GENES AND PROTEIN MOLECULES INVOLVED IN THE CELLULAR ACTIVATION INDUCED BY LOW DOSE RADIATION*

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ABSTRACT The effect of whole-body X-irradiation on the transcription and expression level of genes related to cell survival and cell cycle control, the transcription level of genes related to immune responses as well as the signal molecules of mouse thymocytes and/or splenocytes was reviewed. Opposite effects from low versus high doses of irradiation were demonstrated in most of the parameters examined. The implications of these changes in connection with the cellular responses after different doses of ionizing radiation were analyzed.

KEYWORDS Radiation, Genes, Cell survival, Cytokines, Cell cycle control, Signal transduction

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1 Introduction

At the turn of the century, when we look at the radiobiology research in the future, it is anticipated that the most important issue is probing into the nature of the effects of low level radiation. This is due to the fact that most of the projected radiation exposures associated with human activity in the 21st century will be to low dose and low dose-rate radiation from different sources. The major type of radiation exposures will be low LET (Linear Energy Transfer) ionizing radiation from fission products. Thus studies should concentrate on biological effects of low-LET exposures delivered at low doses and low dose-rates. A key question to be answered is whether low doses of ionizing radiation would cause biological effects different in nature from those evoked by higher doses, or whether the biological effects of low dose radiation occur only in a lesser degree and without difference in nature as compared with those caused by higher doses and can just be extrapolated or predicted from the latter. For answering this question, data on radiobiological studies at cellular and molecular levels has to be reviewed.

The present paper will discuss the changes in the transcription and expression of the genes related to cell survival and death, cell cycle progression and immunological

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responses as well as signal molecules in some of the transduction pathways after different doses of whole-body X-irradiation as disclosed in the authors' laboratory. These we think are important in the understanding of the cellular processes evoked by low dose radiation. The doses concerned are within 0.1Gy for low dose radiation (LDR), mostly 0.075Gy that has been repeatedly found to have a stimulatory effect on biological defense and adaptation[1]. For comparison higher doses are chosen for which 2Gy is used as a representative dose. Low LET radiation is used for all the studies. The dose rate for X-rays delivered at 200kVp/10 mA with 0.5mm Cu and 1.0mm Al as filters is 0.0125Gy·min^{-1} for doses within 0.2Gy/min^{-1} and 0.287Gy·min^{-1} for doses above 0.5Gy/min^{-1}.

2 Genes related to cell survival and death

Ionizing radiation is well known to have a killing effect on cells when the dose is sufficient. For moderate doses this killing effect is related to increased DNA damage that would lead to apoptosis. When the dose-response relationship of apoptosis in the

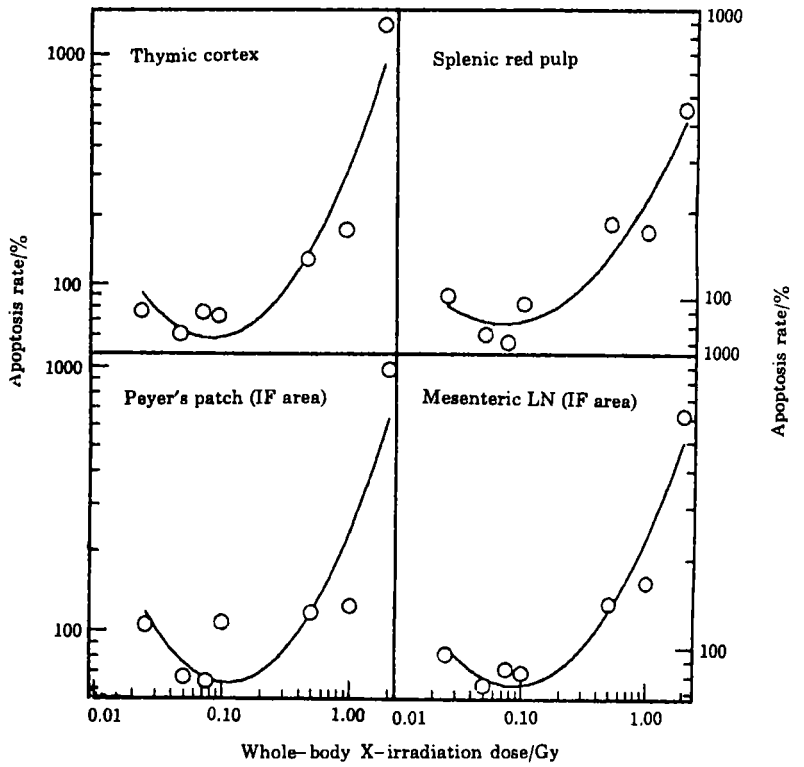

Fig.1 Dose-response curves of apoptosis in immune organs

Apoptotic cells were enumerated in frozen sections of the thymus, spleen, Peyer's patches and mesenteric lymph nodes of mice 12h after whole-body X-irradiation with 0.025 to 2Gy. Three animals were examined for each dose point and positive cells were counted in 5 high power microscopic fields for each animal

immune organs is analyzed after whole-body exposure of mice to different doses of X-rays, a J- shaped curve is found. This phenomenon was observed with different technologies for assaying apoptosis, including measurement of DNA fragmentation rate with two-wave length fluorescence photometry, measurement of apoptotic bodies with flow cytometry and detection of DNA breaks with TUNEL (terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling)[2,3]. Using these different methods a decrease in apoptosis of the cells in the immune organs to the level significantly below normal control was found 12~24h after whole-body irradiation (WBI) with doses below 0.1Gy and an increase in apoptosis rate occurred after doses above 0.5Gy. Fig.1 shows the J-shaped curves of apoptosis as measured by TUNEL in the thymus, spleen, Peyer's patches and mesenteric lymph nodes.

It is easy to understand the increase in apoptosis rate with doses above 0.5 Gy. But the mechanism of the decrease in apoptosis rate in these organs caused by doses within 0.1 Gy remains to be elucidated. This might be explained by stimulation of the biological control systems evoked after exposure to low dose radiation. Fig.2 shows the time course of apoptosis rate measured with TUNEL in the cortex of thymus. The time course of changes in apoptosis rate after WBI with 0.025, 0.05 and 0.075Gy is shown in the left 3 panels, respectively, of Fig.2. It is seen in the case of WBI with 0.05Gy and 0.075Gy that shortly after exposure the apoptosis rate began to rise slightly (statistically insignificant) above the control level followed by a gradual decline until it went down to the level below control at 12h (marked with an asterisk in the figure indicating $p < 0.05$ in comparison

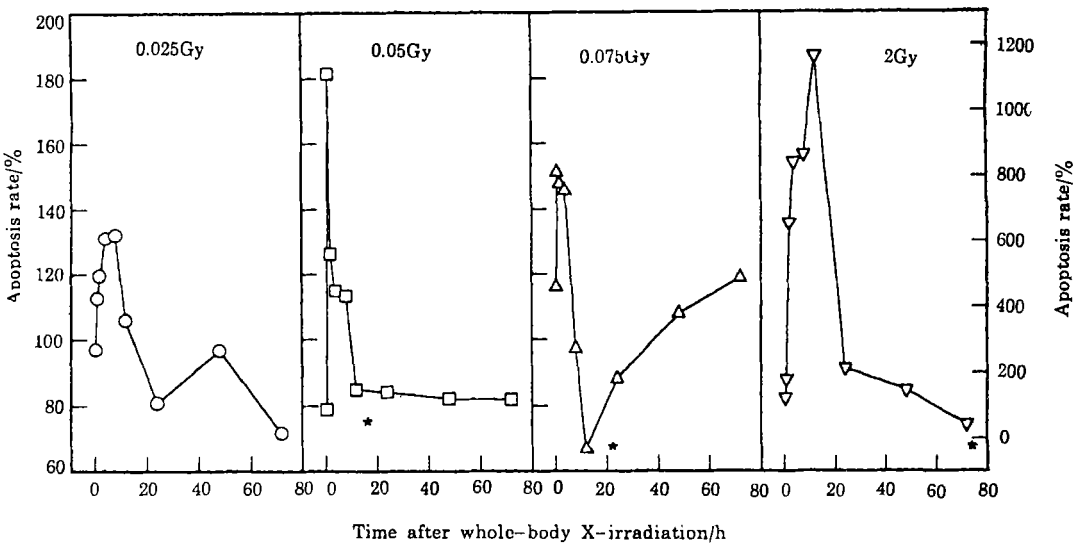

Fig.2 Time course of thymocyte apoptosis after WBI
The illustration of Fig.2 is same as in Fig.1

with the control). WBI with 0.025Gy has a similar effect in inducing an early slight insignificant increase in apoptosis rate that is smaller in amplitude and not followed by a significant drop within 12~24h. These data might implicate that a definite amount of DNA damage occurring early after exposure to low dose radiation may be required to trigger defense mechanisms from the biological control system in the lymphoid organs. These would cause a time-specific decrease of apoptosis rate by complex changes in transcription and expression of genes related to cell survival and death. This will be discussed in more detail in the next paragraph.

As shown in the right panel of Fig.2, the apoptosis rate in the thymus increased rapidly to about 12 times that of the control, returning to a level below control only at 72h after irradiation with 2Gy. Apparently, the large amount of DNA damage caused by a higher dose of radiation would rapidly over-saturate the biological control mechanisms only allowing its response to recover after 72h. A further explanation will be given in the following paragraphs .

As seen in panel A of Fig.3, the transcription level of genes related to cell survival and death reacted differently to LDR (0.075Gy) as compared with that in response to a higher dose (2Gy). The columns show the data obtained by slot blot hybridization (except for *ICE*, *vide infra*) with GAPDH (glyceraldehyde phosphate dehydrogenase) as an internal reference after WBI. Columns 1 and 2 illustrate the transcription level of *c-fos* gene in the thymus and spleen, respectively. There was a marked increase in the transcription level of *c-fos* 0.5h after WBI with 0.075Gy with the peak amounting to 433.9% of control. The increase in transcription of *c-fos* in the spleen was less in degree as compared to that in the thymus. In both organs the transcription was slightly depressed after 2Gy. Columns 3 and 4 show the transcription level of the *c-myc* gene in the thymus and spleen, respectively. Here it is seen that the transcription level of *c-myc* increased in response to the higher dose in the thymus followed by a marked increase of expression of *c-Myc* protein at 24h (panel B). The transcription level of the *bcl-2* gene in both organs was markedly suppressed after WBI with 2Gy while stimulated after 0.075Gy (columns 5 and 6 of panel A in Fig.3). It is very interesting to see that the transcription level of p53 gene reacted in the opposite direction after the two different doses (columns 7 and 8 in panel A of Fig.3). The transcription of the *ICE* gene (semi-quantified by reverse transcriptase polymerase chain reaction with β-microglobulin as an internal reference) was found to be markedly up-regulated after WBI with 2 Gy while there was a depression after 0.075Gy (Columns 9 and 10). As a whole the genes examined in the two organs reacted in the opposite direction after low versus high dose radiation. The up-regulated transcription of *c-fos* and *bcl-2* genes and down-regulated transcription of p53 and *ICE* genes in the thymus followed by increased or decreased expression of the corresponding proteins (see data in panel B of Fig.3) would favor the survival of the cells in the thymus. This would form the basis of increased proliferation of the thymocytes after exposure to LDR.

The protein expression of some of the genes related to cell survival and apoptosis

was also examined. Data in panel B of Fig.3 are calculated from the experimental results with flow cytometry analysis of the thymocytes after WBI, except those for columns 10

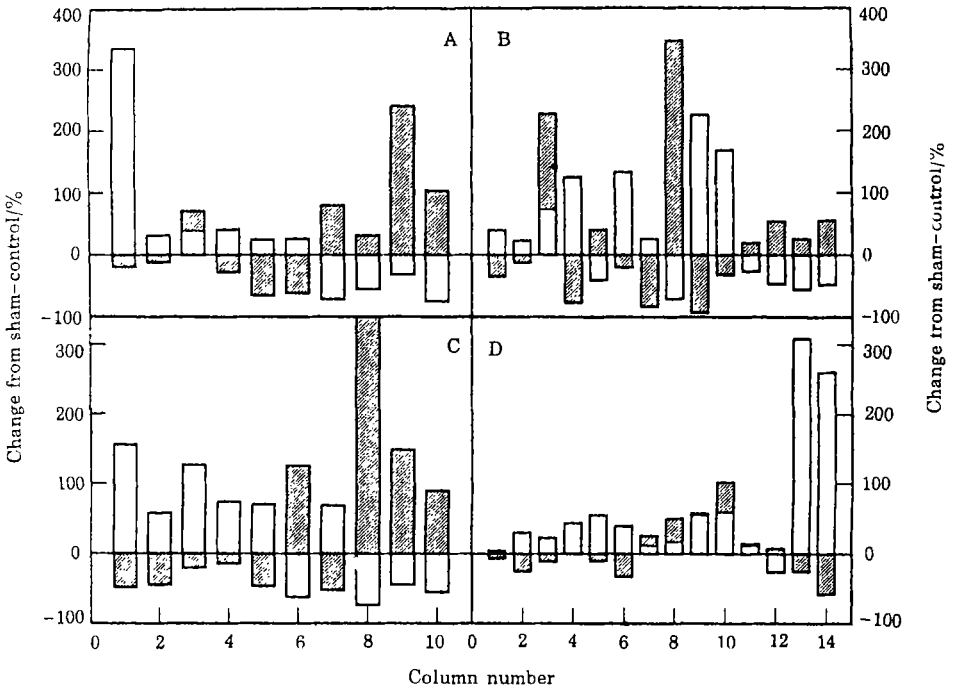

Fig.3 Molecular changes after whole-body X-irradiation with low versus high doses

Time of peak or nadir is shown in parenthesis. Panel A: Transcription level of genes related to cell survival. Odd number for thymus and even number for spleen. Open columns: 0.075Gy, 1. *c-fos* (0.5h), 2. *c-fos* (2h), 3. *c-myc* (1h), 4. *c-myc* (1h), 5. *bcl-2* (2h) 6. *bcl-2*(1h), 7. p53 (8h), 8. p53 (8h), 9. *ICE* (2h) 10. *ICE* (12h). Hatched columns: 2 Gy, 1. *c-fos* (1h), 2. *c-fos* (0.5h), 3. *c-myc* (1h), 4. *c-myc* (72h), 5. *bcl-2* (1h) 6. *bcl-2* (2h), 7. p53 (8h), 8. p53 (8h), 9. *ICE* (1h), 10 *ICE* (0.5h). Panel B: Protein expression of genes related to cell survival. Protein expression was assessed by flow cytometry with immunofluorescence in thymocytes except columns 10 and 14 that stand for changes in Peyer's patch. Open columns: 0.075 Gy, 1. c-Fos (12h), 2. c-Jun (48h), 3. c-Myc (12h), 4. Bcl-2 (24h), 5. Bax (12h), 6. Bcl-2/Bax ratio (12h), 7. Bcl-X_L (48h), 8. Bad (48h), 9. Bcl-X_L/Bad ratio (24h), 10. Bcl-X_L in Peyer' patch (48h), 11. Rb (8h), 12. Gadd45 (12h), 13. FasL (12h), 14. FasL in Peyer's patch (12h). Hatched columns: 2 Gy, 1. c-Fos (8h), 2. c-Jun (24h), 3. c-Myc (24h), 4. Bcl-2 (24h), 5. Bax (12h), 6. Bcl-2/Bax ratio (12h), 7. Bcl-X_L (48h), 8. Bad (24h), 9. Bcl-XL/Bad ratio (48h), 10. Bcl-X_L in Peyer' patch (48h), 11. Rb (48h), 12. Gadd45 (24h), 13. FasL (12h), 14. FasL in Peyer's patch (24h). Panel C: Signal molecules in thymocytes. Open columns: 0.075 Gy, 1. $[Ca^{2+}]_i$ (24h), 2. PKC-α (12h), 3. PKC-β_1 (12h), 4. PKC-β_2 (12h), 5. Calcineurin (24h), 6. cAMP (12h), 7. cGMP (24h), 8. cAMP/cGMP ratio (12h), 9. PKA (24h). 10. PLA_2 (24h) Hatched columns: 2 Gy, 1. $[Ca^{2+}]_i$ (24h), 2. PKC-α (12h), 3. PKC-β_1 (24h), 4. PKC-β_2 (24h), 5. Calcineurin (48h), 6. cAMP (48h), 7. cGMP (48h), 8. cAMP/cGMP ratio (24h), 9. PKA (48h). 10. PLA_2 (48h), Panel D:

Transcription level of cytokine genes. Odd number for thymus and even number for spleen. Open columns: 0.075 Gy, 1. IL-2 (2h) , 2. IL-2 (8h) , 3. LT (4h), 4. LT (4h), 5. IFN-γ(2h), 6. IFN-γ (8h), 7. IL-4 (24h), 8. IL-4 (72h), 9. IL-6 (8h), 10. IL-6 (4h), 11. IL-10 (2h), 12. IL-10 (72h), 13. IL-12p35 (8h), 14. IL-12p35 (8h). Hatched columns: 2 Gy, 1. IL-2 (8h) , 2. IL-2 (2h) , 3. LT (4h), 4. LT (2h), 5. IFN-γ (2h), 6. IFN-γ (2h), 7. IL-4 (2h), 8. IL-4 (24h), 9. IL-6 (2h), 10. IL-6 (8h), 11. IL-10 (8h), 12. IL-10 (8h), 13. IL-12p35 (72h), 14. IL-12p35 (24h)

and 14 that are for the cells from Peyer's patch. The marked increase in Bcl-2/Bax ratio (column 6) and Bcl-X_L/Bad ratio (column 9) and decreased expression of FasL (column 13) after 0.075Gy irradiation are supposed to be important mechanisms for the decreased apoptosis occurring after LDR. The reverse changes of these parameters and the marked increase in expression of c-Myc (column 3), Bad (column 8) and Gadd45 (column 12) after exposure to 2Gy apparently underlie the mechanism of increased apoptosis and decreased cell survival of the thymocytes after this irradiation. The marked up-regulated expression of Bcl-X_L (column 10) and down-regulated expression of FasL (column 14) in the Peyer's patch after exposure to 0.075Gy are also considered as important factors for the decreased apoptosis in this immune organ after LDR.

3 Signal molecules

The studies on signal transduction in cells are crucial for the understanding of the molecular mechanisms of the changes in cellular functions in response to stimuli in the external and internal environment. Many of the genetic changes in the thymus after exposure to LDR are closely related to shifts in the signal molecules in the transduction pathways. It has previously been disclosed that at least two important signal transduction pathways are involved in the activation of thymocytes in response to low dose radiation[1,4]. One is Ca^{2+}-protein kinase C (PKC) pathway and the other is the cAMP pathway. It was found that after WBI with low dose X-rays the Ca^{2+}-PKC pathway was stimulated and the cAMP pathway was down-regulated. Panel C of Fig.3 shows the changes in the molecular cascades of these two pathways after WBI with low versus high dose X-rays. The first column illustrates marked increase in mobilization of $[Ca^{2+}]_i$ after 0.075Gy irradiation with an opposite effect induced by 2Gy irradiation with the intracellular free calcium concentration being measured using a Ca probe Fura-2AM. The expression of PKC isoforms α, β_1 and β_2 as measured by flow cytometry was increased after 0.075Gy irradiation (columns 2, 3 and 4) which is especially marked for PKC-β_1 (column 3). Calcineurin, one of the down-stream molecules of calcium, showed the same pattern of changes as measured by flow cytometry (column 5). The up-regulated expression of these signal molecules would obviously lead to gene induction culminating in cell proliferation and functional activation. The blockade of the stimulatory effect of low dose radiation on thymocyte proliferation by the Ca antagonist TMB-8 is a further evidence to this statement[1]. The concentrations of cAMP and cGMP, as measured by radioimmunoassay, showed changes in opposite directions, i.e., decrease in cAMP concentration

(column 6) and increase in cGMP concentration (column 7), accompanied with lowered cAMP/cGMP ratio (column 8) after WBI with 0.075Gy, and the reaction was reversed after 2Gy irradiation. As a down-stream molecule of cAMP, protein kinase A (PKA) activity was found to be down-regulated after low dose radiation and stimulated by high dose radiation as measured by a [γ-^{32}P]ATP tracer method (column 9). This would result in enhanced proliferation of thymocytes after LDR and its depression after a higher dose irradiation. The fact that cholera toxin, a cAMP stimulant, partially abrogated thymocyte proliferation induced by LDR gives further support to the involvement of the cAMP pathway in stimulation of thymocyte proliferation by LDR[1]. It was recently demonstrated that the down-regulation of cAMP concentration in thymocytes might be related to ligation of CD3/CD28 molecules at the same time[5]. Preliminary studies showed that LDR enhanced the expression of B7 molecules on the splenic cells (Liu and Jin, unpublished data). It is known that expression of CD3 molecules is up-regulated after LDR[6]. It remains to be clarified if low dose radiation would induce changes in CD28 and its reaction with B7 molecules resulting in the induction of a crucial enzyme–PDE7 (phosphodiesterase 7). Another factor to be considered for signal transduction pathways in the lymphocytes is the prostaglandin (PG) system. It is known that PGE antagonizes the action of IL-2 and suppresses immune reactions via stimulation of cAMP production[7]. Phospholipase A is one of the signal molecules that induce PGs[8]. As seen in column 10 of panel C, the activity of PLA_2 was down-regulated after 0.075Gy irradiation and stimulated after 2Gy irradiation using a titration method[9]. The changes in signal molecules illustrated in panel C of Fig.3 would obviously lead to increased proliferation of the thymocytes after LDR. The multiple pathways of signal tranduction involved in the activation process evoked in the immune organs by LDR are closely interrelated. A supposed interrelationship of these signal pathways activated after LDR is illustrated in a schematic diagram in Fig.4. In this diagram, the intercellular changes induced by low dose radiation are also shown as the reaction between the APCs and the T cells. LDR enhances the secretion of IL-12, IL-1β and TNFα which act on the T cells via corresponding receptors to influence the maturation, differentiation and activation of the T cells. LDR may also increase the expression of the surface molecules such as B7-1/2 of the APCs, thus enhancing the intercellular reactions (not shown in the diagram). Three signal pathways are displayed on the left of Fig.4 showing their interrelations resulting in facilitation of nuclear translocation of NF-kB, which would cause induction of a series of genes related to celllular activation. Here IL-2 and IFNγ are shown as representative expression of these genes. It is shown on the right side of Fig.4 that IL-1β and TNFα may also facilitate the nuclear translocation of NF-kB through the mediating action of ROIs and/or NO, the production of which by the macrophages was found to be increased after WBI with 0.075 Gy (Sun and Liu, in press). This diagram is only a simplified sketch of a much more complicated network of signal molecules involved in the biological effect of LDR.

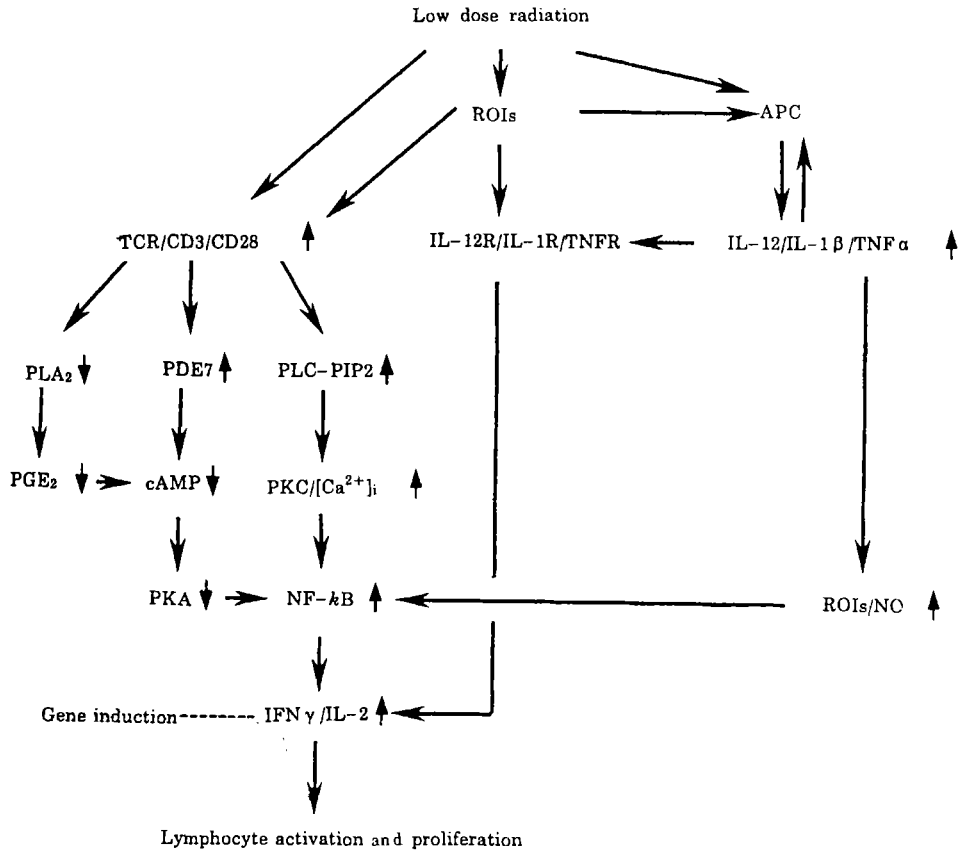

Fig.4 A supposed interrelationship of signal transduction pathways involved in the activation of immune responses evoked by low dose radiation

ROI=reactive oxygen intermediate; APC=antigen presenting cell; TCR=T cell receptor; IL=interleukin; TNF=tumor necrosis factor; R=receptor; PLA=phospholipase A; PDE=phosphodiesterase; PLC= phospholipase C; PIP2= phosphatidylinositol biphosphate; PGE=prostaglandin E; cAMP=cyclic adenosine monophosphate; PKC=protein kinase C; $[Ca^{2+}]_i$ =intracellular concentration of free calcium ions; PKA=protein kinase A; NO=nitric oxide; NF-*k*B=nuclear factor kappaB; IFN=interferon

4 Cytokine genes

Cytokines are important mediators in cellular functions in the immune and other systems. They can act in the modes of autocrine, paracrine and endocrine action in the body as regulatory factors. WBI elicits changes in secretion of cytokines by the immune cells[1]. However, little is known about the changes in the transcription level of the cytokines after WBI. Shown in panel D of Fig.3 are the transcription levels of seven of the cytokine genes in both the thymus and spleen after WBI with low and high doses. All the experiments were done with non-stimulated thymocytes and splenocytes. The transcription of IL-2 and TNFβ (lymphotoxin, LT) was assayed with Northern blot hybridization

and that of IL-12p35 was semi-quantified with RT-PCR, while the transcription of the other four genes was measured by dot blot hybridization. GAPDH was used as an internal reference in all the experiments. Changes in transcription from 1 to 48 h were examined and the transcription levels relative to that of the sham-irradiated control is shown in the figure. More prominent changes are seen in the transcription levels of IFN-γ, IL-6 and IL-12p35 showing more than 50% increase in the thymus or spleen after LDR. Special mention should be paid to IL-12p35 that showed constitutive transcription in many cell types of the immune system. A time course study showed that in the thymus the transcription level of IL-12p35 began to rise to 58.3% above control 2h after 0.075Gy irradiation, going up to 125.0% and 308.3% above control at 4h and 8h, respectively. In the spleen LDR caused an increase by 25% above control at 2h, rising to 140.0% and 260.0% above control 4h and 8h after irradiation, respectively. After WBI with 2Gy the transcription level of IL-12p35 was found to be slightly suppressed in the thymus from 2 to 8h, and it was markedly suppressed in the spleen by 57.7% and 58.6% at 4h and 8h, respectively, after a slight increase by 30.8% at 2h. Since IL-12 is critical both for initiating and sustaining a cellular immune response and the subunit IL-12p35 is essential for the formation of the functional heterodimer IL-12p70 with another subunit IL-12p40, the stimulation of the induction by LDR of the IL-12p35 gene may be of importance in the mechanism of the stimulatory effect of LDR on the anti-tumor cytotoxicity (Fig.5, left panel)[1]. The accompanying increase in the induction of the T_H1 type cytokine IFN-γ is also an indication of the up-regulated induction of IL-12. It is known that IL-12 hinders the development of the T_H2 cells in the immune system and IL-10 is a typical T_H2 type cytokine that exerts a negative effect on the T_H1 cells with suppression of induction of the T_H1 type cytokine IFN-γ. It was observed that in the spleen IL-10 transcription was depressed after LDR and this depression was gradually accentuated (Fig.5, right panel). The increased transcription of IL-6 that stimulates immunoglobulin synthesis may be an important factor in the enhancing effect of low dose radiation on the plaque-forming cell (PFC) reaction in the spleen[1]. From the data shown in panel D of Fig.3 and in Fig.5, it is seen that 0.075Gy induces changes in the cytokine profile in favor of a shift to the T_H1 type reaction in the immune system while 2 Gy irradiation caused an opposite effect. This demonstrated again the different action of LDR from that of higher dose radiation.

5 Cell cycle control genes

It is well known that the cell cycle progression in eukaryotes is controlled by checkpoints, among which the G_1/S and G_2/M transitions are most important. One of the characteristic effects of ionizing radiation on cellular functions is inducing changes in cell cycle progression no matter whether the irradiation is given in vitro or in vivo. Most of

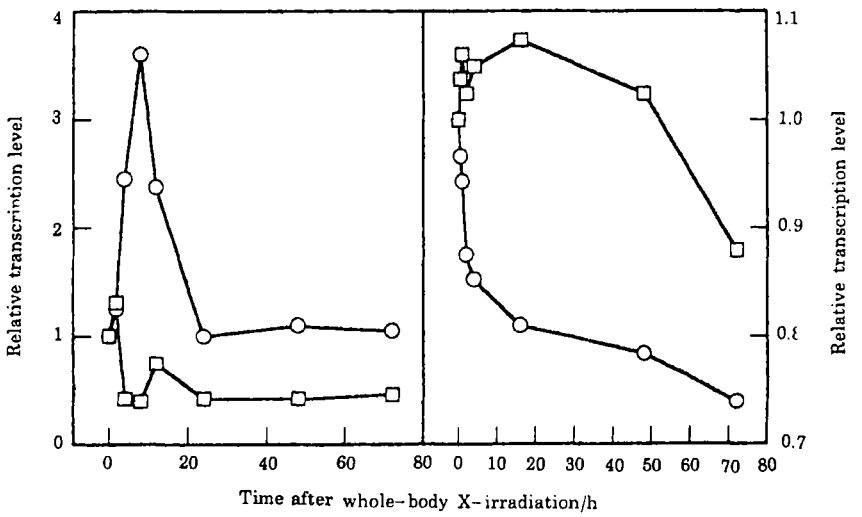

Fig.5 Time course of transcription of IL-12p35 and IL-10 in the spleen of mice after WBI with low versus high doses

Left panel: IL-12p35, Right panel: IL-10, ○: 0.075Gy, □: 2Gy

the previous studies have been concerned with in vitro irradiation of cultured cell lines with medium or high doses. In our laboratory the effect of WBI of mice with doses ranging from 0.05 to 4Gy on cell cycle progression was analyzed with flow cytometry. The time course of the changes in cell cycle progression was also observed within one week after WBI with 0.075Gy and 2Gy[10]. It was found in both the thymus and spleen that there was no G_2 arrest 4~168h after WBI with 0.075Gy and the percentage of G_0/G_1 cells was decreased from 12 to 72h with concomitant increase in percentage of the cells entering S phase. WBI with 2Gy caused G_2 arrest from 8 to 48h after irradiation in the splenocytes while this dose caused G_2 arrest in the thymocytes from 4 to 12h with a significant decrease of G_2 cells 72h after irradiation. The latter observation indicates an accelerated re-entry of cells into cycle after release from the G_2 block. Dose-effect relationship studies demonstrated that when examined 24h after WBI the threshold of G_1 arrest was found to be 0.1Gy for both thymocytes and splenocytes with a decrease in S and G_2/M cells in accompany with an increase in G_0/G_1 cells and 0.2Gy had a similar effect. The threshold dose for G_2 arrest was found to be 1Gy in both the thymus and spleen. It should be pointed out that in synchronized cell populations the threshold dose might vary with the cell cycle phase in which the cells are irradiated. For example, when the $HeLaS_3$ cells were irradiated during the G_2/M phase, the threshold dose for G_2 arrest was found to be 0.05Gy[11]. The higher threshold value for thymocytes and splenocytes observed after WBI may be due to the fact that a mixed population of cells with different radiosensitivities was exposed.

On the basis of the above observations changes in transcription and expression of two important genes controlling S/G_2 and G_2/M transition, viz. cyclin B_1 and *cdcz*, were studied. Northern blot hybridization was used for assessing the transcription levels and immunohistochemistry was used for measuring protein expression in the thymocytes. As seen in Fig.6 the induction of cyclin B_1 both at mRNA and protein levels was significantly suppressed by 2Gy irradiation and slightly up-regulated after 0.075Gy irradiation (the upper two panels). The same phenomenon was observed with the transcription of *cdc*2 mRNA and expression of its protein $p34^{cdc2}$ (the lower two panels). The greatest change for transcription occurred 2h after irradiation and for protein expression at 12h with the exception of *cdc*2 mRNA that gradually came down until 48h after irradiation (left lower

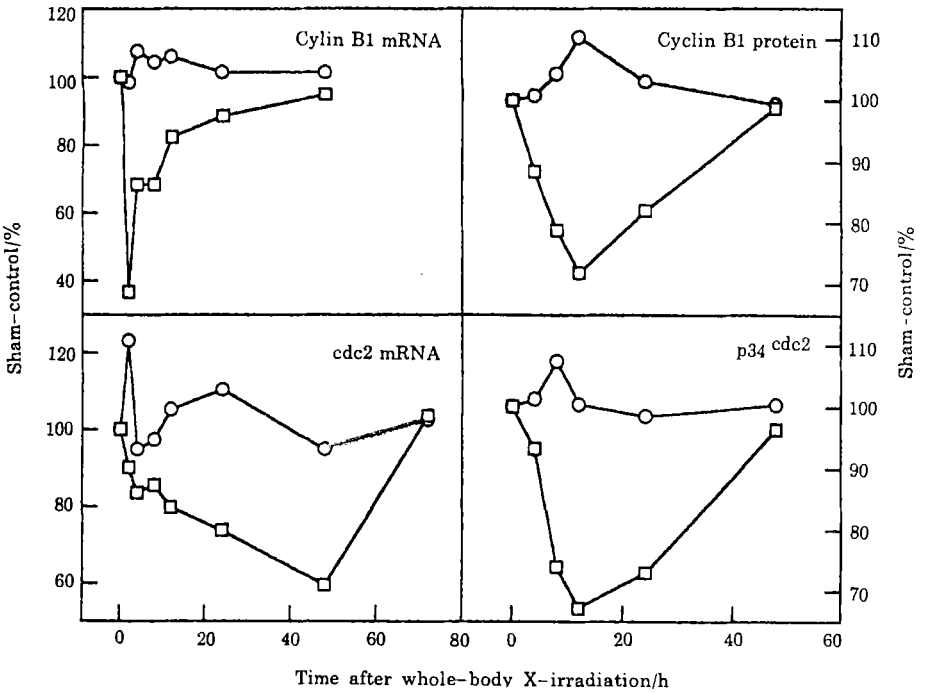

Fig.6 Effect of whole-body X-irradiation on genes related to cell cycle control
○ 0.075Gy, □ 2Gy

panel) when the expression of $p34^{cdc2}$ had recovered to near its original level (right lower panel). Currently there is no explanation for this latter observation.

In summary, when the molecular changes related to cell survival and death, cell cycle control, immune reactions and signal transduction after LDR were compared with those induced by higher dose radiation, a clear distinction was observed. For most of the parameters examined opposite effects were observed after WBI with low versus high doses of radiation. Therefore, clearly different effects were induced by LDR in comparison with those by high dose radiation not only at the systemic and cellular levels

(as previously reported from many laboratories), but also at the molecular level with mRNA transcription and protein expression of relevant genes.

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低剂量辐射诱导细胞激活过程中基因和蛋白分子的变化

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摘要 本文报道全身 X 射线照射后小鼠胸腺和 / 或脾脏中与细胞存活及细胞周期调控相关基因转录和表达水平，与免疫反应相关基因的转录水平以及信号分子表达的变化。结果显示，高、低剂量照射引起所检测的大多数参数的相反效应。分析了这些变化在不同剂量电离辐射所致细胞反应发生中的意义。

关键词 辐射，基因，细胞存活，细胞因子，细胞周期调控，信号传递

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