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REVIEW ARTICLE

INFLUENCE OF IONIZING RADIATION ON DEVELOPMENT OF THYMUS AND THYMOCYTES

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Summary

Purpose: Among other reasons, the deteriorating global security situation and dangers associated with nuclear weapons have increased the need for deeper knowledge of the basic mechanisms involving the human immune system and ionizing radiation (IR). We conducted a review as to the effects of IR on thymic tissue, and particularly on the development of thymocytes and the T lymphocytes population in peripheral blood.

Existing knowledge on this topic is based in part on national registers that store records concerning irradiated people. The majority of studies in this area, however, are based on experimental animal models. The main open question in this subject area regards the delayed effects of IR on thymus tissue, development of thymocytes, and subsequent impact on the immune system. Findings acquired to date on effects of IR are contributing to emerging fields such as immunotherapy, the objective of which is to support or activate natural immunity response.

Methods: Recent research articles were reviewed regarding the influence of IR on thymus tissue and thymocytes development.

Results: Differentiation and proliferation of thymocytes constitute a complex and sensitive process that is partially altered after irradiation, as are, too, the mechanisms for movement of early (derived from bone marrow) and derived (thymus derivatives) precursors. Disruption of these processes may lead to alteration of immune system function.

Conclusions: Low doses (<200 mGy) may lead to changes in or disruption of functions of the thymus, thymocytes, and mechanisms of the immune system. The extent of IR's influence is dependent not only on the individual's radiosensitivity but also on his or her sex and age. With increasing absorbed IR dose, the risk of damage to thymus tissue and thymocytes in the organism rises and the extent of damage increases.

Key words: irradiation; immune system; thymus; T lymphocytes

Introduction

Biological effects of ionizing radiation (IR) on the human organism constitute today a matter that remains partly unexplored. Data not yet completely evaluated exists in national medical registries recording individual cases of irradiated people. One of the first such registries was established after the nuclear bombings of Hiroshima

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and Nagasaki in 1945 (1). In the Czech Republic, the national central registry known as the Overview of Occupational Diseases Caused by the Influence of Ionizing Radiation in the Czech Republic was established in 1996 (2, 3). Currently, however, the majority of findings in this area originate from work using experimental animal models, and a minority of findings originate from modern analyses using data from global and national registries. Those studies and analyses performed have contributed to optimizing treatment of acute radiation sickness (4). Current treatment procedures allow survival of patients irradiated by doses previously considered to render individuals incurably sick. The main questions presently unexplored, therefore, concern not acute symptoms of IR on the human organism itself, but rather its late effects and alteration of immune system mechanisms. Uncovering these complicated biological mechanisms may be of considerable importance not only for treatment of acute radiation sickness but also for patients with oncological diseases.

A summary document publishing the results of IR on the organisms of irradiated people 30 years after the Chernobyl nuclear power plant (NPP) disaster is the extensive UNSCEAR report from 2000 (5). In particular, the interpretation of low, single-irradiation doses on the human immune system was shown in that report to be very difficult (6), even though it is known that even very low doses in the range of 2.5–7 mGy lead to changes in the representation of individual lymphocyte populations in peripheral blood within a matter of months. This concerns in particular lymphocytes because they are among the most radiosensitive cells of the immune system (5).

Irradiation of lymphocytes results in their reduction in number, which is dependent on the absorbed dose. The aforementioned UNSCEAR report from 2000 accordingly states that a slight reduction in absolute numbers of lymphocytes occurred after a whole-body, single-dose irradiation of the organism by up to 7 mGy. Their overall renewal starts within the first year after irradiation, depending on radiosensitivity of the given lymphocyte population and the state of the irradiated organism (5). The report also points out that the absorbed dose of the Chernobyl inhabitants was not always retrospectively determined with absolute precision, and therefore certain published results may differ from some other published studies related to irradiated people.

The UNSCEAR report from 2000 also states that in 85 workers participating in the clean-up work who received a fractionated dose of 1–330 mGy as a result of the disaster, there was a slight reduction in T lymphocytes depending on the absorbed dose between the 9^{th} and 156^{th} days. Over the long term, however, no changes in the absolute number of lymphocytes were found.

Influence of ionizing radiation on lymphocytes, hematopoesis, and immune system

A lymphocyte is a type of white blood cell occurring in vertebrates' peripheral blood. Because there are no granules in its cytoplasm, it is classified as an agranulocyte and represents a functionally diverse group of immune cells divided into a population of B lymphocytes, T lymphocytes, natural killer (NK) cells, and a rare population of NK T cells. The representation of lymphocytes in human peripheral blood is 24–40% of the absolute number of white blood cells [6], which corresponds to $1.2–3.1 \times 10^9$/l (7).

Lymphocytes, as well as other haematopoietic cells, are formed from the common haematopoietic stem cells (HSCs), which have a capability for self-renewal and formation of all blood cell lines. In adult mammals, HSCs occur in very low numbers in the bone marrow (8).

The development of lymphocytes continues from the pluripotent HSCs through the common lymphoid progenitor (CLP), whose surface phenotype is $lin^-CD34^+CD38^+CD10^+$ (9), then through the lymphoblast, which is the first morphologically discernible precursor of lymphopoiesis. These are large cells from which after 2–3 divisions are formed pro-lymphocytes already bearing the characteristics of B and T lymphocytes (10). At that time, NK cells diverge from the lymphoid line and do not bear the differentiation characteristic of either B cells ($CD19^+$) or T lymphocytes ($CD3^+$). Development continues through the stage of small lymphocyte from which the two main and functionally different populations of T and B lymphocytes diverge (11).

Because lymphocytes constitute a radiosensitive population of blood cells, their reduction in absolute cell count is observed 24 h after irradiation by a dose greater than 1 Gy. Detailed analysis has demonstrated a reduced subpopulation of CD4+ T lymphocyte fraction and lower T lymphocyte proliferation ability in irradiated humans

after an atomic bomb drop and the Chernobyl accident. A long-term decrease in $CD4^+$ T lymphocytes was observed in severely exposed individuals (12)

The Chernobyl study divided irradiated people into three groups (group 1: 0.1–0.5 Gy, group 2: up to 4 Gy: and group 3: up to 9 Gy) and the overall decrease in the absolute counts of T lymphocytes was recorded for all groups. A decrease in $CD8^+$ T cells was observed in the least-exposed group and a decrease in $CD4^+$ cells in subjects irradiated with 2–9 Gy. Moreover, alterations in thymic epithelial cell function were observed in all three groups (13).

Decrease of NK cell counts, $CD4^+$ and $CD8^+$ T cells, and the phagocytic activity of neutrophils have been demonstrated in individuals involved in Chernobyl clean-up operations (14). On the other hand, the Kuzmek study of Chernobyl employees did not detect disruption of the T cell subpopulation except for $CD3^+CD16^+CD56^+$ (NKT cells). However, *in vitro* immunophenotyping of phytohemagglutinin (PHA)-activated MNCs (peripheral blood mononuclear cells) after activating blood cells demonstrated a suppression of $CD4^+$ T cells propagation and an increase in $CD8^+$ T cells propagation compared to control individuals (15).

In cases of long-term effects on the organism from very low doses, however, the situation is different. Individuals exposed to daily doses smaller than 10 mSv survived irradiation for several years without organ function failure. In some individual cases, however, a failure of immune surveillance later occurred, which was demonstrated by neoplastic complications categorized as stochastic effects of IR (16).

Daily doses greater than 10 mSv but not exceeding 100 mSv lead to serious damage to haematopoiesis in bone marrow, and that eventually can result in lethal attenuation of haematopoiesis through myeloproliferative syndrome, whereby there occurs uncontrolled increase of myeloid cells and diagnostics point to a leukemic process (16).

Studies concerning the influence of doses greater than 1.5 Gy on the human organism (in particular in nuclear bombing survivors) mention changes in cell immunity defined mainly by changes in the population of T lymphocytes. No reduction of NK cells has been confirmed (18, 19), however, and that is the main lymphocyte population ensuring cytotoxic cell immunity and capable to destroy tumour cells in the organism even before encountering the antigen. Another study observed a slight inflammatory response of the organism, as had been expected in connection with increased production of reactive protein and inflammatory cytokine interleukin 6 (IL 6) (20).

Akley et al. report an absorbed dose of 0.3–0.5 Sv per year to be a threshold dose for immune system damage (21). It can be stated with certainty that when radiation dosage around 1 Gy is reached bone marrow syndrome of acute irradiation disease develops in the organism. Ionizing radiation in bone marrow leads to induced cell destruction with subsequent flooding of bone marrow with erythrocytes, known as "bone marrow bleeding". Renewal of microvascular bone structure, including its sinus parts, is necessary for regenerating production of haematopoietic cells (22). The affection rate of haematopoietic and other tissues after total-body irradiation of the organism is of crucial importance for survival of that organism. Pathological changes in the affected organism's tissues result from compromised integrity of the sensitive stem cells and commonly lead to their death or non-standard development in the direction of cancer cells.

Important long-term changes of the immune system have occurred when absorbed IR doses were high. In one part of the workers participating in cleaning up as a consequence of the Chernobyl disaster in 1986, acute radiation sickness was confirmed on the basis of prodromal, clinical, and manifest symptoms. Fifty workers were irradiated with total dose of 2.2–4.1 Gy and 22 workers received total-body dose in the range of 4.2–6.4 Gy. Median lethal dose (LD_{50} 4.5 Gy) led to a quicker development of bone marrow syndrome of radiation sickness, and long-term regression of the immune system was observed in the irradiated people. Total-body irradiation of the organism with doses of 4.5–8 Gy resulted in serious long-term damage to haematopoiesis in bone marrow. Cytokine factor treatment is currently preferred for renewal. In cases of complete disappearance of haematopoiesis stem cells, however, bone marrow transplantation is preferred (5, 23).

Homeostasis integrity depends primarily on the organism's ability to keep the creation of blood elements in balance. Some of these processes are occurring continuously in the body, while others are started up by a life-threatening state. The mammalian organism normally works such that the main objective of homeostasis

is to maintain physiological absolute numbers of bone marrow stem cells, erythrocytes, thrombocytes, and leukocytes (neutrophils, basophils, eosinophils, lymphocytes, and monocytes). The individual blood elements differ in their own characteristic lifetimes, sensitivity to IR, and time necessary for their renewal. Lymphocytes are among those blood components most sensitive to the effects of IR. The first morphological changes occur as soon as 2 h after a total body irradiation dose of 0.25 Gy. The effect of IR in lymphocytes results in chromosome clustering, pyknosis, nucleus fragmentation, abnormal mitoses, creation of vacuoles in mitochondria, and changes in the membrane structures and cytoskeleton. These pathological changes lead to interphase death in cells outside of the cell cycle. At doses greater than 5 Gy, interruption of mitosis in lymphatic tissues occurs within 30 minutes after irradiation, followed by disappearance of lymphocytes from the spleen and lymph nodes. A rapid reduction in lymphocytes can also be observed in peripheral blood. A maximal reduction of lymphocytes in the blood occurs, depending on the dose size, within 3 days after irradiation of the organism. In case lymphocytes are reduced to below 50% (1×10^9/l) within 48 h, the patient can be expected to develop symptoms of acute radiation sickness. Estimated prognoses for patients considering the total numbers of lymphocytes in blood are shown in Table 1.

Table 1. Estimated prognoses for patients according to total numbers of lymphocytes in blood (19).

Absolute number of lymphocytes	Estimated dose and prognosis
$> 1.5 \times 10^9$/l	Insignificant radiation dose, good prognosis
$1–1.5 \times 10^9$/l	Medium reduction of granulocytes and thrombocytes after 3 weeks, good prognosis
$0.5–1 \times 10^9$/l	Serious form of bone marrow syndrome, prognosis dependent on early initiation and method of treatment
$< 0.5 \times 10^9$/l	Radiation dose may be lethal
0	Radiation dose is lethal

Lymphopenia and symptoms of functional disruption in mechanisms caused by damage to lymphocytes last for months. In a horizon measured in years, however, there occurs a recovery of the immune system in survivors, as indicated by data acquired from people affected by the bombings of Hiroshima and Nagasaki (20).

Based on results acquired after the Chernobyl NPP disaster, it can be stated that, even in case of overcoming the consequences of acute radiation sickness, the patients die prematurely within a matter of several years. The largest number of patient deaths was recorded 2 to 10 years after irradiation. A majority of lethal cases (up to 95%) was among 20 irradiated patients who absorbed total-body doses of 6.5 Gy and greater. Those irradiated in the first years after the disaster died mainly due to lung damage manifested by prolonged inflammation of the pulmonary alveoli transforming into lung fibrosis caused by higher occurrence of beta radiation during the Chernobyl NPP disaster. Two years after this disaster, a person died due to lung gangrene. Along with red bone marrow and tissue of the large intestine, lungs are among these tissues with the largest tissue factor in accordance with ICRP 103. In addition, lungs are classified in the radiosensitivity group of late-responding tissues whose responses are highly dependent on the volume of irradiated tissue. This fact appears to result in a much higher probability of developing lung gangrene in irradiated patients than in the non-irradiated population.

In the period 7–8 years after irradiation, part of the surviving patients began to experience signs of bone marrow damage or failure characterized by acute or chronic myeloproliferative disease (5, 21). Leukaemia develops due to the immune system's not recognizing the occurrence of atypical blast cells in bone marrow. Atypical blast cells remain in the bone marrow, where they continue uncontrollably to divide and thereby lead to disrupting the homeostasis. Many studies have examined risk rates of developing leukaemia (22, 26, 27).

The thymus and ionizing irradiation in the organism

The thymus is a central lymphoid organ ensuring the development of T lymphocytes, which process is governed by chemokines produced by the supportive connective tissue of the thymus (28). Anatomically, the thymus is located

behind the sternum. It is covered in a sheath of connective tissue that reaches into the interior of the parenchyma and divides it into the individual lobes. Each lobe consists of a cortex and a medulla, the latter of which stains at a lighter colour on histological samples due to the lower density of lymphocytes. In the thymus cortex, there occur considerable numbers of small and large T lymphocytes, dispersed epithelial reticular cells, and macrophages. The thyroid medulla contains, in addition to lymphocytes, especially epithelial cells, Hassall's corpuscles, and macrophages. The size of the thymus and its histological composition depend on many factors, such as an individual's age and occurrence of diseases earlier in the organism's life. The thymus is fully functional from birth. In people 12–14 years of age, first the cortex of the individual lobes disappears, being replaced by adipose tissue (28, 29). Its functions are then taken over by lymphatic organs.

The cell population of the thymus is supplemented throughout an individual's lifetime with precursors of T lymphocytes (pre thymocytes) having phenotype $CD4^{-}CD8^{-}CD25^{-}CD44^{+}$, $CD4^{-}CD8^{-}CD25^{+}CD44^{+}$ and which migrate through the blood vessels from red bone marrow to thymus tissue (30). Immature thymocytes may be divided into four stages of development with differing surface expression of CD44 and CD25. The least mature (naive) subpopulation of thymocytes has the surface characteristics $CD44^{+}$ and $CD25^{-}$. These cells then differentiate into a subpopulation of pro-thymocytes ($CD44^{+}CD25^{+}$). Pro thymocytes start binding to TCRβ and lose the CD44a receptor ($CD44^{-}CD25^{+}$). The most mature thymocytes are termed post-pre thymocytes, have surface characteristics $CD44^{-}CD25^{-}$, and have completed binding of the TCRβ gene (7).

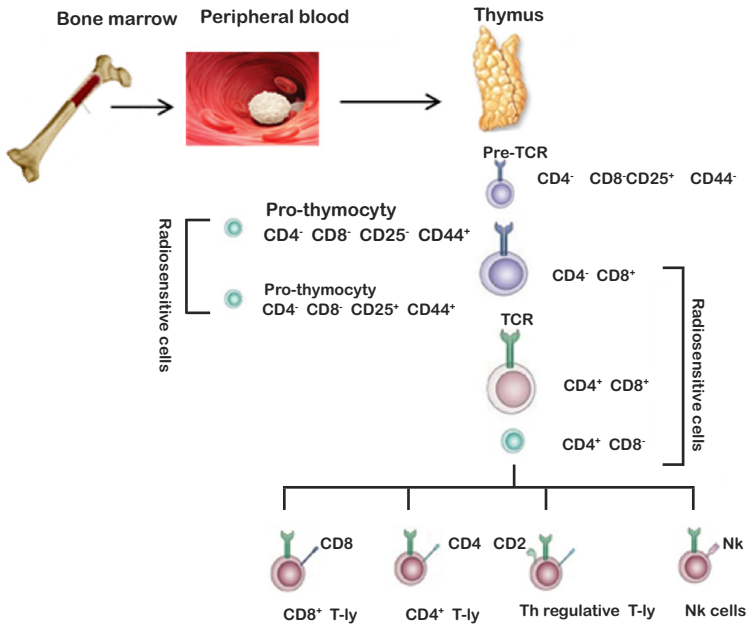

Figure 1. Lymphocyte populations in human thymus

*T-ly – T lymphocytes. Value w_t for other tissues (0,12) is related to the arithmetic average of mean doses in 13 organs and tissues of both sexes stated below. Other tissues: adrenal gland, extrathoracic region, gall bladder, heart, kidney, lymph nodes, muscles, mucosa of the oral cavity, pancreas, prostate (for males), small intestine, spleen, thymus, uterus / cervix (for females). bb – cells

Qualitative factors Q

Linear transmission of energy L [keV/μm]	Quality factor Q (L)
<10	1
10–100	$0.32.L^{-2.2}$
>100	$300.L^{-0.5}$

Annex 3 to Decree No. 422/2016 Coll.

The process of migration and nesting of pre-thymocytes into the thymus cortex is governed by chemokines produced by the supportive connective tissue of the thymus. Pre-thymocytes are large, double-negative ($CD4^-CD8^-CD44^-CD25^-$) cells, expressing the CD7 and CD2 molecules and later also CD5. On their surface are bound the CD38 and CD71 activation molecules. In the thymus, these cells gradually proliferate and undergo rigorous selection, with only 1–3% of their total number passing (9, 31). Pre-thymocytes first colonize the organ's cortex, where maturation of T cells occurs in 4 degrees, including both the transformation of molecule phenotype and regrouping of genes for TCRβ (αβ-T) and TCRδ (γδ-T) (32). The binding of the antigen-specific receptor TCR (the process for eliminating cells with non-functional TCR) is followed by the selection process (interaction of the MHCI and MHCII glycoproteins with surface characteristics of CD4, CD8). Glycoproteins of the MHCI or II groups on the surface of cells present antigenic peptides from pathogens. Cells which passed the two previous selections leave the cortex and move to the thymus medulla, where so-called negative selection for medullary epithelial cells occurs.

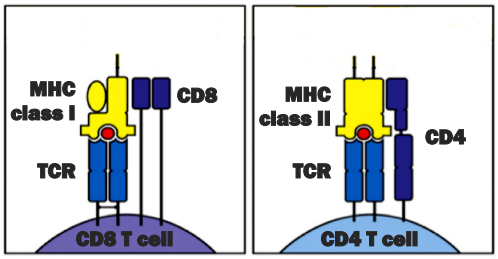

Figure 2. Binding locations for CD4 and CD8 on MHC molecules classes I and II (33).

In the thymus medulla, T cells learn to recognize histocompatible antigens. T cells that were unsuccessful in the selection process undergo cell death (apoptosis) (3). Successful but immature T lymphocytes subsequently leave the thymus and are transported into thymus dependent areas of non-thymic lymphoid organs, where they settle, mature, and differentiate into the subpopulations of auxiliary (Th, $CD3^+CD8^+CD4^-$), regulatory (Treg, nTregs "natural" $CD4^+CD25^{int/high}CD127^{low}$, iTreg "induced" Tr1 $CD4^+CD25^-$, Tr2 $CD4^+CD25^+$), killer (Tc, $CD3^+CD8^+CD4^-$), and memory (Tm, Tcm "central memory T cell" $CD25^+CD45RA^-CD45RO^+CD127^+$, Tsm "T-stem cell memory" $CD62L^+CCR7^+CD45RA^+CD45RO^+$) cells (34).

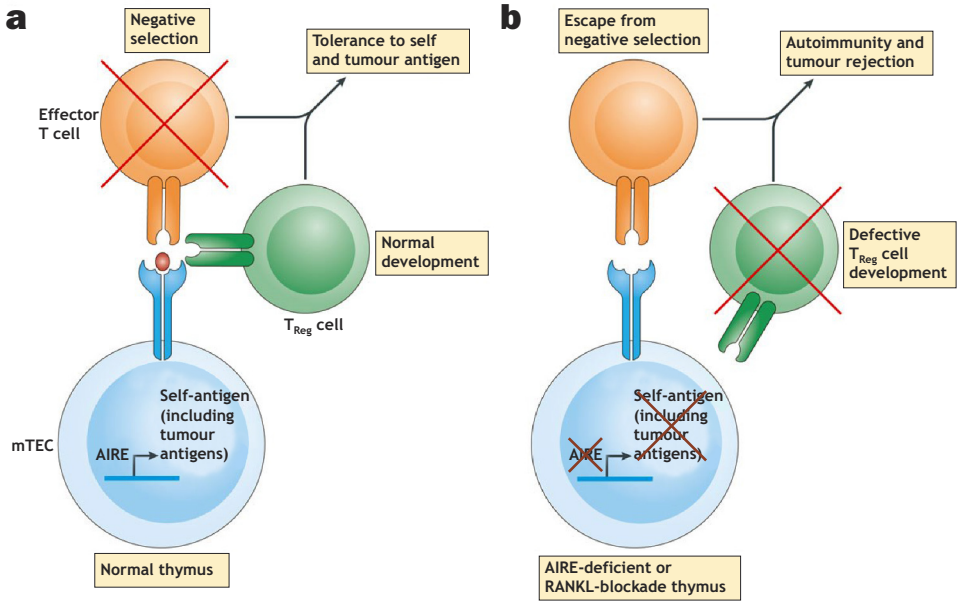

Figure 3. The process of positive and negative selection in the thymus (35).
a) Negative selection tolerance of own and tumour
b) Escape from negative selection

As described above, thymopoiesis is a highly sophisticated process and its disturbance leads to immunity disorders that may themselves cause autoimmunity response of the organism and failure of immunity control mechanisms resulting in carcinogenesis.

The development of the thymus and related mechanisms logically indicate that the most serious disorders occur in the early stages of thymus development. An interruption in thymus function may give rise to serious disorders of the immune system, reproduction organs, thyroid, or the external side of the colon. The thymus can also be endangered by the formation of tumours (thymomas), and particularly in patients with the autoimmunity disease Myasthenia gravis, who face a high probability (25–50%) for the occurrence of a tumour. All thymomas are potentially malignant. Tumours may also develop from thymocytes (thymic lymphomas).

Incomplete proliferation or differentiation processes of blood elements due to thymus damage may occur in an unexpected radiation accident, especially during an individual's prenatal development and during examinations using sources of IR on pregnant women. Unexpected irradiation or contamination of individuals can occur in cases of nuclear accidents and disasters, where acute symptoms of radiation sickness develop depending on the dose received.

Utilizing knowledge of effects of irradiation in therapy

In recent years, the importance of the study of T lymphocytes, their migration and differentiation has been shown to be of increasing importance. Among other areas, oncological studies have examined immune surveillance of cancer, which was first hypothesized in the mid-20th century.

Modern medicine is in many cases able to treat some of the symptoms of acute radiation syndrome and damage to the body due to radiation, but the suppression and prevention of late effects in irradiated individuals is still an open chapter. Knowledge gained from survivors after radiation accidents and disasters suggests, however, that there exists a high probability that the immune system's mechanisms will be transformed even at low doses.

Similar conclusions have been drawn from research into the study of thymus tissue from 165 people exposed to the 1945 bombing in Hiroshima. The estimated doses were 5 mGy to 3 Gy. Increased characteristics of thymic involution have been observed in subjects receiving low (5–200 mGy) and moderate (<200 mGy) radiation doses (36). As the S. Xiao study shows, the effect of radiation on thymopoiesis in mice is substantially influenced by sex, dose, and age of the irradiated organism. The overall impact on hematopoietic lineages is more pronounced in women. Long-term suppression of thymopoiesis following sublethal irradiation of the organism is primarily dependent on a reduced number of progenitors in the bone marrow together with a reduced number of pro-thymocytes. The number and ability of HSCs to produce T lymphocytes can be dramatically and permanently impaired after only one relatively low total body dose, thereby leading to early thymus aging (37).

Restoration of thymic epithelial cells leading to T cell differentiation, proliferation, and selection requires a fully functional thymus. Disruption of the T lymphocyte and thymus development process appears to be directly associated with suppression of the body's specific immune response, as manifested by increased susceptibility of patients to infectious diseases, relapse, and, in the case of bone marrow transplantation, host graft rejection. Clinical studies also suggest that a lower-intensity cytoreduction regimen leads to increased T cell lymphopoiesis, thus suggesting a direct link between thymus tissue damage and T cell formation. The studies described above have led to a more in-depth examination of processes aimed at the mechanisms of protecting and restoring thymus and thymopoiesis tissue (38). Greater attention is drawn to this subject area within today's dynamically developing field of cancers immunotherapy, which primarily is directed to supporting and activating the natural immune response to eliminate tumours in the body. This therapy utilizes both immune system cells, such as T lymphocytes, and their natural products, such as cytokines and interferons. A new development in immunotherapy encompasses research into T lymphocytes that are genetically modified by viral vectors to function to the maximum benefit of the immune system (39, 40).

Conclusion

The aim of our review was to summarize older and more recent findings in the field of IR effects on thymic tissue and thymopoiesis, as well as to determine the impacts of their damage to the immune system. Studies have shown

that low doses (<200 mGy) may lead to alteration or impairment of thymus and changes of T lymphocyte population in peripheral blood. Doses of 5–200 mGy can bring irreversible changes in the body that over a course of years can lead to impairment or damage to the immune system and in some cases to the development of cancer or autoimmune diseases, including multiple sclerosis, arthritis, as well as kidney and endocrine gland diseases. These, in turn, increase the likelihood of such other serious illnesses as diabetes and thyroid and genital diseases.

The extent of IR influence depends not only on the type of radiation and the individual's radiosensitivity, but also on his or her sex and age. Risk of damage to the thymus and thymocyte tissue in the body increases in direct proportion to the absorbed dose. Exposure to higher radiation doses leads to long-term impairment of thymus and thymopoiesis, as manifested by a long-term decreasing proportion of the T subpopulation in the body. Recovery in the number of T lymphocytes in the body depends on the restoration of thymic epithelial cells and hence of thymus function. Studies also show a direct impact of impaired thymic function and thymopoiesis on the immune system. In the long term, the body may develop autoimmune diseases or its ability to conduct immune surveillance of cancer may be suppressed. Thus, it is apparent that deeper exploration of the processes and mechanisms leading to disruption and alteration of the thymic and thymocyte functions, and with a view to preventing their being damaged and promoting their renewal, will be important in addressing the late effects of IR.

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Conflict of Interest

The authors declare that they have no conflicts of interest regarding the publication of this article.

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Adherence to Ethical Standards

Ethics approval and consent to participate not applicable.

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