

综述

CURRENT STATUS OF RESEARCH ON RADIATION HORMESIS IN THE IMMUNE SYSTEM AFTER LOW LEVEL RADIATION

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ABSTRACT The present paper highlights the chief results of experimental studies recently carried out in the author's laboratory on the stimulatory effects of low level radiation on immunity. The intercellular relationship within the immune system after whole-body irradiation (WBI) with low doses of X- and gamma-rays was briefly outlined with the emphasis on the potentiating effect of low dose radiation (LDR) on the helper T cells which was thought to occupy a pivotal position in the process of immuno-stimulation. Data suggesting the facilitation by LDR of the signal transduction process within the T cells were presented. Some hypotheses prevailing in the literature for the explanation of the stimulatory effect of LDR were critically evaluated. Existing experimental data both from the literature and from the author's laboratory were analysed giving no strong support to the speculation of either the preferential deletion of the radiosensitive suppressor T subset or the increased apoptosis of the T cell "precursors" in the thymus leading to secondary immunologic augmentation by low doses which stimulate immune functions. The possible influence of systemic changes, especially those in the neuroendocrine regulation, on the T cell potentiation following LDR was suggested. Finally the biological implications of the hormetic effects of LDR were discussed.

KEYWORDS Low level radiation, Hormesis, Immune system, T subsets, Apoptosis, Intracellular signal transduction, Neuroendocrine regulation

Introduction

It has been repeatedly demonstrated that whole-body irradiation (WBI) with low doses of ionizing radiation could up-regulate the immunologic reactions^[1-3]. This up-regulation of immunity following low dose radiation (LDR) involves a series of cellular as well as molecular reactions. The cellular reactions occurring in the immune organs after LDR are quite complicated with the activation of the T lymphocytes occupying a pivotal position. It has been confirmed that the following changes occurred after WBI with doses of X- or gamma-rays within 0.1 Gy:

1) The T lymphocytes are stimulated as exemplified by increased reactivity of both the splenic and thymic cells to ConA while the reactivity of the splenic

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cells to LPS showed no significant changes^[1,3].

2) Thymocyte renewal is potentiated, as expressed in the increase in percentage of the CD₄/CD₈ double negative cells which include the stem cells, prothymocytes and immature thymocytes^[4].

3) The expression of the TCR/CD 3 complex on the thymocytes is potentiated, implicating expedited maturation and differentiation process in the thymus^[5].

4) The secretion of colony-stimulating factor (CSF) by the thymocytes is increased which would stimulate the macrophages to produce IL 1^[6,7]. IL 1 exerts at least two actions one of which is providing a maturation signal to the helper T cells (Th) and the other is a positive feedback to the macrophage itself.

5) Increased thymocyte renewal, maturation and differentiation are accompanied with an enhanced proliferative process in the thymus as evidenced by the augmented spontaneous incorporation of ³H-TdR into the thymocytes and increase in their number^[1]. These changes occurring after LDR would form a positive feedback loop, resulting in an increased supply of T cells to the periphery, including the spleen and other peripheral lymphoid tissues.

6) The macrophages are stimulated with enhanced phagocytic and digestive activity against foreign materials and increased cooperative effect on the T cells^[7].

7) The interaction of the macrophages by presenting the processed antigen determinant and the MHC II molecule with the TCR/CD 3 complex of the Th result in an increased secretion of IL 2 and interferon-gamma (IFN-gamma) by the Th as well as enhanced expression of IL 2 receptor on these cells, finally leading to clonal expansion^[1,8].

8) Activation of Th with its increased IL 2 secretion promotes B cell activity finally enhancing antibody formation, with the potentiation of the plaque-forming cell (PFC) reaction in the spleen as its expression^[1,9].

9) The natural killer (NK) cell activity and the antibody-dependent cell cytotoxicity (ADCC) are stimulated, indicating increased tumor-suppressive action of the immune system^[3,10,11]. The increased IL 2 and IFN secretion apparently participate in this stimulation.

The mechanism of the stimulatory effect of LDR on the immunologic parameters listed above is realized through different pathways which will be analyzed in the following sections. It should be emphasized that T cell potentiation occupies a pivotal position in the whole process of LDR-induced immunologic augmentation no matter whether this potentiation is mediated through direct or indirect effects of radiation.

1 Facilitation of signal transduction in T-lymphocytes

The molecular basis of T cell activation following LDR has not yet been fully elucidated. It is known that perturbation of the TCR/CD 3 complex on the plasma membrane of the T cells by antigenic, allogenic, mitogenic or monoclonal antibody (McAb) stimulation would initiate the process of intracellular signal transduction leading to activation and clonal expansion of the T cells^[12,13]. Our studies have shown that WBI with 75 mGy X-rays could facilitate this process, as summarized in figure 1^[8]. A very important change after LDR is the acceleration of the process of maturation and differentiation in the thymus with up-regulation of the

expression of TCR/CD 3 molecules on the plasma membrane of the thymocytes^[5,8]. This forms the basis of facilitation of the signal transduction process in the T cells in response to ConA and anti-CD 3 McAb stimulation. This facilitation is manifested in mobilization of intracellular Ca^{2+} and activation of protein kinase C, and the coordinated activation of these two second messengers results in the up-regulation of transcription of the immediate early genes c-fos and c-jun^[8,14]. In a recent study with patch clamping of the thymocytes an increased frequency of Ca^{2+} -dependent K^{+} channel opening in response to ConA was observed after LDR, further confirming the significance of up-regulated expression of TCR/CD 3 complex in the facilitation of signal transduction. All these molecular changes lead to enhanced secretion of IL 2 and IFN-gamma^[1,11] and increased expression of IL 2 receptor on the T cells^[8] as stated in the first section of the present paper. The ultimate outcome would consequently be activation and clonal expansion of the T cells^[1].

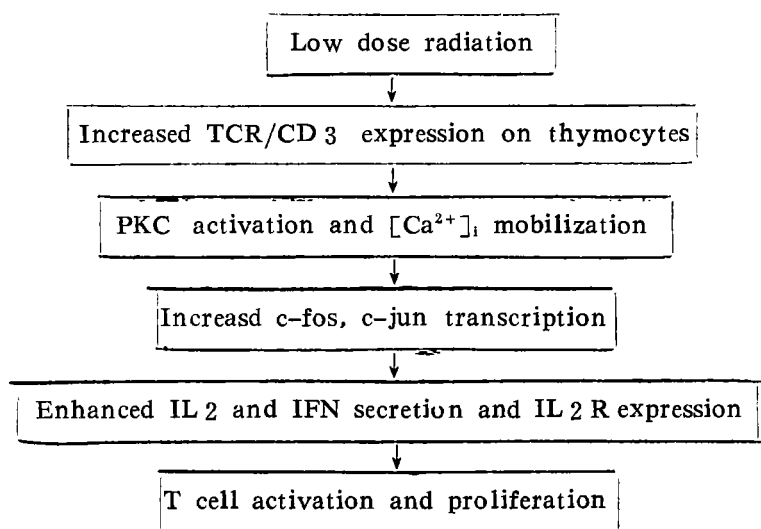


Fig 1. Diagram of signal transduction in T lymphocytes after low dose radiation

The facilitation of the intracellular signal transduction after LDR would affect the expression of protein molecules in the lymphocytes. It has been reported that in vitro irradiation of human peripheral blood lymphocytes or tumor cell lines with low doses could induce the expression of a number of proteins with different molecular weights^[15,16]. We have demonstrated that WBI of mice with 75mGy X-rays could induce the expression of a number of proteins in the cytoplasm and nucleus of the splenic as well as thymic lymphocytes. At the same time there was repression of expression of a few other protein molecules.

The possible biological effect of the changes in protein expression following LDR has been studied by testing the effect of the protein fractions separated with gel filtration (Sephadex G-100) and ion exchange chromatography (DE 52) on the proliferation of normal splenic lymphocytes in response to ConA. Several protein

fractions were found to have a potentiating effect on T lymphocyte proliferation^[17]. Further analysis of the protein fractions with high performance liquid chromatography (HPLC) showed that the potentiating effect of the protein fractions was either due to the repression of expression of some protein molecules normally present in the extract from the lymphocytes, or due to the induction of some new protein molecules not found in the extracts from lymphocytes of the sham-irradiated mice. These experimental results implicate that LDR might repress the expression of some protein molecules with a suppressive effect and at the same time induce some other protein molecules with a stimulatory effect. The nature of these protein molecules, their mode of action and genetic control remain to be elucidated.

2 Evaluation of some existing hypotheses

2.1 The speculation of preferential damage of suppressor T subset (Ts) by LDR

It is known that Ts is more sensitive to ionizing radiation than Th. Thus it has been speculated that LDR would preferentially damage the Ts resulting in a rise in Th/Ts ratio, which would lead to up-regulation of the helper effect within the immune system and consequently immunologic potentiation. However, it must be pointed out that such a difference in radiosensitivity between the Ts and Th is only manifested with doses above 0.25 Gy^[18]. As mentioned above, stimulation of immunity by LDR usually occurred with doses below 0.25 Gy, most markedly following WBI with doses within 0.1 Gy. The hypothesis of raised Th/Ts ratio as an explanation of the stimulatory effect of LDR on immunity was proposed by Anderson et al in the late 70's and the early 80's^[19-21], and has since been repeatedly cited by others. However, no convincing experimental data were given in their reports to support the hypothesis. In one of the papers the percentage of Th and Ts was measured with flow cytometry using fluoresceinated McAb's (Lyt 1⁺2⁻ for Th and Lyt 1⁻2⁺ for Ts) to see the changes after irradiation with 0.15 Gy which was found to increase the anti-tumor effect of the splenic cells. The Th/Ts ratio did not rise, and, on the contrary, dropped from the control value of 22:2 (=11) to 26:10 (=2.6), with the lowering of the ratio being apparently the result of increase in Ts cells^[21].

We have tested the feasibility of this hypothesis since the early 80's using different techniques. The inhabitants of an area of high natural radioactivity in South China (radiation exposure rate being 3 times as high as that in the adjacent control area) who had increased reactivity of the T lymphocytes to PHA and higher level of unscheduled DNA synthesis (UDS) showed no change in percentage of the Ts subset as measured by surface receptors^[22]. Irradiation of human blood in vitro with doses within 0.25 Gy did not cause numerical changes of Ts or the Th to Ts ratio as measured by flow cytometry with double immunofluorescence (Figure 2 and Table 1)^[23]. In mice exposed to single or chronic LDR the Th and Ts count of the splenic and peripheral blood lymphocytes remained at the same level of the control as assessed by a cytoplasmic marker (acid alpha naphthoacetyl esterase)^[24]. Flow cytometric analysis (using anti-L3T4-PE and anti-Lyt 2-FITC) of thymic and splenic T subsets in mice exposed to WBI with 75 mGy X-rays showed no significant changes of Th to Ts ratio within one week following irradiation (Figure 3)^[25].

It has been reported that chronic irradiation of C 57 BL/6 J mice with a daily dose of 0.04 Gy gamma-rays at a dose rate of 0.051Gy/min was found to potentiate the immune reaction when the cumulative dose reached even 0.8 Gy^[26]. When the T subsets of the splenic and thymic lymphocytes were assayed by flow cytometry with fluoresceinated McAb's (L 3 T 4 for Th and Lyt 2 for Ts), there was a statistically insignificant increase in the Th to Ts ratio among the thymic lymphocytes, from 7.5/3.5 (=2.14) in the normal to 13.5/4.5(=3.00) in the irradiated, which was due to the more marked increase in Th cells and a lesser increase in Ts cells in the irradiated mice, while the ratio of Th to Ts among the splenic lymphocytes remained unchanged, being 43.3/29.5(=1.47) in the control and 49.5/34.0(=1.43) in the irradiated mice. Therefore, data from different laboratories, including those from Anderson's own, do not give support to the hypothesis of a rise in Th to Ts ratio due to a decrease of the Ts subset as an explanation of the immunologic stimulation following LDR.

It can be seen from data in figures 2 and 3 and table 1 that doses within 0.25 Gy would not decrease the number of Ts in the peripheral blood and that the Th to Ts

Tab 1. Changes of T subsets in human peripheral blood after LDR^{a)}

		Dose/mGy			
		0	50	75	100
Th/%	0 h	37.3±0.6	39.1±1.0	38.0±1.0	36.7±0.6
	72 h	45.7±1.6	47.3±2.1	48.0±0.1	47.3±1.5
Ts/%	0 h	32.3±0.6	32.3±0.6	32.0±0.1	32.3±1.2
	72 h	32.7±1.2	33.3±1.5	34.3±0.6	32.0±0.1
Th/Ts ratio	0 h	1.15±0.03	1.19±0.02	1.19±0.03	1.16±0.02
	72 h	1.40±0.09	1.42±0.13	1.42±0.12	1.48±0.05

^{a)}Peripheral blood lymphocytes were cultured for 72 h, and Th and Ts were analysed with FCM using anti-leu 3-FITC and anti-leu 2-PE at 0 h and 72 h of culture

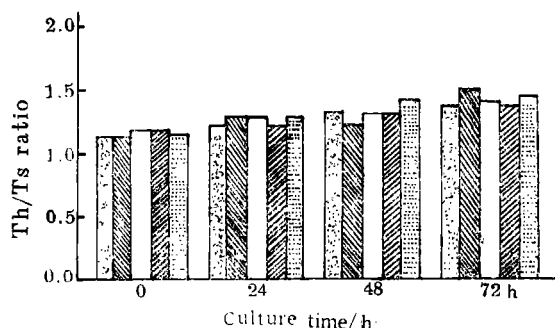


Fig 2. Th/Ts ratio of human peripheral blood lymphocytes after irradiation with 25-100 mGy in vitro

(□) 0 mGy (▨) 25 mGy (▤) 50 mGy
(▥) 75 mGy (▧) 100 mGy

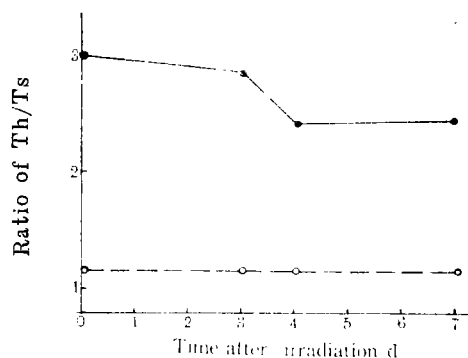


Fig 3. Ratio of Th to Ts subsets after WBI of mice with 75 mGy X-rays

(●) thymic Th/Ts
(○) splenic Th/Ts

ratio remained unchanged after such low doses of X-rays.

It may be argued that the suppressive function of the Ts might be lowered in spite of the maintenance of an essentially normal number. Our experiments showed, however, that neither the Ts activity in the spleen induced by ConA nor the short life-span Ts activity of both the thymic and splenic lymphocytes was depressed by WBI of mice with 75 mGy X-rays^[1]. Recently it was reported that after in vitro irradiation of the separated CD 4⁺ and CD 8⁺ T subsets from human peripheral blood with doses ranging from 50 to 100 mGy both the helper function of Th and the suppressor function of Ts on the B cell response to LPS were augmented^[27]. Therefore, existing experimental data are not in favor of the hypothesis based on the speculation of rise in Th/Ts ratio due to a preferential structural damage or functional suppression of the Ts subset.

2.2 Speculation of increased apoptosis of the thymocytes after LDR

Apoptosis, or programmed cell death (PCD), is a basic biological phenomenon with wide-ranging implications in tissue kinetics^[28]. It has been considered as a “physiological” type of cell death occurring under circumstances in which cell death is apparently a regulated event, such as in embryogenesis, metamorphosis, hormone-dependent atrophy as well as normal and neoplastic cell turnover^[29]. Regulation of apoptosis in thymocytes has been given special attention^[30,31]. A major mechanism of intrathymic T lymphocyte self-tolerance induction is clonal deletion. Clonal deletion of immature thymic T cells appears to be achieved by apoptosis which is an active cellular process leading to a series of intracellular events including DNA fragmentation by endonucleases, cytoplasmic condensation, membrane blebbing and release of apoptotic bodies. The CD 4/CD 8 double positive thymocytes with intermediate to high density of TCR/CD 3 expression are most sensitive to apoptosis. It has been established that this intrathymic subset has the highest radiosensitivity (Figure 4).

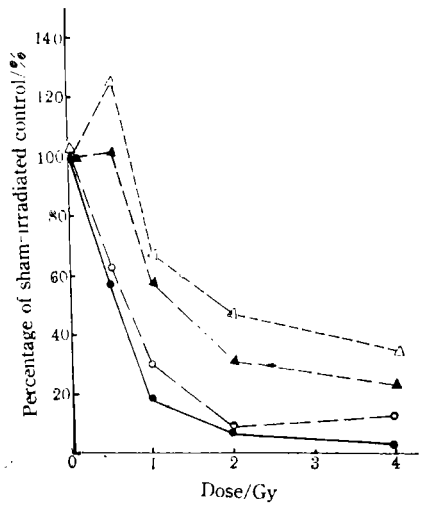


Fig 4. Dose-effect relationship of thymic T subsets in mice
(●) CD 4⁺CD 8⁺ (○) CD 4⁻CD 8⁻
(▲) CD 4⁻CD 8⁺ (△)CD 4⁺CD 8⁻

It was proposed that increased apoptosis by LDR of the radiosensitive thymocytes would lead to proliferation of the more mature T cells, leading to immunologic potentiation. Such a phenomenon was named “altruistic cell suicide”

Tab 2. Thymocyte apoptosis after WBI of mice with low dose X-rays^{a)}

Dose/Gy	Apoptosis/%	P
0	1.28±0.29	
0.05	1.13±0.31	>0.05
0.075	1.25±0.47	>0.05
0.10	1.40±0.34	>0.05
0.20	1.45±0.20	>0.05

a) FCM was carried out 12 h after WBI, mean±SD, n=6, Student's t test for statistical evaluation

which was thought to underlie the mechanism of immunoenhancement induced by LDR^[32]. We have tested this hypothesis by assessing the dose-effect relationship of apoptosis with different techniques, including the appearance of the "ladder pattern" characteristic of DNA fragmentation, membrane permeability and flow cytometric analysis of apoptotic bodies. It was found that WBI of mice with X-rays caused definite DNA fragmentation in the thymocytes with ladder pattern in agarose electrophoresis only after doses above 0.2 Gy. LDR which stimulated immune reactions showed no effect on the permeability of thymocytes to propidium iodide^[33]. Enumeration of apoptotic bodies of mouse thymocytes by flow cytometry following in vivo and in vitro irradiation gave dose-dependent increase of thymocyte apoptosis with doses above 0.2 Gy. However, when the radiation doses were lowered, the picture was different. Following WBI of mice with doses within 0.2 Gy the percentage of apoptotic bodies did not depart from that of the sham-irradiated control (Table 2). The mouse lymphoma cell line EL 4 was also irradiated in vitro with different doses of X-rays. It was observed that X-irradiation with 2Gy caused marked increase of apoptosis beginning from 8 h after irradiation and reaching a very high level (276% of that in the sham-irradiated sample) at 24 h. When the dose was lowered to within 0.2 Gy, no significant increase in apoptosis was observed. Further studies are needed to clarify the threshold dose which causes definite increase in thymocyte apoptosis after in vivo and in vitro irradiation.

It is evident that data mentioned above do not give support to the speculation of either the preferential deletion of the Ts subset or the facilitation of apoptosis of immature thymocytes as the cellular basis of stimulation of immune functions following WBI with low doses of X- or gamma-rays.

It is necessary to further probe into the molecular basis of the behavior of apoptosis after different ranges of radiation doses. It has been reported that a number of genes, such as bcl-2, p53, Rb, Rp-8, topoisomerase IIa,b, cyclins A,B and others, are involved in cell growth and apoptosis and the effect of high dose radiation on some of these genes have already been studied^[34-38]. It is known that expression of ced-3 and ced-4 increases apoptosis while that of ced-9 decreases it; SGP-2 promotes apoptosis while bcl-2 (the mammalian homologue of cedg) prevents it; thymocyte apoptosis induced by high dose radiation requires the expression of p53; the expression of some immediate early genes like c-fos, c-jun, c-myc, PADPRP, etc. are upregulated both during cell growth and in apoptosis, but with different time courses. It is necessary to study the dose-response relationship of these genes in the low versus high dose ranges.

3 Neuroendocrine factors in low dose radiation effects

There exists a bidirectional regulation between the neuroendocrine and immune systems under normal conditions^[37-39]. The hypothalamic-pituitary-adrenocortical (HPA) axis normally exerts a tonic suppression on the immune organs, especially the thymus. It has been repeatedly observed in our laboratory that there occurred a down-regulation of the function of the HPA axis, expressed as lowering of plasma level of ACTH and corticosterone (CS), in mice exposed to WBI with 75 mGy X-rays^[40-41]. Glucocorticoids are well known immunosuppressants widely used clinically. Such a suppressive effect on immunity only manifests at concentrations above 10 to 100 nmol/L. We found that CS at concentrations of 0.1 to 1 nmol/L had apparently no effect on the proli-

ferative response of the T lymphocytes to ConA, while it stimulated the proliferation of the T lymphocytes at concentrations of 0.001 to 0.05 nmol/L^[42]. It is known that epinephrine (E) in concentrations from 1 nmol/L to 1 μ mol/L has a dose-dependent stimulatory effect on T lymphocyte proliferation, while it is ineffective on this process at 0.01 to 0.1 nmol/L^[42]. It has been observed that WBI of mice with 75 mGy X-rays potentiated both the thymic and splenic lymphocyte proliferation in response to ConA in the course of 1 week, and ineffective concentrations of CS and E (0.1 nmol/L for each of them) together stimulated the normal response of T lymphocytes to ConA and further up-regulated the already potentiated mitogenic response of these cells after LDR (Figure 5)^[43]. The amplitude of this up-regulation of mitogenic response of the T lymphocytes of both normal and irradiated mice is greater than that induced by the calcium ionophore A23187 or the phorbol ester PMA.

These data may implicate that a lowered concentration of CS in the body of low dose-irradiated mice may play its role in modulating the immune reactions of the T cells through the signal transduction pathway. Therefore, in the analysis of the possible mechanistic factors of immunoenhancement following LDR the influence of changes in the microenvironment of the immunocytes as a result of shift in systemic regulation after LDR has to be considered in addition to the direct action of radiation on the cells.

Data in figure 5 indicate that after LDR T cell proliferation caused by ConA, which stimulates the TCR/CD 3 complex, is more marked than normal. This is apparently related to the up-regulation of expression of the TCR/CD 3 molecules on the T cells after LDR as mentioned above. Perturbation of the TCR/CD 3 complex leads to T cell proliferation through raising $[Ca^{2+}]_i$ and PKC activity. It is known that A 23187 acts to mobilize Ca ions from the intracellular stores and PMA stimulates PKC. Now these two factors further up-regulate the already augmented proliferative response of the T cells to ConA. This may implicate that the activation of the signal transduction pathway elicited by TCR/CD 3 perturbation has not been saturated. E and CS act, respectively, through the adrenergic receptor (AR) and glucocorticoid receptor (GR), suggesting that, after LDR modulatory factors in the microenvironment might further increase T cell proliferation through signal transduction pathways other than the TCR/CD3 cascade. Therefore, in the intact organism changes in the microenvironment could influence the functional state of the immune cells through multiple pathways. Further studies on the interrelationship of different signal transduction pathways elicited by TCR/CD 3, AR, GR and other receptors might promote our understanding of the molecular mecha-

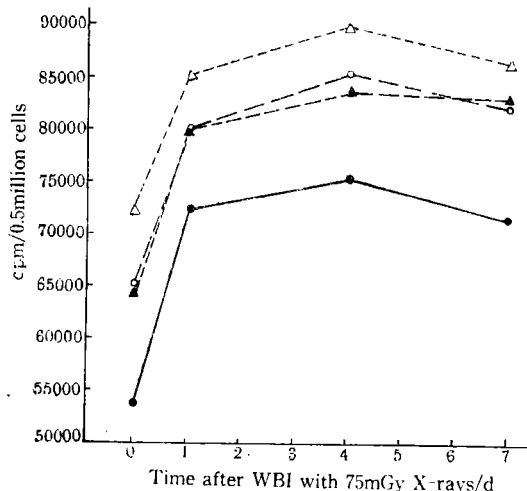


Fig 5. Effect of modulatory factors on T lymphocyte proliferation
 (●) ConA 5 μ g/ml
 (○) ConA 5 μ g/ml + PMA 5 ng/ml
 (▲) ConA 5 μ g/ml + A 23187 1 μ g/ml
 (△) ConA 5 μ g/ml + corticosterone and epinephrine 0.1 nmol/L for each

nism of systemic regulation, and thus coordinate the changes at the cellular, molecular and systemic levels.

4 Biological significance of stimulation of immunity after LDR

The immunologic capability of the body is closely related to its resistance to infection and neoplasm. The effectiveness of enhanced immunologic reactivity has to be assessed with challenge experiments. It has been reported from our laboratory that pre-exposure of mice to LDR (50~200 mGy X-rays) could suppress the tumor growth of subcutaneously implanted Lewis lung carcinoma and markedly reduce the pulmonary dissemination of intravenously injected Lewis lung cancer cells and melanoma cells^[44,45]. Recently it was observed that pre-exposure of C57BL/6 mice with 75 mGy X-rays 6~24 h before the split-dose irradiations prevented the occurrence of thymic lymphoma in all the mice. The split-dose regimen was a WBI with 1.75 Gy X-rays once a week for 4 continuous weeks which caused the appearance of thymic lymphoma in 71.4% of the irradiated mice within the observation period of 6 months. When each split-dose of 1.75 Gy was preceded by a single WBI with 75 mGy X-rays within 6~24 h, none of the mice showed thymic lymphoma within the same period. The mechanism of this prevention of radiation oncogenesis by preexposure to LDR remains to be clarified. With the present knowledge two possibilities should be considered. The first is the reduction of mutagenic effect of high dose radiation in lymphoid cells by preexposure to LDR. It was reported that split-dose irradiation of mice caused novel rearrangement of the TCR genes in the prelymphomatous state around 1 month after irradiation^[46]. LDR-induced adaptation includes reduction of chromosomal damage and mutagenic effect caused by high dose radiation^[47]. It would be interesting to examine whether preexposure with a low dose would influence the novel rearrangements in the TCR genes caused by the split-dose irradiation. Another possibility to be considered is the effect of the augmented anticancer immune reactions after LDR. The enhanced immunologic capability after LDR may be effective in eradication of the transformed clones of the lymphoid system before the formation of solid tumors. These possibilities have to be probed into by designing special experiments.

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低水平辐射诱导免疫系统兴奋效应的研究现状

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摘要 本文扼要地叙述了近年来有关低水平辐射刺激免疫功能的主要实验研究结果。指出了低水平辐射全身作用后免疫增强过程中细胞间的相互关系, 强调辅助性 T 细胞激活的中心地位。提供了低水平辐射促进 T 细胞信息传递的主要环节的资料。对文献中流行的两种解释免疫兴奋效应的假说进行了分析评价, 指出低水平辐射优先损伤抑制性 T 细胞或促进前体细胞凋亡的设想未能获得实验资料的支持。提出了低水平辐射改变神经内分泌调节功能在免疫兴奋效应发生机理中的可能作用。讨论了低水平辐射增强抗肿瘤效应的生物学意义。

关键词 低水平辐射, 兴奋效应, 免疫系统, T 细胞亚组, 细胞凋亡, 细胞内信息传递