Increased Levels of p53 and PARP-1 in EL-4 Cells Probably Related with the Immune Adaptive Response Induced by Low Dose Ionizing Radiation *in vitro*[1]

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Objective This paper is to explore the DNA repair mechanism of immune adaptive response (AR) induced by low dose radiation (LDR), the changes of mRNA levels and protein expressions of p53, ATM, DNA-PK catalytic subunit (DNA-PKcs) and PARP-1 genes in the LDR-induced AR in EL-4 cells. **Methods** The apoptosis and cell cycle progression of EL-4 cells were detected by flow cytometry in 12 h after the cells received the pre-exposure of 0.075 Gy X-rays (inductive dose, D1) and the succeeding high dose irradiation (challenge dose, D2; 1.0, 1.5, and 2.0 Gy X-rays, respectively) with or without wortmannin (inhibitor of ATM and DNA-PK) and 3-aminobenzamid (inhibitor of PARP-1). And the protein expressions and mRNA levels related to these genes were detected with flow cytometry and reverse transcription-polymerase chain reaction in 12 h after irradiation with D2. **Results** The mRNA and protein expressions of p53 and PARP-1 in EL-4 cells in the D1 + D2 groups were much lower than those in the D2 groups, and those of PARP-1 in the 3-AB + D2 and the 3-AB + D1 + D2 groups were much lower than those in the D2 and the D1 + D2 groups. The percentage of apoptotic EL-4 cells in the 3-AB + D1 + D2 groups was much higher than that in the D1 + D2 groups, that in the G_0/G_1 and the G_2 + M phases was much higher, and that in the S phase were much lower. Although the ATM and DNA-PKcs mRNA and protein expressions in wortmannin + D1 + D2 groups were much lower than those in the D1 + D2 groups, there were no significant changes in the apoptosis and cell cycle progression between the wortmannin + D1 + D2 and the D1 + D2 groups. **Conclusion** PARP-1 and p53 might play important roles in AR induced by LDR.

Key words: Low dose radiation (LDR); Adaptive response (AR); DNA repair

INTRODUCTION

Many efforts have been made recently to prove that low dose radiation (LDR) could induce adaptive response (AR) with regularity[1-3]. However, the mechanism underlying the induction of AR by LDR has not been fully clarified[4-6]. It was demonstrated in previous researches that AR might be mainly related to the improvement of DNA repair[7]. Importantly, recent studies of DNA damage repair mechanism of AR induced by LDR provide a strong and direct piece of evidence that non-homologous end-joining (NHEJ) repair of DNA double strand break (DSB) might be the main factor in the five ways of DNA damage repair to induce AR[8-9]. And p53 might be indeed a crucial mediator of DNA repair[10]. However, the effects of p53, phosphatidylinositol 3-kinase (PI3K) families (ataxia-telangiectasia mutated gene, ATM; DNA-dependent protein kinase, DNA-PK) and poly-(ADP ribose) polymerase (PARP) in AR induced by LDR, remain obscure up to now, though they might be important regulatory genes in the NHEJ repair way. To explore the DNA repair mechanism of immune AR induced by LDR, the

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changes of mRNA and protein expressions of p53, ATM, DNA-PK catalytic subunit (DNA-PKcs) and PARP-1 genes in the LDR-induced AR in EL-4 cells were studied in the present paper. Based on these gene changes, the apoptosis and cell cycle progression of EL-4 cells under the conditions with wortmannin (inhibitor of ATM and DNA-PK) and 3-aminobenzamid (3-AB, inhibitor of PARP-1) were detected at the same time.

MATERIALS AND METHODS

Cell Culture

EL-4 cells (mouse lymphoma cell line) in RPMI 1 640 medium supplemented with 10% fetal calf serum were cultured in glass Petri dishes at 37 ℃ in a CO_2 incubator.

Irradiation

X-rays of 200 kVp and 10 mA with 0.5 mm Cu and 1.0 mm Al as filters were given according to previous reports[11-12]. The EL-4 cells received pre-exposure with the dose of 0.075 Gy (D1 with a dose-rate of 0.0125 Gy/min), and were followed by a succeeding X-irradiation with the doses of 1.0, 1.5, and 2.0 Gy (D2 with a dose-rate of 0.287 Gy/min) 6 h later, respectively. The sham-irradiation and the D2 groups were presented.

Inhibitors of ATM, DNA-PK, and PARP-1

EL-4 cells were cultured in microplate (6 wells with flat bottom). One hour before D1 and D2 irradiation, wortmannin (inhibitor of ATM and DNA-PK) at a final concentration of 20 nmol/L or 3-aminobenzamid (3-AB, inhibitor of PARP-1) at a final concentration of 5 mmol/L was added to each well of the microplate.

Detections of Apoptosis and Cell Cycle Progression

In 12 h after irradiation with D2, EL-4 cells were collected and treated with RNase (0.1 mg/mL) and stained with propidium iodide (0.05 mg/mL, with 0.03% Triton X-100). Each sample was measured with flow cytometry (Becton-Dickinson, U.S.) by counting 10 000 cells, and cell cycle progression and apoptotic bodies were analyzed with Cellfit and Lysys software, respectively.

Detection of Protein Expression

The protein expressions of p53, ATM, DNA-PKcs, and PARP-1 in EL-4 cells 12 h after irradiation with D2 were analyzed with flow cytometry. Briefly, the cells were incubated with homologous monoclonal antibodies (Santa Cruz, U.S.) for 45 min at 4 ℃. After the secondary antibodies stained with FITC were used, ten thousand cells were counted under the laser excitation wavelength of 488 nm.

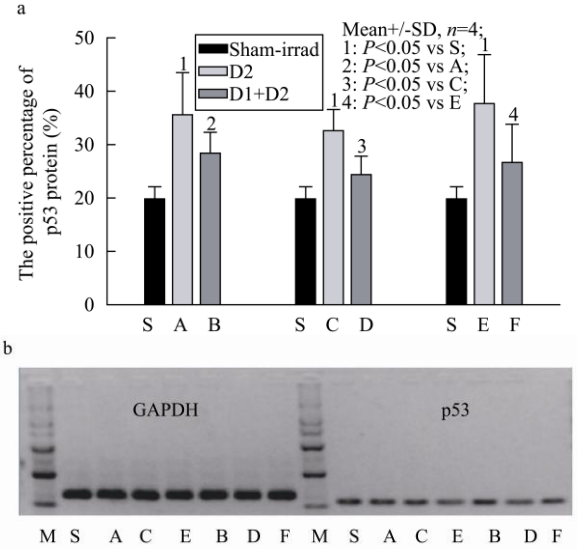

FIG. 1. Changes of p53 protein and mRNA expressions in EL-4 cells. (a) The positive percentage of p53 protein expression. (b) Electrophoresis picture of p53 mRNA expression. S: Sham-irradiation; A: 1 Gy; B: 0.075 Gy + 1 Gy; C: 1.5 Gy; D: 0.075 Gy + 1.5 Gy; E: 2 Gy; F: 0.075 Gy + 2 Gy; M: DNA Marker. Data are presented as mean ± SD for n=4 independent experiments.

Detection of mRNA Expression

The total RNA samples from EL-4 cells 12 h after irradiation with D2 were extracted with trizol reagent. The cDNA was produced by reverse transcription reaction. PCR amplification was performed with primers from the sequences of p53, ATM, DNA-PKcs, and PARP-1 genes. The PCR products were completely detected with an agarose gel followed by ethidium bromide staining. The expressions of these genes were measured by the gray scale analysis with an imaging system (Bio-Rad, U.S.). The housekeeping gene (GAPDH) was used for normalizing the gray scale of PCR products. The primers used for PCR amplification were as follows: p53 (forward primer: 5'-GGCAACTATGGCTTCCACCT-3'; reverse primer: 5'-AACTGCACAGGGCACGTCTT-3'), ATM (forward primer: 5'-GGGCGGTTGGTTGTATTGTT-3'; reverse primer: 5'-AGCCACTCTGGATTCCCACA-3'), DNA-PKcs (forward primer: 5'-GTAAAGATGAGCACCAGCCC-3'; reverse primer: 5'-ATTGGCGGGTTAGACGAAAA-3'), PARP-1 (forward primer: 5'-GTCCAAC

AGGAGCATGTGCA-3'; reverse primer: 5'-CCAGCGGTCAATCATACCCA-3') and GAPDH (forward primer: 5'-ATCTTCCAGGAGCGAGACCC-3'; reverse primer: 5'-GCGGAGATGATGACCC TTTT-3').

Statistics

The results were presented as the mean ±SD and one-way ANOVA was used to evaluate the statistical significance.

RESULTS

Changes of p53 Protein and mRNA Expressions in EL-4 Cells Irradiated with Challenge Dose after Inductive Irradiation with 0.075 Gy

As compared with that in the sham-irradiation group, the protein expression of p53 in the D2 groups increased significantly in 12 h after irradiation with D2. The level of p53 protein expression in the D1 + D2 groups was much lower than that in the D2 groups (Fig. 1 a). The change tendency of p53 mRNA expression was identical with that of protein expression (Fig. 1 b). The results show that p53 might play an important role in the AR.

Changes of Apoptosis, Cell Cycle Progression, Protein and mRNA Expressions in EL-4 Cells Induced by Inductive Irradiation with 0.075 Gy before Challenge Dose Irradiation with or without Wortmannin

The percentage of apoptotic EL-4 cells in the D2

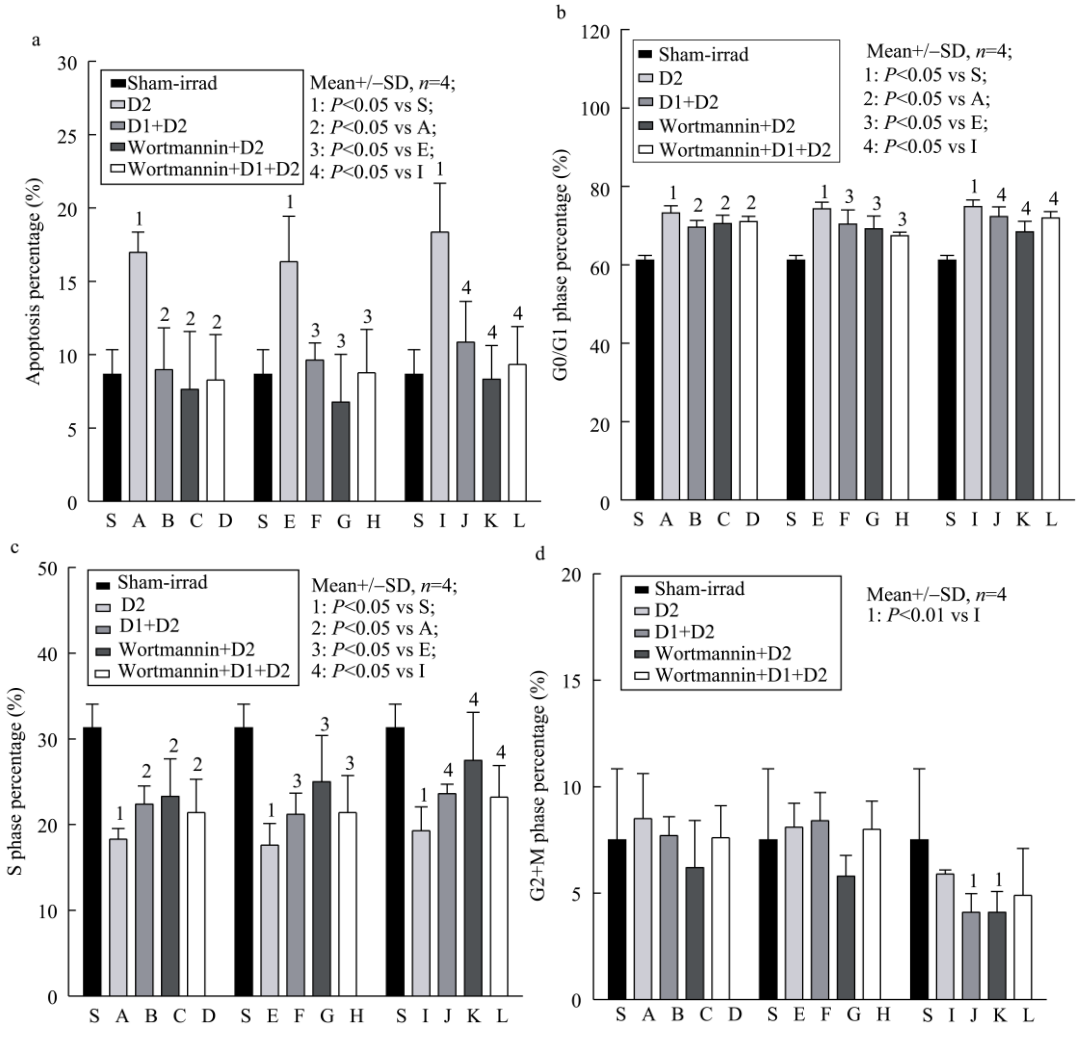

FIG. 2. Changes of apoptosis and cell cycle progression in EL-4 cells. (a) Percentage of EL-4 cells apoptosis. (b) Percentage of EL-4 cells in the G_0/G_1 phase. (c) Percentage of EL-4 cells in the S phase. (d) Percentage of EL-4 cells in the G_2 + M phase. S: Sham-irradiation; A: 1 Gy; B: 0.075 Gy + 1 Gy; C: Wortmannin + 1 Gy; D: Wortmannin + 0.075 Gy + 1 Gy; E: 1.5 Gy; F: 0.075 Gy + 1.5 Gy; G: Wortmannin + 1.5 Gy; H: Wortmannin + 0.075 Gy + 1.5 Gy; I: 2 Gy; J: 0.075 Gy + 2 Gy: K: Wortmannin + 2 Gy; L: Wortmannin + 0.075 Gy + 2 Gy. Data are presented as mean ± SD for n = 4 independent experiments.

groups increased significantly 12 h after challenge dose irradiation as compared with that in the sham-irradiation group. As compared with that in the D2 groups, the percentage of apoptotic EL-4 cells in the D1 + D2, the wortmannin + D2 and the wortmannin + D1 + D2 groups decreased significantly. But there were no significant changes in apoptotic percentage between the wortmannin + D1 + D2 and the D1 + D2 groups (Fig.2 a).

As compared with that in the sham-irradiation group, the percentage of EL-4 cells in the G_0/G_1 phase increased significantly in the D2 groups. The percentage of EL-4 cells in the G_0/G_1 phase in the D1 + D2, the wortmannin + D2 and the wortmannin + D1 + D2 groups decreased significantly, as compared with that in the D2 groups. But there were no significant changes in EL-4 cell percentage in the G_0/G_1 phase between the wortmannin + D1 + D2 and the D1 + D2 groups (Fig.2 b).

The percentage of EL-4 cells in the S phase decreased significantly in the D2 groups as compared with that in the sham-irradiation group. As compared with that in the D2 groups, the percentage of EL-4 cells in the S phase in the D1 + D2, wortmannin + D2 and wortmannin + D1 + D2 groups increased significantly. But there was no significant difference in EL-4 cells in the S phase between the wortmannin + D1 + D2 and the D1 + D2 groups (Fig.2 c).

The percentage of EL-4 cells in the G_2 + M phase in the D1 + 2.0 Gy and the wortmannin + 2.0 Gy groups was much lower than that in the 2.0 Gy group, but no statistical significance was present in comparison with that in the rest groups (panel d of Fig. 2).

As compared with that in the sham-irradiation group, the protein expression of ATM and DNA-PKcs in the D2 groups was up-regulated significantly. The protein expression of ATM and DNA-PKcs in the wortmannin + D2 groups decreased significantly as compared with that in the D2 groups. The protein expression of ATM and DNA-PKcs in wortmannin + D1 + D2 groups was much lower than that in the D1 + D2 groups (see Fig. 3 a and b). The changes of ATM and DNA-PKcs mRNA expressions were identical with those of protein expression (Fig.3 c and 3 d).

The results show that the changes of mRNA and protein expressions of ATM and DNA-PKcs were not significant in AR induced by LDR. Wortmannin could induce the AR followed by challenge dose irradiation through the imitation of the effect of inductive irradiation. Although wortmannin inhibited the gene expressions of ATM and DNA-PKcs, it could induce AR.

Changes of Apoptosis, Cell Cycle Progression, Protein and mRNA Expressions in EL-4 Cells Induced by Inductive Irradiation with 0.075 Gy before Challenge Dose Irradiation with or without 3-AB

In 12 h after challenge dose irradiation, the percentage of apoptotic EL-4 cells in the D2 groups increased significantly as compared with that in the sham-irradiation group, while the percentage of apoptotic EL-4 cells in the D1 + D2 groups decreased significantly compared with that in the D2 groups,. The percentage of apoptotic EL-4 cells in the 3-AB + D1 + D2 groups was much higher than that in the D1 + D2 groups. Nevertheless, there was no significant difference in apoptotic percentage between the 3-AB + D2 and the D2 groups (Fig. 4 a).

As compared with that in the sham-irradiation group, the percentage of EL-4 cells in the G_0/G_1 phase increased significantly in the D2 groups, whereas the percentage of EL-4 cells in the G_0/G_1 phase in the D1 + D2 groups decreased significantly as compared with that in the D2 groups. The percentage of EL-4 cells in the G_0/G_1 phase in the 3-AB + D1 +D2 groups was much higher than that in the D1 + D2 groups. However, there was no significant difference in EL-4 cell percentage in the G_0/G_1 phase between the 3-AB + D2 and the D2 groups (Fig. 4 b).

The percentage of EL-4 cells in the S phase decreased significantly in the D2 groups as compared with that in the sham-irradiation group. In comparison with that in the D2 groups, the percentage of EL-4 cells in the S phase in the D1 + D2 groups increased significantly. The percentage of EL-4 cells in the S phase in the 3-AB + D1 + D2 groups was much lower than that in the D1 + D2 groups. But there was no significant difference in EL-4 cell percentage in the S phase between the 3-AB + D2 and the D2 groups (Fig. 4 c).

The percentage of EL-4 cells in the G_2 + M phase in the D1 + 2.0 Gy group was much lower than that in the 2.0 Gy group, but the percentage in the 3-AB + D1 + 2.0 Gy group was much higher than that in the D1 + 2.0 Gy group. However, a comparison of EL-4 cell percentage in the G_2 + M phase between the rest groups showed no statistical significance (Fig. 4 d).

As compared with that in the sham-irradiation group, the protein expression of PARP-1 in the D2 groups was up-regulated significantly. The protein expression of PARP-1 in the D1 + D2 groups

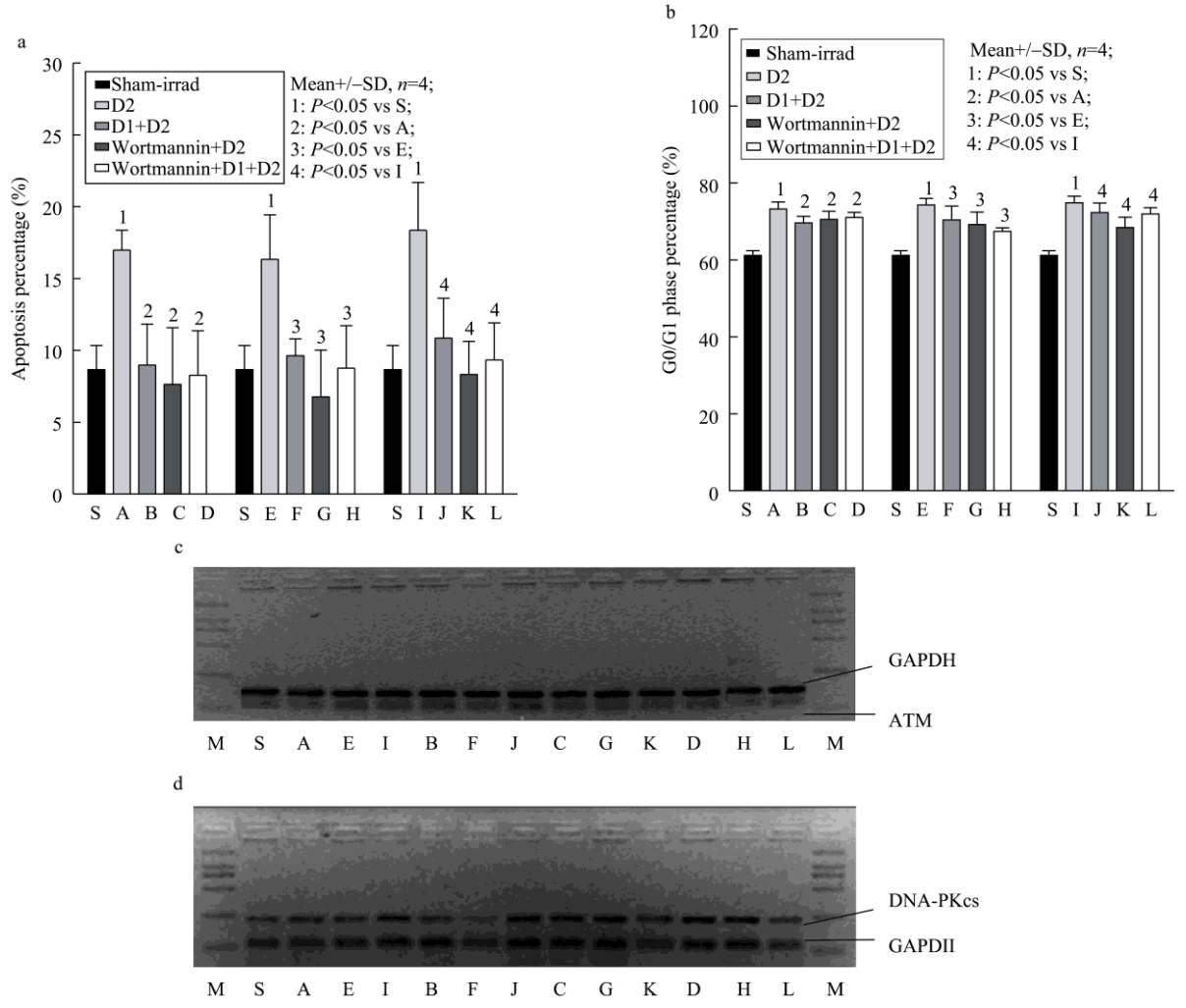

FIG. 3. Changes of ATM and DNA-PKcs protein and mRNA expressions in EL-4 cells. (a) The positive percentage of ATM protein expression. (b) The positive percentage of DNA-PKcs protein expression. (c) Electrophoresis picture of ATM mRNA expression. (d) Electrophoresis picture of DNA-PKcs mRNA expression. S: Sham-irradiation; A: 1 Gy; B: 0.075 Gy + 1 Gy; C: Wortmannin + 1 Gy; D: Wortmannin + 0.075 Gy + 1 Gy; E: 1.5 Gy; F: 0.075 Gy + 1.5 Gy; G: Wortmannin + 1.5 Gy; H: Wortmannin + 0.075 Gy + 1.5 Gy; I: 2 Gy; J: 0.075 Gy + 2 Gy; K: Wortmannin + 2 Gy; L: Wortmannin + 0.075 Gy + 2 Gy; M: DNA Marker. Data are presented as mean ± SD for $n = 4$ independent experiments.

increased significantly as compared with that in the D2 groups. The protein expression of PARP-1 in the 3-AB + D2 and the 3-AB + D1 + D2 groups was much lower than that in the D2 and the D1 + D2 groups (panel a of Fig.5). The changes of PARP-1 mRNA expression in AR induced by LDR had an identical tendency with the changes of protein expression (Fig.5 b).

It was demonstrated that the mRNA and protein expressions of PARP-1 changed significantly in the AR induced by LDR. 3-AB, the inhibitor of PARP-1, could prevent the initiation of AR. PARP-1 might play an important role in the AR.

DISCUSSION

Adaptive response (AR) is a widespread phenomenon in the living nature and a potential in the adaptation of the living body to the external environment. Biological effects of low dose radiation (LDR) are distinguishable from those of high dose radiation, which can induce AR. The concept of cytogenetic AR induced by LDR, presented by Olivieri, *et al*. in 1984[13], aroused much interest among many researchers. Subsequent studies have made further investigations on the immunological AR induced by LDR. It has been repeatedly found that LDR could potentiate most immune reaction and induce AR, and higher dose radiation often elicits opposite effects[14-16].

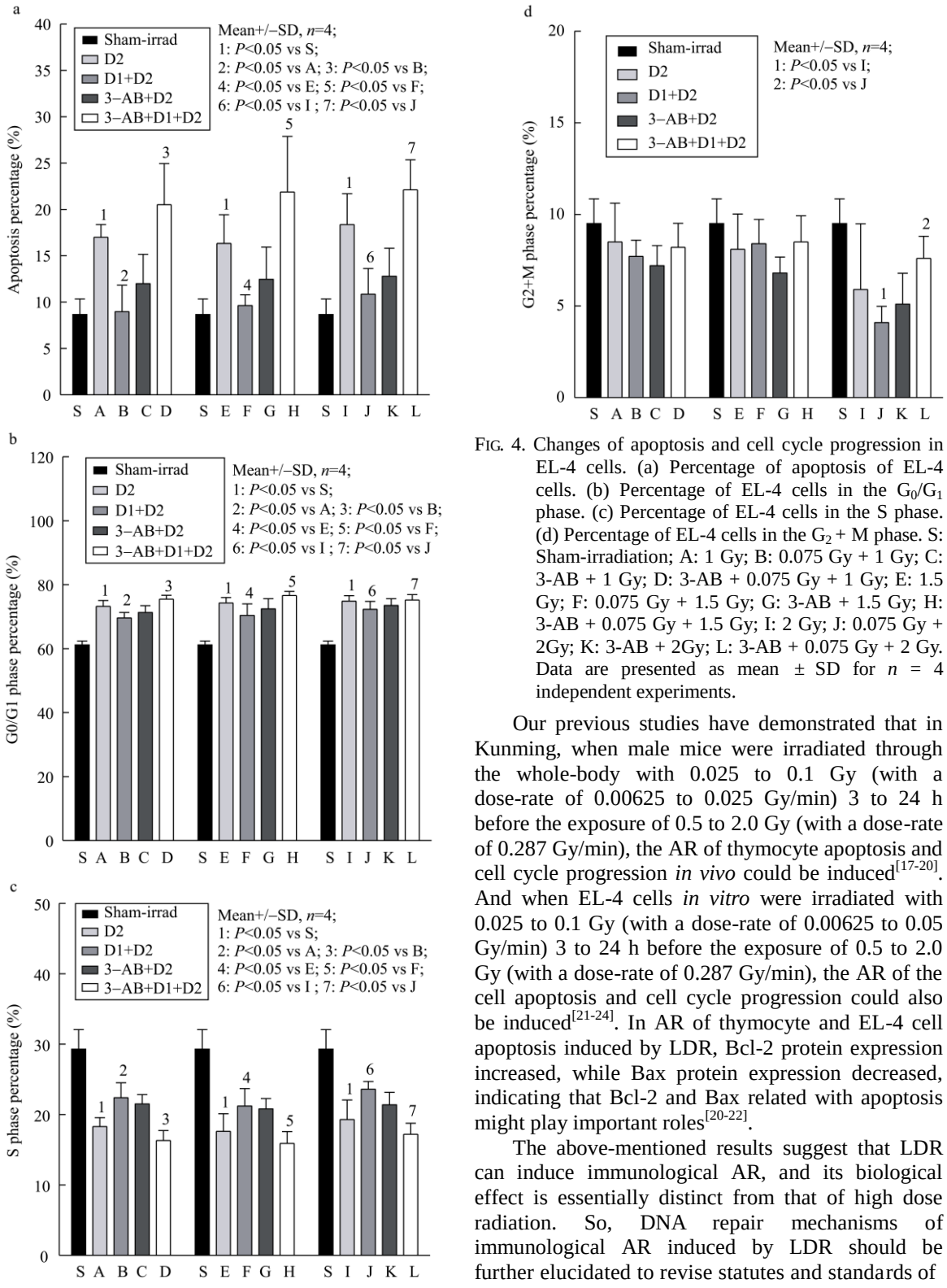

FIG. 4. Changes of apoptosis and cell cycle progression in EL-4 cells. (a) Percentage of apoptosis of EL-4 cells. (b) Percentage of EL-4 cells in the G_0/G_1 phase. (c) Percentage of EL-4 cells in the S phase. (d) Percentage of EL-4 cells in the G_2 + M phase. S: Sham-irradiation; A: 1 Gy; B: 0.075 Gy + 1 Gy; C: 3-AB + 1 Gy; D: 3-AB + 0.075 Gy + 1 Gy; E: 1.5 Gy; F: 0.075 Gy + 1.5 Gy; G: 3-AB + 1.5 Gy; H: 3-AB + 0.075 Gy + 1.5 Gy; I: 2 Gy; J: 0.075 Gy + 2Gy; K: 3-AB + 2Gy; L: 3-AB + 0.075 Gy + 2 Gy. Data are presented as mean ± SD for n = 4 independent experiments.

Our previous studies have demonstrated that in Kunming, when male mice were irradiated through the whole-body with 0.025 to 0.1 Gy (with a dose-rate of 0.00625 to 0.025 Gy/min) 3 to 24 h before the exposure of 0.5 to 2.0 Gy (with a dose-rate of 0.287 Gy/min), the AR of thymocyte apoptosis and cell cycle progression *in vivo* could be induced[17-20]. And when EL-4 cells *in vitro* were irradiated with 0.025 to 0.1 Gy (with a dose-rate of 0.00625 to 0.05 Gy/min) 3 to 24 h before the exposure of 0.5 to 2.0 Gy (with a dose-rate of 0.287 Gy/min), the AR of the cell apoptosis and cell cycle progression could also be induced[21-24]. In AR of thymocyte and EL-4 cell apoptosis induced by LDR, Bcl-2 protein expression increased, while Bax protein expression decreased, indicating that Bcl-2 and Bax related with apoptosis might play important roles[20-22].

The above-mentioned results suggest that LDR can induce immunological AR, and its biological effect is essentially distinct from that of high dose radiation. So, DNA repair mechanisms of immunological AR induced by LDR should be further elucidated to revise statutes and standards of

radiation protection and develop nuclear science and nuclear technology.

The stimulatory effects (hormesis) following LDR involve a series of cellular and molecular changes[25-26]. The signal of injury in AR induced by LDR might produce a marked effect with a degenerative feedback pathway of PKC-p38MAPK-PLC; however, the underlying mechanisms remain obscure so far[27]. It has been widely accepted that pre-exposure of lymphocytes and other cells to a few cGy (inductive dose, D1) could protect the chromosome from the damage caused by a succeeding high dose irradiation (challenge dose, D2)[28]. Therefore, in the present study, the effects of p53, ATM, DNA-PKcs and PARP-1 mRNAs and proteins mainly involved in non-homologous end-joining (NHEJ) repair of DSB in AR of the apoptosis and cell cycle progression of EL-4 cells induced by LDR under the above conditions were investigated with wortmannin and 3-AB of their inhibitors.

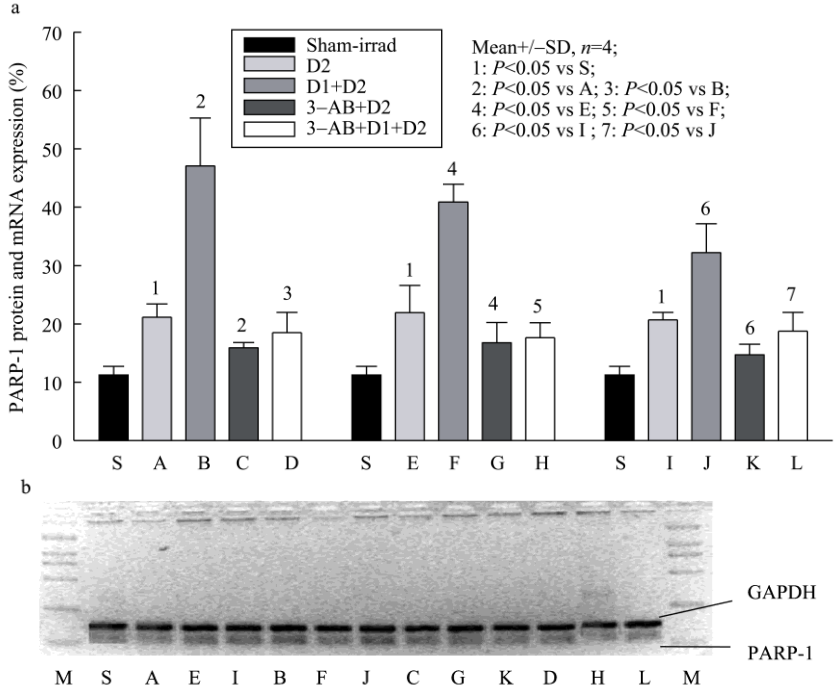

FIG. 5. Changes of PARP-1 protein and mRNA expressions in EL-4 cells. (a) The positive percentage of PARP-1 protein expression. (b) Electrophoresis picture of PARP-1 mRNA expression. S: Sham-irradiation; A: 1 Gy; B: 0.075 Gy + 1 Gy; C: 3-AB + 1 Gy; D: 3-AB + 0.075 Gy + 1 Gy; E: 1.5 Gy; F: 0.075 Gy + 1.5 Gy; G: 3-AB + 1.5 Gy; H: 3-AB + 0.075 Gy + 1.5 Gy; I: 2 Gy; J: 0.075 Gy + 2 Gy; K: 3-AB + 2 Gy; L: 3-AB + 0.075 Gy + 2 Gy; M: DNA Marker. Data are presented as mean ± SD for $n = 4$ independent experiments.

In the present paper, D1 (0.075 Gy with a dose-rate of 0.0125 Gy/min) and D2 (1.0, 1.5 and 2.0 Gy with a dose-rate of 0.287 Gy/min) 6 h later were chosen for the research. It was demonstrated that there was no significant difference in ATM and DNA-PKcs expressions in EL-4 cells between the D1 + D2 and the D2 groups. The mRNA and protein expressions of ATM and DNA-PKcs decreased significantly after their comitant inhibitor (also known as wortmannin) was used. Nevertheless, AR could be induced in the wortmannin + D1 + D2 groups, implying that wortmannin had no effects on AR. The trigger of DNA double-strand break to ATM, DNA-PK and PARP-1, resulted in activation of p53 in the cells, leading to expressions of a series of repair proteins and initiation of NHEJ repair[29]. The expression of p38MAPK was up-regulated by LDR, which caused p53 activation and AR induction through the PKC-p38MAPK-p53 pathway[30]. In this paper, AR could be induced in the wortmannin + D1 + D2 groups, most probably owing to the up-regulated activity of PKC-p38MAPK-p53 induced by wortmannin, which was associated with its ability to compensate for the activity of PI3K family genes (such as ATM and DNA-PK)-activation signal conduction pathway inhibited by wortmannin. Accordingly, ATM and DNA-PKcs might not be important mediators of AR induced by LDR.

The results show that the expression of PARP-1 has increased significantly in AR induced by LDR, and the down-regulated expression of PARP-1 has been induced by its inhibitor[31]. In a separate

experiment, 3-AB could rapidly inhibit the PARP expression of Hela cells, and enhance the apoptosis and block G_2 arrest induced by irradiation[32]. The expression of p53 was up-regulated in the D2 groups and decreased in AR induced by LDR, indicating that PARP-1 and p53 might play important roles in AR[33]. However, it is demonstrated by the present results that the tendency of both PARP-1 and p53 expressions was opposite in AR induced by LDR. As previously reported, the phosphorylation of PARP-1 resulted in the activation of p53, leading to the up-regulation of p53 under the condition of DNA double-strand break[34]. However, another study reported that PARP-1 down-regulated the expression of p53 through the inhibition of ATM activity and overexpression[35]. It is therefore assumed that the inhibition factors might play important roles in AR induced by LDR. But the effects of p53 activation induced by PARP-1 and ATM, and the mechanisms of their interaction remain obscure up to now[36-37]. It has been found in previous researches that the AR induced by LDR could not be reduced in the cells with deletion of p53, which indicates that p53 might be a key point in AR induced by LDR.

DNA damage repair might be the principal contributor to the induction of AR by LDR. It involves the enhancement of the reparative process induced by DNA damage and changes of a series of gene expressions in the activation of the signal transduction pathway. However, the underlying mechanisms remain to be identified.

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