

Recent advances in radiobiology with respect to pleiotropic aspects of tissue reaction

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ABSTRACT

DNA double-strand breaks (DSBs) induced by ionizing radiation are the major cause of cell death, leading to tissue/organ injuries, which is a fundamental mechanism underlying the development of tissue reaction. Since unscheduled senescence, predominantly induced among epithelial tissues/organs, is one of the major modes of cell death in response to radiation exposure, its role in tissue reaction has been extensively studied, and it has become clear that senescence-mediated secretion of soluble factors is an indispensable component of the manifestation of tissue reaction. Recently, an unexpected link between cytoplasmic DSBs and innate immunity was discovered. The activation of cyclic GMP-AMP (cGAMP) synthase (cGAS) results in the stimulation of the cGAS–stimulator of interferon genes (STING) pathway, which has been shown to regulate the transactivation of a variety of secretory factors that are the same as those secreted from senescent cells. Furthermore, it has been proven that cGAS–STING pathway also mediates execution of the senescence process by itself. Hence, an autocrine/paracrine feedback loop has been discussed in previous literature in relation to its effect on the tissue microenvironment. As the tissue microenvironment plays a crucial role in cancer development, tissue reaction could be involved in the late health effects caused by radiation exposure. In this paper, the novel findings in radiation biology, which should provide a better understanding of the mechanisms underlying radiation-induced carcinogenesis, are overviewed.

Keywords: radiation; tissue reaction; cGAS-STING pathway; cancer risk

INTRODUCTION

Radiation exposure involves manifestation of two major health effects, one of which is tissue reaction (formerly called deterministic effect) and the other stochastic effect. It has been recognized that excess cell death in tissues/organs compromises their function, which results in the manifestation of tissue reaction, whereas stochastic DNA damage induction is involved in the stochastic effect, e.g. cancer development. In fact, stochastic induction of oncogenic mutation by radiation exposure has been assumed to trigger radiation-induced carcinogenesis. This is the theoretical basis of the so-called linear-no-threshold (LNT) model. From a radiation protection point of view, the LNT model has been adopted for the purpose of radiation protection for a long time, even though its applicability to low-dose/low-dose-rate radiation is still in debate. Furthermore, the development of a comprehensive model to understand low-dose/low-dose-rate effects, which is still indispensable, requires recent advances in radiation biology [1–3].

Recently, our knowledge on the physiology of the tissue microenvironment has greatly improved. Advances in stem cell biology have demonstrated the spatiotemporal behavior of tissue stem cells and their

microenvironment in response to radiation exposure [4], and advances in molecular and cell biology have described the existence of cell-to-cell competition and non-targeted effects [5], all of which play indispensable roles in modifying cancer risks from radiation exposure [6].

More recently, an unexpected link between DNA damage, innate immunity and senescence has been discovered. It has been described that senescent cells secrete a variety of soluble factors that make alterations to the tissue microenvironment, resulting in chronic inflammation, tissue remodeling and regeneration. Thus, accumulating scientific evidence has suggested that tissue reaction could play a role in cancer development through modification of the tissue microenvironment. In this paper, an overview of recent radiobiological studies is provided, and the significance of novel findings on the dose-dependency of cancer risk is discussed.

INDUCTION OF UNSCHEDULED SENESCENCE FOLLOWING RADIATION EXPOSURE

It is well established that double-strand breaks (DSBs) execute DNA damage response through activation of the ataxia-telangiectasia

mutated (ATM)–p53 axis [7]. Upon activation of ATM as a protein kinase, thousands of the intra-nuclear proteins are phosphorylated. For example, ATM phosphorylates histone H2AX [8], a member of nucleosome core components histone H2A, and phosphorylated histone H2AX is recognized by MDC1, which recruits the MRE11–RAD50–NBS1 complex as well as the RNF8/UBC13 complex. The former complex is involved in DSB repair, while the latter is a histone ubiquitinase that results in ubiquitination of histone H1, by which RNF163 is recruited. Finally, RNF163 ubiquitinates H2A, and together with the exposure of methylated histone H4, 53BP1 is recruited to the chromatin neighboring the initial DSB sites. The formation of a multiple protein complex is essential for the transduction of DNA damage signals to p53, whose activation executes the cellular response to DNA damage, including apoptosis induction and arrest of the cell cycle [7].

While apoptosis is a frequently observed cell death mode in some of the tissues/organs, such as bone marrow, thymus, spleen and intestine, many other tissues/organs induce cell cycle arrest in response to radiation exposure [9, 10]. Importantly, when the amount of DSBs exceeds the capacity of DNA damage repair and some of the initial DSBs are left unrejoined, continuing p53 activation persistently arrests the cell cycle at G1 [11, 12]. Previously, it was reported that permanently arrested cells exhibited premature senescent phenotypes. Since premature senescence takes place without telomere shortening [12], which is the major cause of physiological senescence, it is apparently not a scheduled senescence. Therefore, in this paper, such unexpected senescence is designated as unscheduled senescence.

Cell cycle arrest by itself is a reversal process, however, cells harboring unreparable DSBs persist in cell cycle arrest and enter into a senescence-like state. While several explanations for the initiation of unscheduled senescence have been proposed, none of them can fully explain the phenomenon. For example, the involvement of mammalian target of rapamycin (mTOR) in the initiation of the senescent state was suggested, however, mTOR inhibition could only suppress senescence in part [13]. Thus, it was hypothesized that multiple overlapping mechanisms might be involved in the initiation, perpetuation and continuation of unscheduled senescence.

More recently, it has been shown that senescent cells can be eliminated by the synthetic induction of apoptosis. In order to discover senolytic drugs, which are able to kill senescent cells, several approaches, including siRNA screening, a hypothesis-driven bioinformatics-based approach and low-molecular weight chemical mass-screening, have been carried out [14, 15], and one potent senolytic compound, named ABT263, has been identified. ABT-263 is a specific inhibitor of the anti-apoptotic proteins BCL-2 and BCL-xL [16]. It was confirmed that the effect was limited to senescent cells. Furthermore, ABT263 was shown to eliminate senescent cells *in vivo*, which rejuvenated aged hematopoietic stem cells in mice [17]. Thus, senolytic drugs are expected to mitigate senescence-associated pathologies, such as fibrosis, an adverse effect brought about by radiation therapy.

SENESCENCE-ASSOCIATED SECRETORY PHENOTYPES AND NON-TARGETED RADIATION EFFECTS

Subsequent studies have demonstrated that senescent cells are metabolically active. They secrete several soluble factors including

Table 1. Soluble factors secreted from senescent cells mediating cGAS–STING signaling

Factors	Functions
IL-6	Cytokine
IL-8	Cytokine
IL-1a	Cytokine
MCP-1	Cytokine
CXCL1	Chemokine
CCL2	Chemokine
CCL5	Chemokine
TGF-b1	Growth modulator
IGFBP3	Growth modulator
bFGF	Growth modulator
VEGF	Growth modulator
MMP-3	Matrix remodeling factor
PAI-1	Matrix remodeling factor

cytokines, chemokines, growth regulators and matrix remodeling proteases, whose characteristics are collectively called the senescence-associated secretory phenotype (SASP) (Table 1) [18–21]. Many of the factors trigger inflammation, so that the inflammatory cells are attracted to the damage sites and elimination of the senescent cells is enhanced. SASP factors also include growth modulators and matrix remodeling proteases, which modify the tissue microenvironment and stimulate repair and regeneration of injured tissues/organs. Although the SASP response plays a physiological role under permissive levels of tissue/organ injuries, it might cause unfavorable reaction when the injuries exceed physiological levels, such as tissue/organ damage provoked by a high dose of ionizing radiation (generally >6Gy).

Previously, secretory phenotypes have also been described in radiation-induced bystander effects [22], which is the phenomenon that irradiated cells indirectly induce radiation effects in non-irradiated cells through cell-to-cell contact as well as secreted soluble factors, named bystander factors [23]. It is interesting to note that almost all known bystander factors are identical to the SASP factors, indicating that bystander effects are mediated by unscheduled senescence caused by radiation exposure.

While the physiological role of senescence and its secretory phenotype in cancer induction and prevention have already been discussed [21], the close relationship between SASP and age-related diseases has just been unveiled [24–28], indicating that radiation-induced unscheduled senescence is likely to be involved in the manifestation of age-related diseases, including not only cancer development but also the induction of non-cancer diseases, such as heart diseases, strokes and respiratory diseases. As discussed below, this might also be the endogenous cause of the acceleration of aging by itself. Such possibilities have to be examined in detail, since it could greatly improve our understanding of the basic mechanisms underlying the dose–response relationship of late radiation health effects, as well as the cancer risk estimation at low-dose and low-dose-rate exposure caused by nuclear accidents and occupational exposure.

CYTOPLASMIC DSBs AND INNATE IMMUNITY

DSBs are a well-documented form of DNA damage predominantly generated in response to ionizing radiation in the cellular nucleus. DSBs

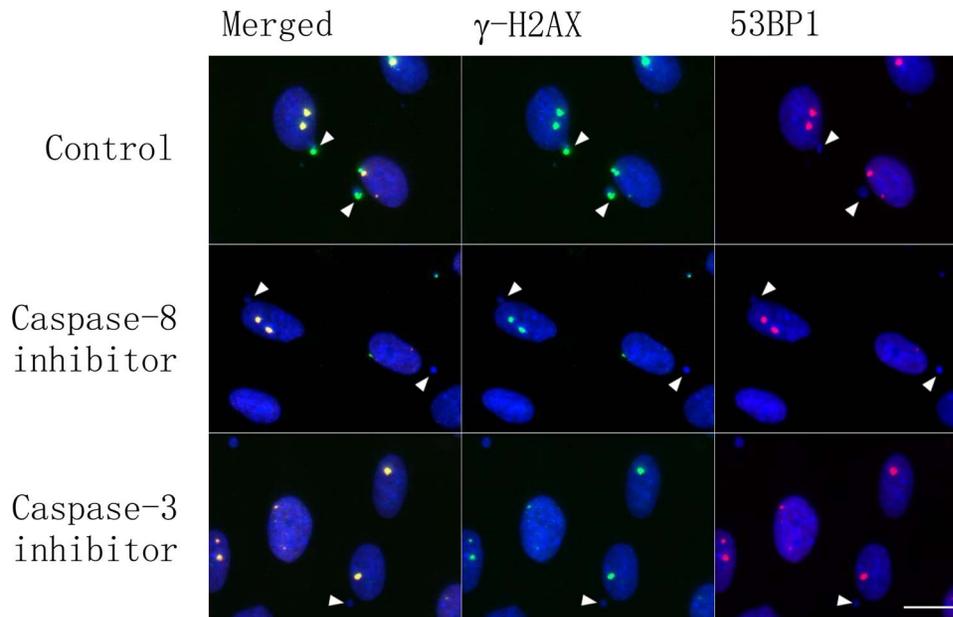


Fig. 1. Caspase-dependent DNA fragmentation in micronuclei. Exponentially growing normal human diploid cells were exposed to 1 Gy of γ -rays and incubated for a further 24 h before fixation with methanol. The samples were then incubated with anti-phosphorylated histone H2AX mouse antibody and anti-53BP1 rabbit antibody, which were detected by Alexa488-conjugated anti-mouse antibody and Alexa555-conjugated anti-rabbit antibody, respectively. The cells were treated with caspase-8 inhibitor (middle row) or with caspase-3 inhibitor (bottom row) 30 min before irradiation. The white arrow heads indicate micronuclei. Scale bar, 10 μ m.

activate intranuclear phosphorylation-dependent signal transduction known as DNA damage signaling, and the ATM-p53 axis is the indispensable pathway executing the cellular response to DSBs [7]. These are the essential components of the cellular response that maintain the integrity of the genome.

Recently, an unexpected role of cytoplasmic DSBs has enabled mechanisms of radiation effects through exo-nuclear signaling to be deciphered. Micronuclei are exo-nuclear DNA and are created by nondisjunction of un-rejoined chromosome fragments through cell division. Usually, normal human cells harboring the ATM-p53 axis do not permit so many micronuclei after radiation exposure, however, human cancer cells, in which the ATM-p53 axis is severely compromised, frequently cause the formation of multiple micronuclei through abnormal mitosis, named mitotic catastrophe. This was frequently observed in human cancer cells exposed to high doses equivalent to those received in radiotherapy. DNA in micronuclei was shown to be eliminated through degradation by apoptosis-dependent DNA fragmentation (Fig. 1) [29]. Apoptotic DNA fragmentation is accompanied by the degradation of the nuclear lamina, which results in the release of DNA fragments into the cytoplasm. Such fragmented DNA, particularly in the cytoplasm, has been proven to execute the innate immune response through the activation of the cyclic GMP-AMP (cGAMP) synthase (cGAS)-stimulator of interferon genes (STING) pathway [30–33]. cGAS is originally described as a sensor of microbial DNA, and it becomes clear that it is also able to recognize endogenous double-stranded DNA. The cGAS protein has a positively charged surface as well as a zinc ribbon, through

which the fragmented DNA duplex interacts (Fig. 2). Activated cGAS catalyzes the cyclization of ATP and GTP, resulting in the formation of cGAMP. cGAMP then activates STING, which transactivates interferon (IFN) regulatory factor 3 (IRF3) and nuclear factor kappa B (NF- κ B), thereby stimulating transcription and secretion of type I IFNs and the inflammatory cytokines (Fig. 2). Subsequently, it has been reported that many of the secretory factors, such as interleukin 1 beta (IL-1 β), IL-6, IL-8 and transforming growth factor beta (TGF- β), were the same as those secreted from senescent cells, which were involved in senescence-associated phenotypes (Table 1) [30, 34, 35]. Furthermore, since micronuclei are commonly induced by ionizing radiation, cGAS has been shown to be involved in radiation-induced premature senescence [36]. Thus, the cGAS-STING pathway is also a critical pathway, mediating senescence induction after radiation exposure. It is interesting to note that senescence by itself is also an inducer of cytokines, such as IL-1 β and IL-6, and therefore, it further amplifies the effect of cGAS-STING activation. Until now, there has been no study demonstrating the dose-dependency of cGAS-STING activation, which should be examined with respect to carcinogenic aspects of radiological protection.

As discussed above, it turns out to be clear that non-targeted radiation effects, including the bystander effect, are mediated by the secretory phenotype of unscheduled senescence. Two pathways have been reported to be involved in bystander effects, one of which is through the secretion of soluble factors, while the other pathway is through gap-junction-dependent cell-to-cell communication. Since

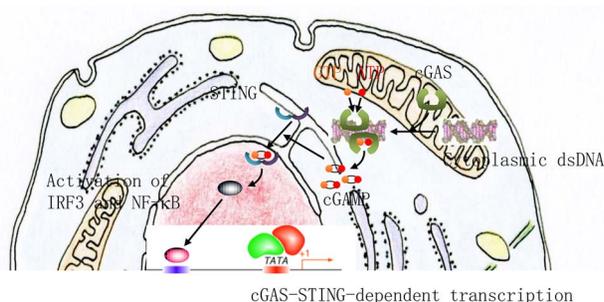


Fig. 2. cGAS–STING signaling pathway. Cytoplasmic double-stranded DNA activates the cGAS–STING signaling pathway. cGAS is able to recognize cytoplasmic double-stranded DNA through its unique structure, thereby turning on the enzymatic activity catalyzing the cyclization of AMP and GMP, which results in the formation of cGAMP. cGAMP then binds to STING and activates it as an adaptor, which modulates transcription through IRF3 and NF- κ B. Thus, the cGAS–STING signaling pathway plays a critical role in senescence induction after radiation exposure.

cGAMP is a transmissible molecule through gap-junctions, this might be the factor mediating bystander effects through cell-to-cell contact.

TISSUE REACTION AND CANCER DEVELOPMENT IN RESPONSE TO IONIZING RADIATION

Although cancer induction is classified into the stochastic effect, recent advances in radiobiology have cast doubt on its categorization. Historically, DNA damage has been believed to be the primary cause of oncogenic mutations, so that cancer induction should be stochastic. This simple hypothesis has long been adopted for radiation safety regulation as the LNT model. Considering that direct radiation-induced mutations are involved in cancer induction, there should be radiation signatures in driver mutations, which are critical for developing cancer. However, molecular and epidemiological studies so far have provided no apparent evidence of radiation signatures, indicating that the role of radiation exposure in radiation-induced cancer might not be the induction of driver oncogenic mutations. A good example supporting this idea has been seen in childhood thyroid cancer cases after the Chernobyl nuclear power plant (CNPP) accident [37–39].

According to a recent UNSCEAR report, a total of 19 233 thyroid cancer cases were documented in 1991–2015 among those who were <18 years of age at the time of the Chernobyl accident [40]. The fraction of thyroid cancer incidence attributable to radiation exposure was estimated to be ~ 0.6 for evacuated children and adolescents. Recent comprehensive targeted next-generation sequencing and RNA-seq analyses have identified driver gene mutations in 96.9% of cases, of which 70.8% showed gene fusions [41]. Since the cases with oncogenic gene fusions show a close link to thyroid doses, thyroid tumors with fusions were obviously induced by radiation exposure. In other words, the frequency of thyroid cancer with gene fusions was increased dependent upon thyroid doses. However, we should be

cautious in concluding that radiation exposure is a primary cause of the gene fusions, since oncogenic gene fusion is also a predominant driver mutation in sporadic pediatric cases [38, 39, 42]. If radiation exposure is the primary cause of gene fusions, the ratio of the cases with gene fusions vs point mutations should not be like that observed in pediatric sporadic cases. Thus, it can be hypothesized that radiation exposure could not be the direct cause of oncogenic gene fusions, rather it provides a tissue microenvironment allowing the thyroid follicular cells with a spontaneous oncogenic fusion to propagate. As discussed above, tissue microenvironment exposed to radiation involves unscheduled senescence, which initiates inflammation and stimulates tissue regeneration. While it should be emphasized that tissue reaction by itself is an essential physiological response to amend a damaged tissue/organ, if the radiation dose exceeds the tolerable level an irreversible reaction will take place. Moreover, there are different pathways to keep the integrity of the tissue/organ, including stem cell competition, and senescence itself is also considered to be a mechanism to prevent cancer initiation. Beyond such protective roles, an excessive amount of dead cells executes chronic inflammation and provides circumstances in which the initiated cells give rise to clonal expansion as discussed elsewhere [27]. In fact, thyroiditis with chronic inflammation was shown to include rearranged during transfection (RET)/papillary thyroid carcinoma (PTC) positive cells [43]. Thus, in such circumstances, tissue/organ injuries and the resultant tissue reaction could be a critical processes that lead to radiation-induced carcinogenesis.

A non-stochastic mechanism of radiation-induced cancer has also been proposed recently. Several investigations using experimental rodent models have demonstrated that radiation exposure accelerates aging of mice. Dependent on radiation doses, the survival curve showed a tendency to shift to the left, indicating acceleration of aging [44–46]. As a result, aging-associated cancer development showed earlier onset [47], which was previously explained as ‘induced’.

CONCLUSION

Tissue reaction is a process by which tissue/organ injuries are amended. Recent advances in radiation biology have demonstrated that it could also be a fundamental mechanism involved in the manifestation of a radiation health effect. Obviously, the ATM–p53 axis-dependent DNA damage response as well as cGAS–STING-dependent innate immunity execute unscheduled senescence, predominantly among epithelial tissues exposed to ionizing radiation, causing secretion of soluble factors that mediate non-targeted effects and perpetuate the senescence phenotype. This autocrine/paracrine feedback loop promotes modification of the tissue microenvironment, which is highly likely to accelerate propagation of pre-cancer cells with spontaneous oncogenic driver mutations. Although the involvement of tissue reaction in late radiation health effects still needs further verification, it should improve our knowledge of the biological mechanisms underlying the dose–response relationship of late radiation health effects, especially the dose-dependency of cancer risks from low-dose/low-dose-rate radiation exposure. Since senescent cells have been demonstrated to be eliminated by low-molecular weight chemicals, this might provide a clue to mitigate cancer risk from radiation exposure. Finally, future advances in radiation biology are expected to keep providing novel findings that should shed light on and

improve our understanding of the mechanisms underlying radiation-induced carcinogenesis.

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CONFLICT OF INTEREST

There is no conflict of interest.

REFERENCES

- Paunesku T, Haley B, Brooks A et al. Biological basis of radiation protection needs rejuvenation. *Int J Radiat Biol* 2017;93:1056–63.
- Paunesku T, Woloschak G. Reflections on basic science studies involving low doses of ionizing radiation. *Health Phys* 2018;115:623–7.
- Ruhm W, Azizova T, Bouffler S et al. Typical doses and dose rates in studies pertinent to radiation risk inference at low doses and low dose rates. *J Radiat Res* 2018;59:1–10.
- Niwa O, Barcellos-Hoff MH, Globus RK et al. ICRP publication 131: Stem cell biology with respect to carcinogenesis aspects of radiological protection. *Ann ICRP* 2015;44:7–357.
- Hei TK, Zhou H, Chai Y et al. Radiation induced non-targeted response: Mechanism and potential clinical implications. *Curr Mol Pharmacol* 2011;4:96–105.
- Brooks AL, Hoel DG, Preston RJ. The role of dose rate in radiation cancer risk: Evaluating the effect of dose rate at the molecular, cellular and tissue levels using key events in critical pathways following exposure to low LET radiation. *Int J Radiat Biol* 2016;92:405–26.
- Blackford AN, Jackson SP. ATM, ATR, and DNA-PK: The trinity at the heart of the DNA damage response. *Mol Cell* 2017;66:801–17.
- Paull TT, Rogakou EP, Yamazaki V et al. A critical role for histone H2AX in recruitment of repair factors to nuclear foci after DNA damage. *Curr Biol* 2000;10:886–95.
- Chan ASL, Narita M. Short-term gain, long-term pain: The senescence life of cycle and cancer. *Genes Dev* 2019;33:127–43.
- Lee S, Schmitt CA. The dynamic nature of senescence in cancer. *Nat Cell Biol* 2019;21:94–101.
- Di Leonardo A, Linke SP, Clarkin K et al. DNA damage triggers a prolonged p53-dependent G1 arrest and long-term induction of Cip1 in normal human fibroblasts. *Genes Dev* 1994;8:2540–51.
- Suzuki K, Mori I, Nakayama Y et al. Radiation-induced senescence-like growth arrest requires TP53 function but not telomere shortening. *Radiat Res* 2001;155:248–53.
- Tomimatsu K, Narita M. Translating the effects of mTOR on secretory senescence. *Nat Cell Biol* 2015;17:1230–2.
- Zhu Y, Tchkonja T, Pirtskhalava T et al. The achilles' heel of senescent cells: From transcriptome to senolytic drugs. *Aging Cell* 2015;14:644–58.
- Zhu Y, Tchkonja T, Fuhmann-Stroissnigg H et al. Identification of a novel senolytic agent, navitoclax, targeting the Bcl-2 family of anti-apoptotic factors. *Aging Cell* 2016;15:428–35.
- Yosef R, Pilpel N, Tokarsky-Amiel R et al. Directed elimination of senescent cells by inhibition of BCL-W and BCL-XL. *Nat Commun* 2016;7:11190.
- Chang J, Wang Y, Sha L et al. Clearance of senescent cells by ABT263 rejuvenates aged hematopoietic stem cells in mice. *Nat Med* 2016;22:78–83.
- Suzuki M, Boothman DA. Stress-induced premature senescence (SIPS)-influence of SIPS on radiobiology. *J Radiat Res* 2008;49:105–12.
- Munoz-Espin D, Serrano M. Cellular senescence: From physiology to pathology. *Nat Rev Mol Cell Biol* 2014;15:482–96.
- Ohtani N. Deciphering the mechanism for induction of senescence-associated secretory phenotype (SASP) and its role in ageing and cancer development. *J Biochem* 2019;166:289–95.
- Faget DV, Ren Q, Stewart SA. Unmasking senescence: Context-dependent effects of SASP in cancer. *Nat Rev Cancer* 2019;19:439–53.
- Prise KM, O'Sullivan JM. Radiation-induced bystander signalling in cancer therapy. *Nat Rev Cancer* 2009;9:351–60.
- Hei TK, Zhou H, Ivanov VN et al. Mechanism of radiation-induced bystander effects: A unifying model. *J Pharm Pharmacol* 2008;60:943–50.
- Hodes RJ, Sierra F, Austad SN et al. Disease drivers of aging. *Ann N Y Acad Sci* 2016;1386:45–68.
- Loeser RF, Collins JA, Diekmann BO. Ageing and the pathogenesis of osteoarthritis. *Nat Rev Rheumatol* 2016;12:412–20.
- Jeon OH, David N, Campisi J et al. Senescent cells and osteoarthritis: A painful connection. *J Clin Invest* 2018;128:1229–37.
- Furman D, Campisi J, Verdin E et al. Chronic inflammation in the etiology of disease across the life span. *Nat Med* 2019;25:1822–32.
- Khosla S, Farr JN, Tchkonja T et al. The role of cellular senescence in ageing and endocrine disease. *Nat Rev Endocrinol* 2020;16:263–75.
- Medvedeva NG, Panyutin IV, Panyutin IG et al. Phosphorylation of histone H2AX in radiation-induced micronuclei. *Radiat Res* 2007;168:493–8.
- Dou Z, Ghosh K, Vizioli MG et al. Cytoplasmic chromatin triggers inflammation in senescence and cancer. *Nature* 2017;550:402–6.
- Harding SM, Benci JL, Irianto J et al. Mitotic progression following DNA damage enables pattern recognition within micronuclei. *Nature* 2017;548:466–70.
- Mackenzie KJ, Carroll P, Martin CA et al. cGAS surveillance of micronuclei links genome instability to innate immunity. *Nature* 2017;548:461–5.
- Wang H, Hu S, Chen X et al. cGAS is essential for the antitumor effect of immune checkpoint blockade. *Proc Natl Acad Sci U S A* 2017;114:1637–42.

34. Glück S, Guey B, Gulen MF et al. Innate immune sensing of cytosolic chromatin fragments through cGAS promotes senescence. *Nat Cell Biol* 2017;19:1061–70.
35. Yang H, Wang H, Ren J et al. cGAS is essential for cellular senescence. *Proc Natl Acad Sci U S A* 2017;114:E4612–20.
36. Li T, Chen ZJ. The cGAS-cGAMP-STING pathway connects DNA damage to inflammation, senescence, and cancer. *J Exp Med* 2018;215:1287–99.
37. Williams D. Radiation carcinogenesis: Lessons from Chernobyl. *Oncogene* 2009;27:S9–18.
38. Suzuki K, Mitsutake N, Saenko V et al. Radiation signatures in childhood thyroid cancers after the Chernobyl accident: Possible roles of radiation in carcinogenesis. *Cancer Sci* 2015;106:127–33.
39. Suzuki K, Saenko V, Yamashita S et al. Radiation-induced thyroid cancers: Overview of molecular signatures. *Cancers (Basel)* 2019;11:E1290.
40. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2018. *Evaluation of data on thyroid cancer in regions affected by the Chernobyl accident*. New York: United Nations, 2018, 1–20.
41. Efanov AA, Brenner AV, Bgdanova TI et al. Investigation of the relationship between radiation dose and gene mutations and fusions in post-Chernobyl thyroid cancer. *JNCI* 2018;110:371–8.
42. Cordioli MI, Moraes L, Bastos AU et al. Fusion oncogenes are the main genetic events found in sporadic papillary thyroid carcinomas from children. *Thyroid* 2017;27:182–8.
43. Rhoden KJ, Unger K, Salvatore G et al. RET/papillary thyroid cancer rearrangement in nonneoplastic thyrocytes: Follicular cells of Hashimoto's thyroiditis share low-level recombination events with a subset of papillary carcinoma. *J Clin Endocrinol Metab* 2006;91:2414–23.
44. Mewissen DJ, Cornar CL, Trum BF et al. A formula for chronic radiation dosage versus shortening of life span: Application to a large mammal. *Radiat Res* 1957;6:450–9.
45. Richardson RB. Ionizing radiation and aging: Rejuvenating an old idea. *Aging* 2009;1:887–902.
46. Tanaka K, Kohda A, Satoh K et al. Dose-rate effectiveness for unstable-type chromosome aberrations detected in mice after continuous irradiation with low-dose-rate γ -rays. *Radiat Res* 2009;171:290–301.
47. Nakamura N. A hypothesis: Radiation carcinogenesis may result from tissue injuries and subsequent recovery processes which can act as tumor promoters and lead to an earlier onset of cancer. *Br J Radiol* 2020;92:20190843.