferroptosis may be a means to extend health span. Ferroptosis has been implicated in the pathogenesis of various diseases associated with aging adults including cardiovascular disease, neurological disorders and cancer.[74] Recent studies suggest that radiotherapy induces ferroptosis and that it may play an important role in RT mediated cancer death, especially when combined with cytotoxic or immunomodulating systemic therapies.[75]

Myelosuppression

Hematopoietic stem cell (HSC) injury is the major cause of mortality after accidental or intentional exposure to a moderate or high dose of ionizing radiation (IR). Bone marrow (BM) suppression is also the important dose-limiting side effect of chemotherapy and radiotherapy for cancer. It has been well established that acute myelosuppression induced by IR and/or chemotherapy is the result of induction of apoptosis in the rapidly proliferating hematopoietic progenitor cells (HPCs) and to a lesser degree in the relatively quiescent hematopoietic stem cells (HSCs).[76,77] Management of acute myelosuppression has been significantly improved in recent years by the use of various hematopoietic growth factors (HGFs) such as granulocyte-colony stimulating factor, granulocyte/macrophage-colony stimulating factor, or erythropoietin.[78]

However, many patients receiving chemotherapy and/or ionizing radiation (IR) also exhibit long-term residual damage to BM hematopoietic function manifested by a defect in (HSC) self-renewal and a decrease in HSC reserves.[79,80] Unlike acute myelosuppression, residual BM injury is latent and long lasting and shows little tendency for recovery. Unfortunately, the mechanisms of this residual BM injury have not been clearly defined. It has been hypothesized that ionizing radiation (IR)induce latent bone marrow injury mainly through the induction of HSC senescence which impairs HSC replication and self-renewal leading to the reduction in HSC reserves[81,82]

Conclusions

In this article, our current understanding of the biology of aging and the impact of ionizing radiation was reviewed. An appreciation of the biological processes involved in aging make it apparent that ionizing radiation accelerates many of the normal processes of aging.

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