

REVIEW

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Radiation-induced inflammation and autoimmune diseases

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Abstract

Currently, ionizing radiation (IR) plays a key role in the agricultural and medical industry, while accidental exposure resulting from leakage of radioactive sources or radiological terrorism is a serious concern. Exposure to IR has various detrimental effects on normal tissues. Although an increased risk of carcinogenesis is the best-known long-term consequence of IR, evidence has shown that other diseases, particularly diseases related to inflammation, are common disorders among irradiated people. Autoimmune disorders are among the various types of immune diseases that have been investigated among exposed people. Thyroid diseases and diabetes are two autoimmune diseases potentially induced by IR. However, the precise mechanisms of IR-induced thyroid diseases and diabetes remain to be elucidated, and several studies have shown that chronic increased levels of inflammatory cytokines after exposure play a pivotal role. Thus, cytokines, including interleukin-1(IL-1), tumor necrosis factor (TNF- α) and interferon gamma (IFN- α), play a key role in chronic oxidative damage following exposure to IR. Additionally, these cytokines change the secretion of insulin and thyroid-stimulating hormone(TSH). It is likely that the management of inflammation and oxidative damage is one of the best strategies for the amelioration of these diseases after a radiological or nuclear disaster. In the present study, we reviewed the evidence of radiation-induced diabetes and thyroid diseases, as well as the potential roles of inflammatory responses. In addition, we proposed that the mitigation of inflammatory and oxidative damage markers after exposure to IR may reduce the incidence of these diseases among individuals exposed to radiation.

Key words Radiation, Inflammation, Autoimmune diseases, Thyroid, Diabetes

Background

Every year, millions of people are exposed to ionizing radiation resulting from diagnostic or interventional radiology and radiotherapy. In addition, nuclear and radiologic disasters pose a threat to all individuals worldwide. In addition to the killing effects of ionizing radiation at high doses, exposure to sub-lethal doses may result in various diseases, such as carcinogenesis, cataract, and cardiovascular disease[1,2].

Although genomic instability and carcinogenesis are the most important concerns of ionizing radiation, studies have revealed that exposure to IR can strongly affect immune system responses, leading to changes in the normal functions of immune responses[3]. These effects may be responsible for various diseases among exposed people. Studies have proposed that chronic inflammation and continuous free

radical production are responsible for several diseases after radiotherapy or radiation accident. Several studies have proposed that 25% to 50% of all cancers may be related to chronic inflammation [4–6]. Moreover, continuous free radical production, resulting from inflammatory responses, can disrupt organ function. For example, chronic oxidative damage in the kidneys of individuals with diabetes is mediated by increased insulin like growth factor 1 (IGF-1) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzymes[7,8]. This situation has been confirmed for other organs, such as Crohn's disease and ulcerative colitis in the gastrointestinal system, pancreatitis, and rheumatoid arthritis[9–13].

Under normal conditions, there is a balance between the levels of free radicals and the antioxidant defenses that help prevent reactive intermediates from damaging cells and tissues. Free radicals play an important role in cell signaling; however, excessive amounts of reactive oxygen species (ROS), as observed following exposure to IR, can cause damage to cellular genetic contents, proteins, and lipids[14]. Free radicals

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have different types in cells, including superoxide ($O_2^{\cdot-}$), nitric oxide (NO), and the hydroxyl radical (OH^{\cdot}). However, other types of molecular species, such as hydrogen peroxide (H_2O_2) and peroxyxynitrite ($ONOO^-$), can be produced by IR interactions or subsequent metabolites[15, 16].

There is a strong relationship between chronic inflammation and oxidative damage after exposure to IR[17]. IR can alter the numbers and functions of immune system cells in irradiated organs. Increased numbers of macrophages and lymphocytes T (T-cells) induce the secretion of several inflammatory mediators, such as NF- κ B and SMAD2/3, and cytokines, such as IL-1, IL-2, IL-6, IL-8, IL-33, tumor necrosis factor (TNF- α), transforming growth factor beta (TGF- β), and interferon gamma (IFN- γ)[18]. The elevated level of these inflammatory mediators is associated with the release of prostaglandins and free radicals, including reactive oxygen species (ROS) and nitric oxide (NO)[19]. Under conditions, such as exposure to high doses of IR during a radiation disaster, these inflammatory responses may continue for years after exposure[20]. In this situation, chronic inflammation and its consequences may disrupt the functions of irradiated organs[21].

Radiation toxicity in radiological and nuclear disasters

Ionizing radiation is responsible for the production of free radicals, including reactive oxygen species and reactive nitrogen species. When bone marrow or gastrointestinal systems receive an acute high dose of radiation (typically more than 4 Gy), exposed people can die as a result of acute radiation syndrome[22]. However, studies have shown that the exposure of other organs, such as the lung and heart, to radiation resulting from inhaling radionuclides or external exposure can cause acute reactions, leading to the inactivation of these organs and death after a number of months[23,24]. In addition to the risk of death after a radiological or nuclear disaster, many people exposed to radiation-contaminated areas show signs of disease in years long after exposure[25,26].

Hundreds of radiological and nuclear events have occurred since the World War II [27]. The nuclear disaster in Hiroshima and Nagasaki during the World War II is the most important example of the importance of radiation toxicity in the development of various types of diseases. In this disaster, more than 150,000 people immediately died, while thousands of people received sublethal doses[28]. Subsequently, the Chernobyl disaster was the most important environmental nuclear disaster[29]. Epidemiological studies performed some decades after the nuclear disaster have confirmed chronic changes in several biological factors, particularly the factors

related to cancer and the immune system[30]. Increased incidences of thyroid diseases resulting from radioactive iodine was one of the most common diseases in some adjacent countries to Chernobyl[31]. The incidence of cancer and increased level of inflammatory markers have been reported among Hiroshima and Nagasaki survivors[32]. The chronic inflammation induced by IR as a result of changes in adaptive and innate immune responses is responsible for various disorders among exposed people. These disorders include cardiovascular diseases, diabetes, and damage to thyroid function[33,34].

Innate and adaptive immune responses: Mechanisms of autoimmunity diseases

The innate immune system provides the host with an immediate response against pathogens. This system senses pathogens and damaged cells through damage associated molecular patterns (DAMPs) by pattern recognition receptors (PRRs). PRRs are ligands primarily expressed by innate immune system cells, such as macrophages, T-cells, and dendritic cells (DCs)[35]. The most important type of PRRs is toll-like receptors (TLRs). TLRs detect a variety of DAMPs, such as oxidized DNA, high-mobility group box 1 (HMGB1), and uric acid[36,37]. Studies have proposed that TLR2, TLR4, TLR5, TLR7, and TLR9 are the main PRRs, which stimulate inflammatory responses following the exposure of innate immune cells to pathogens or damaged cells[38,39]. These TLRs, through the stimulation of myeloid differentiation primary response 88 (MyD88), induce the upregulation NF- κ B and other transcription factors, leading to the secretion of pro-inflammatory cytokines[40]. For example, the ligation of DAMPs to TLR7 and TLR9 can stimulate the secretion of IFN- γ from inflammatory cells, while TLR2 and TLR4 can upregulate the secretion of IL-1 β , IL-6, and IL-8[41].

Another part of the immune system includes the adaptive immune system mediated by B and T cells. The B cells mediate humoral immunity, while T cells mediate cellular immunity. These cells distinguish self-antigens from foreign antigens. The B cell receptors (BCRs) and T cell receptors (TCRs), which are generated through VDJ recombination, are responsible for the recognition of antigens[42]. However, antigen-presenting cells (APCs), including DCs, B-cells, and macrophages, present antigens to these cells. The interaction of these immune cells is necessary for the detection and response of the adaptive immune system. Presenting antigens by APCs is associated with the activation of T cells, including CD8⁺ cytotoxic T cells (CTL) or CD4⁺T helper cells[43,44].

Typically, autoimmune diseases result from altering the

T cell-dependent control of self-reactive T cells. Abnormal changes in the levels of some cytokines and activities of APCs can result in the abnormal activation of CTLs. DCs play a key role in presenting danger alarms to T cells, leading to the reaction of these cells[45]. Studies have shown that increasing the level of some cytokines, such as IL-1, TNF- α and IFN- γ , lead to alterations in DCs homeostasis. These cytokines may induce the differentiation of immature DCs into mature DCs. The increased differentiation of immature DCs has been associated with various autoimmune diseases[46]. IL-6 is another cytokine involved in the pathogenesis of autoimmune diseases[47,48]. Blocking these cytokines by their antagonists and using anti-inflammatory cytokines, such as TGF- β 1, can reduce the severity of autoimmune processes[49,50]. These results indicated that there is a strong link between chronic inflammation after exposure to IR and autoimmune disorders.

Radiation-induced inflammation

Inflammation is one of the most important responses of tissues to IR, which can cause damage to various organs for years after exposure. Inflammation is a complicated process that appears as damage of the vasculature, migration of leukocytes into the irradiated area and the release of various immune system mediators[51,52]. The responses of normal tissues to IR are highly dependent on the radiation dose. With increasing radiation dose, the incidence of vascular damage, hypoxia and cell necrosis increases. This effect is associated with changes in the immune system response, leading to changes in the cytokine profile. The exposure of body cells to low doses of IR (lower than 1 Gy) can stimulate anti-inflammatory effects. This effect results from the high incidence of apoptosis compared to necrosis, while exposure to higher doses of IR (more than 1 Gy) leads to necrosis, rather than apoptosis, causing inflammation responses[18,53].

Although vascular damage and necrosis are responsible for the initiation of inflammation, under stress conditions, such as exposure to a heavy dose of IR, other types of cell death, such as apoptosis, autophagy, and senescence, can stimulate inflammatory responses[54]. Massive DNA damage and cell death following exposure to high doses of IR (more than 1 Gy) lead to the release of cellular contents, such as danger alarms or DAMPs. The most important released DAMPs after exposure to IR include HMGB1, uric acid, and heat-shock proteins (HSPs). In response to IR, TLR2, TLR4, TLR5 and TLR9 play a central role in the activation of inflammation pathways *via* the identification of DAMPs[54,55].

TLRs through the up-regulation of inflammatory mediators, such as MAPKs, NF- κ B, and COX-2, trigger the

secretion of inflammatory cytokines, including IL-1, IL-6, IL-8, TNF- α , IL-33, and IFN- γ . However, these cytokines further amplify the regulation of inflammatory mediators in a positive feedback loop[56]. In addition to inflammatory mediators, continuous ROS and nitric oxide production amplify the toxic effects of radiation-induced inflammation on normal tissues. When this response is not inhibited by anti-inflammatory mechanisms, the inflammatory cytokines and free radicals induced by chronic inflammation disrupt the normal function of organs[56,57] (Fig. 1).

Evidence of IR-induced autoimmune diseases

Epidemiological studies of the atomic-bomb survivors have recommended that IR can functionally break self-tolerance and induce various organ-specific autoimmune diseases[30,58]. Impaired DNA damage responses are postulated as key mechanisms involved in some autoimmune diseases, such as type I diabetes, rheumatoid arthritis, gastritis, thyroiditis, and orchitis[59]. An *in vivo* study showed that induction of autoimmune diseases occurs following the irradiation of both the thymus and peripheral lymphoid organs[60]. However, there is clear evidence that lymphocytes from patients with autoimmune diseases, such as systemic sclerosis and rheumatoid arthritis, exhibit higher radiosensitivity and delayed DNA damage repair responses compared to lymphocytes from healthy donors[61,62]. Thus, autoimmune diseases induced by radiation may be involved in carcinogenesis in years long after exposure in the irradiated population. To the best of our knowledge, thyroid diseases and diabetes are two important autoimmune diseases linked to radiation exposure in the population.

Thyroid autoimmune diseases

There are several reports linking autoimmune thyroid disease to therapeutic and environmental radiation exposures. Examples for this claim include Japanese atomic bomb survivors, children exposed to radioactive iodine from ¹³¹I therapy and nuclear weapons testing at the Nevada test site, and Chernobyl disaster survivors. Several studies have reported abnormal incidences of autoimmune reactions in the pathogenesis of thyroid diseases and impaired natural killer (NK) cells activity against tumor cells[63–68]. Additionally, occupational exposures to IR among nuclear power plant, medical and laboratory workers are related to a higher risk of autoimmune reactions[69]. A study on Hiroshima and Nagasaki atomic bomb survivors and children exposed to radioactive iodine from nuclear weapons testing showed a linear radiation dose response for thyroid tumors and nodules but not for autoimmune thyroid diseases[66,70]. However,

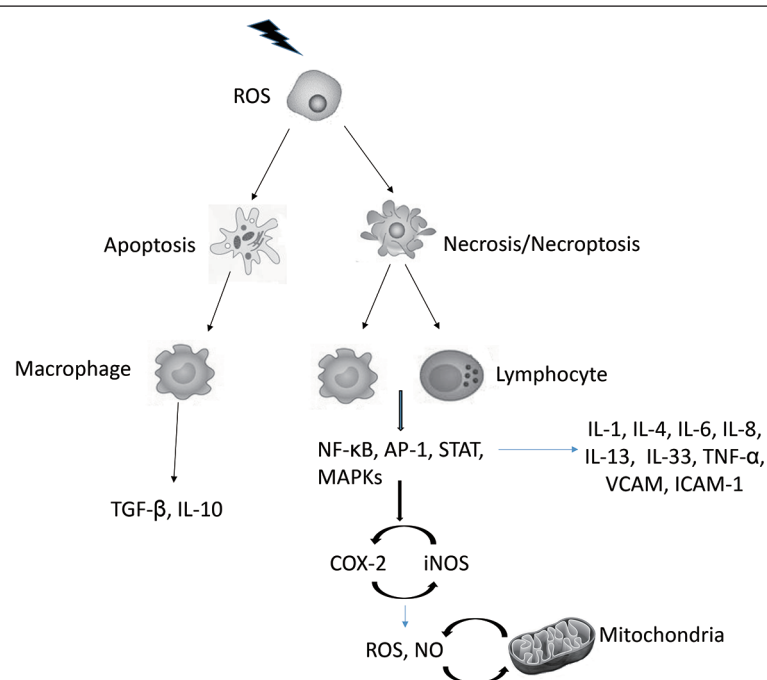


Fig. 1 The mechanisms of IR-induced inflammation or anti-inflammatory responses.

After apoptosis, macrophages detect apoptotic bodies, leading to the secretion of anti-inflammatory cytokines, such as transforming growth factor beta (TGF-β). This response is observed for low doses of ionizing radiation (IR) (less than 1 Gy), where apoptosis is more common than necrosis. However, damage associated molecular patterns (DAMPs) released by necrotic cells after exposure to high doses of IR stimulate T-cells and dendritic cells (DCs) to up-regulate inflammatory mediators and the secretion of inflammatory cytokines

the increased risk of autoimmune thyroid diseases may have contributed to the elevated cancer incidence among the irradiated population[70].

In addition to high doses of IR in radiation therapy or disasters, several studies have proposed that exposure to occupational doses of IR may be associated with thyroid autoimmune disease. In a cross-sectional study, Völzke *et al.*[66] examined the potential role of the low-dose occupational exposures to IR (mostly lower than 1–2mSV in a year) associated with the increased risk of thyroid diseases. These authors used thyroid ultrasound and antithyroxiperoxidase antibodies to detect the incidence of this disease. The results showed an unusual thyroid pattern in ultrasound imaging, particularly for females. Moreover, the results showed that this risk is higher for workers of a nuclear power plant, particularly those that have been exposed for more than 5 years[71].

Imaizumi and colleagues evaluated the risk of thyroid diseases among atomic bomb survivors exposed in utero. Among the 319 participants that received an equal radiation dose of 25cGy, no significant thyroid disease was detected. However, the authors proposed that a limited statistical power may be involved in the negative result of this study[72]. As the radiosensitivity of the uterus is similar to that of the child,

further studies with a higher population number are needed to investigate the potential role of IR in thyroid diseases in utero.

Potential mechanisms of IR-induced thyroid autoimmune diseases

Studies have proposed that autoimmune thyroid disease is related to genetic background, while exposure to toxic agents, such as ionizing radiation, is also involved[73,74]. Mechanisms of autoimmune thyroid diseases are different, which can be observed as changes in thyroid hormone action, resulting in a change in circulating hormones. However, thyroid malfunctions may result from pituitary and thyrotropin secretion[75].

The most common thyroid diseases following exposure to ionizing radiation are hypofunction and thyroid nodules. However, the increased incidence of thyroid cancers may be involved in these diseases[76]. A reduction in function of the thyroid is the most common autoimmune disease induced by IR. Graves' disease has been implicated in hypothyroidism or hyperthyroidism following exposure. In addition, a reduction of the thyroid-stimulating hormone (TSH) receptor in patients treated with radioiodine is associated with the increased probability of autoimmune hyperthyroidism[77].

Several studies have proposed that inflammatory responses

may be involved in autoimmune diseases. For example, the production of inflammatory cytokines, such as IL-1 and IL-6, in thyroid-infiltrating mononuclear and follicular cells has been associated with Graves' disease[78]. Macrophages and NK cells play a central role in the secretion of IL-1 and IL-6. IL-1 can stimulate the release of IL-6 in thyrocytes. Moreover, this effect may be potentiated by TNF- α . The upregulation of these inflammatory cytokines can suppress the secretion of thyroid hormones, such as TSH, and reduce the serum levels of Thyroxine (T4) and Triiodothyronine (T3)[79,80].

Diabetes

Several studies have reported a link between whole body or abdomen irradiation and the increased risk of diabetes[81–83]. A previous study showed a two-fold increased risk of diabetes mellitus (especially type 2) for cancer survivors treated by radiotherapy for acute myeloid leukemia (AML), neuroblastoma, Wilms tumor, and Hodgkin lymphoma. Additionally, survivors of acute lymphoblastic leukemia (ALL) and brain tumors showed an increased risk of obesity in adulthood. The results of this study showed that neuroblastoma survivors have the highest likelihood of becoming diabetic compared with siblings. This issue is more obvious for individuals who have been exposed to whole body irradiation and abdomen radiotherapy for childhood cancer[84,85]. The association between Hodgkin lymphoma treatment and the increased risk of diabetes mellitus has been confirmed[86]. In a 30-year follow-up study of 2520 childhood cancer survivors, Vathaire *et al.*[83] showed that irradiation to the tail of the pancreas is closely associated with the increased risk of diabetes. This study showed that the risk of diabetes has a strong relationship with radiation dose. The irradiation of other parts of the pancreas did not show any relationship with diabetes risk[87]. The mechanisms of IR-induced diabetes are not fully understood. However, the impairment of specific β -cell and insulin release among cancer survivors may be involved[88].

Potential mechanisms of IR-induced diabetes

In contrast to the aforementioned reports, several studies have indicated that low-dose radiation (0.5Gy) has a prevention effect on the development of diabetes. Mechanisms may include the induction of pancreatic antioxidants and protection of the β cells from oxidative damage and immunomodulation to preserve pancreatic function[89]. However, the precise molecular mechanism of β -cell damage after irradiation is not known, and chronic inflammation likely plays a key role in this process. It is feasible that pro-inflammatory cytokines, such as IL-1 β and IFN- γ , be involved in the signaling pathways that cause pancreatic β -cell death and dysfunction[90]. Moreover, activation of the NLRP3 inflammasome may stimulate oxidative damage through hyperglycemia[91–93].

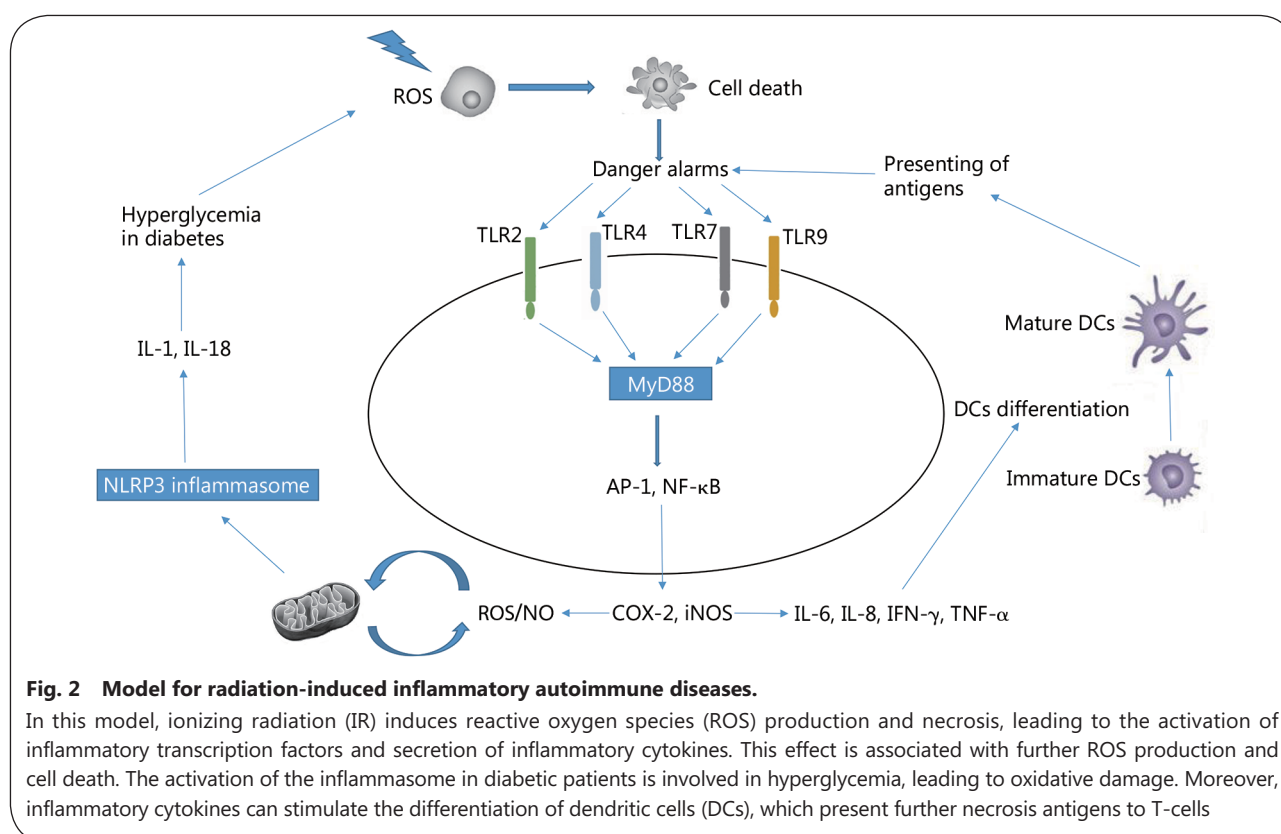
However, there is some evidence that the proposed genotype is involved in the risk of radiation-induced diabetes. A study of atomic-bomb survivors showed a relationship between human leukocyte antigen (HLA) genotypes and diabetes. Survivors with the DQA1*03-DRB1*09 or DQA1*0401-DRB1*08 haplotypes showed an increased risk of diabetes with radiation dose[94].

Gastritis

Autoimmune gastritis is a chronic inflammatory gastric condition characterized by the increased number and activity of inflammatory cells, such as lymphocytes. Chronic gastritis results from the destruction of the mucosa, leading to pain, atrophy, inflammation and bleeding[95]. This type of autoimmune disease is common for clinical tumor treatment in which the stomach is within the field of radiotherapy. Gastritis typically appears after the gastric exposure to doses higher than 40–50Gy[96]. Although the molecular mechanisms of gastritis following exposure to radiation have not been completely determined, several studies have reported that the suppression of inflammation using anti-inflammatory drugs can help control this condition[97–99]. Graziani *et al.* proposed that radiation-induced gastritis in patients with pancreatic cancer can be stimulated by other drugs, such as erlotinib, which is an antagonist for the expression of epidermal growth factor receptor[100] (Fig. 2).

Potential role of radiation mitigators to prevent radiation-induced inflammation diseases

Although the administration of antioxidants or other radiation modifiers prior to exposure has the highest efficiency, several studies have proposed that chronic treatment with antioxidant agents may reduce the long term consequences of radiation. For example, the treatment of Chernobyl survivors with antioxidants, such as beta-carotene, reduced the serum level of oxidative damage markers[101]. As previously described, several studies have confirmed that chronic inflammation plays a key role in the detrimental effects of radiation, including continuous oxidative stress and even carcinogenesis. Treatment with some antioxidants, such as ascorbic acid, selenium, and other antioxidant mixtures, have exhibited the ability to ameliorate increased oxidative damage and the levels of inflammatory cytokines, such as IL-1, IL-6, TNF- α , IFN- γ , and TGF- β [102–104]. *In vivo* studies have confirmed the mitigatory effects of certain antioxidants and immunomodulators for other radiation-induced inflammation diseases, such as nephrotoxicity, pneumonitis and fibrosis[105–109]. As autoimmune diseases have a direct relation to these factors, it is likely that the amelioration of



chronic inflammation may help reduce the incidence of various radiation-induced diseases, including autoimmune diseases.

Conclusions

Although there is a long way to illustrate the complete mechanisms of IR-induced diabetes and thyroid diseases, recent studies suggest that the chronic up-regulation of inflammatory mediators and cytokines play a key role. It is feasible that long-term exposure to a high level of some cytokines, particularly IL-1 β and IFN- γ , can disrupt the normal function of thyrocytes in the thyroid, as well as beta cells in the pancreas. However, it is likely that genetic background plays a key role in the appearance of autoimmune diseases. Although there is no suggested strategy for the prevention or reduction of autoimmune diseases following exposure to IR during radiotherapy or radiation accidents, there may be several solutions, such as the administration of radio protectors, anti-inflammatory agents, or radiation mitigators. However, to date, there is no evidence to confirm this idea.

Abbreviations

AP-1: Activator protein 1; COX-2: Cyclooxygenase-2; DCs: Dendritic cells; HMGB1: High-mobility group box 1; HSPs: Heat-shock proteins; ICAM-1: Intercellular adhesion molecule 1; IFN- γ : Interferon gamma; IGF-1: Insulinlike growth factor 1; IL: Interleukin; iNOS: Inducible nitric

oxide synthase; IR: Ionizing radiation; MAPKs: Mitogen-activated protein kinases; NADPH: Nicotinamide adenine dinucleotide phosphate; NF- κ B: Nuclear factor- κ B; NO: Nitric oxide; ROS: Reactive oxygen species; STAT: Signal transducers and activators of transcription; T3: Triiodothyronine; T4: Thyroxine; T-Cells: Lymphocytes T; TGF- β : Transforming growth factor beta; TLR: Toll-like receptor; TNF- α : Tumor necrosis factor- α ; TSH: Thyroid stimulating hormone; VCAM: Vascular cell adhesion molecule 1

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The authors declare that they have no competing interests.

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