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# Inhibition of PARP1 Increases IRF-dependent Gene Transcription in Jurkat Cells*

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**Summary**: Poly(ADP-ribose) polymerase 1 (PARP1) plays important roles in the regulation of transcription factors. Mounting evidence has shown that inhibition of PARP1 influences the expression of genes associated with inflammatory response. Interferon regulatory factor 1 (IRF1) is a critical transcription factor for the development of both the innate and adaptive immune responses against infections. However, the molecular mechanism through which PARP1 mediates the effects has not been clearly demonstrated. Jurkat cells were exposed to dexamethasone (Dex) or PARP1 inhibitor PJ34. The expression levels of IL-12, LMP2, OAS1 and PKR were detected using real-time RT-PCR. The interactions between PARP1 and IRF1 were examined by co-immunoprecipitation (co-IP) assays. We further explored the mechanism of PARP1 suppressing IRF1 by assessing the activities of interferon stimulated response element (ISRE). The mRNA expression of IL-12, LMP2, OAS1 and PKR was obviously suppressed by Dex in Jurkat cells, which could be rescued by PJ34 treatment. Luciferase study revealed that poly(ADP-ribosyl)-ation suppressed IRF1-mediated transcription through preventing the binding of IRF1 to ISREs. PARP1 inhibited IRF1-mediated transcription in Jurkat cells by preventing IRF1 binding to ISREs in the promoters of target genes. It is suggested that PARP1 is a crucial regulator of IRF1-mediated immune response. This study provides experimental evidence for the possible application of PARP1 inhibitors in the treatment of IRF1-related immune anergy.
**Key words**: poly(ADP-ribose) polymerase 1; interferon regulatory factor 1; Jurkat cells; gene transcription; interferon stimulated response element

Innate immune responses have the capacity to both combat infectious microbes and drive pathological inflammation, which contributes to diseases such as sepsis, atherosclerosis, obesity, autoimmunity and cancer. A large number of studies have revealed that interferon regulatory factor 1 (IRF1) is a pleiotropic transcription factor, critical for cell defense against viral and intracellular bacterial infections but also crucial for the development of both the innate and adaptive responses and immune cell differentiation[1]. IRF1 is a transcription factor that participates in interferon (IFN) signaling and it is the first factor identified from the IRF family which is comprised of nine members in mammals. Inhibition of IRF1 results in the transcriptional repression of several genes involved in antiviral functions, immunomodulatory activities as well as antigen presentation, such as IL-12, low molecular-mass polypeptide 2 (LMP2), 2', 5'-oligoadenylate synthetase 1 (OAS1), and double-stranded RNA-dependent protein kinase R (PKR)[2–4]. The IRF1 gene is responsive to a number of hormones. Recent researches revealed that the glucocorticoid steroid hormone, dexamethasone (Dex), could block IFN induction of IRF1 mRNA levels[5–7] at multiple time points and in all cell types examined from GEO data sets, and then inhibit the production of many mediators of immune and inflammatory response, such as cytokines, chemokines and cell adhesion molecules as a consequence. Although some studies have shown that IRF1 plays central roles in gene expressional regulation of immunological functions, the underlying molecular mechanisms still remain to be defined.

Poly(ADP-ribose) polymerase 1 (PARP1) is the most abundant member of the PARP family, which accounts for more than 90% of cellular PARP activity.

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Upon activation, PARP1 catalyzes polymerization of ADP-ribose units from donor NAD+ molecules on target proteins to form linear or branched polymers. Mounting evidence has indicated that both genetic inactivation of PARP1 and pharmacological inhibition of poly(ADP-ribosyl)ation influence the expression of several genes, including those of the inflammatory response[8–10]. Recent studies have shown that PARP1 might be involved in the immunocompromise caused by the effects of glucocorticoids, which is exemplified by the resistance of mice lacking the gene for PARP1 to the immunocompromising effects of glucocorticoids. Considering that IRF1 is the master regulator of innate immunity, we next explored whether PARP1 is implicated in the transcriptional activation of IRF1 in the innate and adaptive responses.

In the present study, we found that inhibition of PARP1 enhanced IRF1-dependent target gene expression and promoted the IRF1 transactivation by increasing the IRF1 binding to ISRE in Jurkat cells. Furthermore, we demonstrated that PARP1 could bind to the poly(ADP-ribosyl)ated IRF1. Thus, PARP1 served as an important regulator of IRF1-mediated transcription.

## 1 MATERIALS AND METHODS

### 1.1 Cell Lines and Culture

Human Jurkat T-cell leukemia cells were purchased from the American Type Culture Collection (USA). Cells were cultured in RPMI 1640 supplemented with 10% fetal calf serum (FCS), 2 mmol/L L-glutamine, and 1% penicillin/streptomycin at 37°C in humidified atmosphere of 5% $CO_2$. After 24 h of serum starvation, cells were exposed to the compounds containing Dex (Sigma-Aldrich, USA), *N*-(6-oxx-5,6-dihydro-phenanthridin-2-(*N*, *N*-dimethylamino) acetamide (PJ34, ALX-270-289, Alexis Biochemical, USA), hydrogen peroxide ($H_2O_2$, Sigma, USA) or the relevant vehicle.

### 1.2 RNA Extraction and Real-time RT-PCR

Total RNA from Jurkat cells was isolated using Trizol reagent (Takara Biotechnology, Japan) according to the manufacturer's instruction. A total of 1 μg RNA was reversely transcripted using RNA PCR Kit (Takara Biotechnology, Japan) and the resulting cDNA was used as a PCR template. The mRNA levels were determined by real-time PCR with ABI PRISM 7900 Sequence Detector system (Applied Biosystem, USA) according to the manufacturer's instructions. β-actin was used as an invariant internal control. The sequences of primers for PCR are listed in table 1.

**Table 1 The sequences of primers for real-time RT-PCR**

| Genes | Primer sequences (forward and reverse) |
|---|---|
| β-actin | 5′-GGCACCCAGCACAATGAA-3′ |
| | 5′-GGAAGGTGGACAGCGAGG-3′ |
| IL-12β | 5′-ACCCTGACCATCCAAGTCAAA-3′ |
| | 5′-TTGGCCTCGCATCTTAGAAAG-3′ |
| LMP2 | 5′-GCACCAACCGGGGACTTAC-3′ |
| | 5′-CACTCGGGAATCAGAACCCAT-3′ |
| OSA1 | 5′-TGTCCAAGGTGGTAAAGGGTG-3′ |
| | 5′-CCGGCGATTTAACTGATCCTG-3′ |
| PKR | 5′-GCCGCTAAACTTGCATATCTTCA-3′ |
| | 5′-TCACACGTAGTAGCAAAAGAACC-3′ |

### 1.3 Plasmids Construction

The mammalian expression vectors pcDNA3.1-Flag-PARP1 encoding Flag-tagged wild-type PARP1 were kindly provided by Dr. Yun Zhang (Qilu Hospital, Shandong University, China). The mammalian expression vectors pcDNA3.1-HA-IRF1, 3, 4, 7, 8, 9 and the ISRE-luc construction were kindly provided by Dr. Hongliang Li (Wuhan University, China).

### 1.4 Preparation of Whole Extracts and Nuclear Extracts

For preparation of whole cell extracts, cells were solubilized in lysis buffer (50 mmol/L Tris-HCl, pH 7.2, 1 mmol/L EDTA, 150 mmol/L NaCl, 0.1% SDS, 0.5% sodium deoxycholate, 1% Nonidet P-40, 1 mmol/L phenylmethylsulfonyl fluoride, 10 μg/mL aprotinin). After incubation on ice for 30 min, whole cell extracts were obtained by centrifugation at 12 000×g for 10 min. Nuclear extracts were prepared as follows. Briefly, cells were solubilized in buffer A (10 mmol/L HEPES, pH 7.9, 1 mmol/L $MgCl_2$, 10 mmol/L KCl, 0.5 mmol/L dithiothreitol, 0.2% Nonidet P-40, 1 mmol/L phenylmethylsulfonyl fluoride, 10 μg/mL aprotinin) and vortexed vigorously for 15 s. After cytoplasmic extracts were obtained by centrifugation at 16 000×g for 5 min, the pellets were resuspended in buffer B (20 mmol/L HEPES, pH 7.9, 25% glycerol, 0.42 mmol/L NaCl, 1.5 mmol/L $MgCl_2$, 0.5 mmol/L dithioththretol, 0.2 mmol/L EDTA, 1 mmol/L phenylmethylsulfonyl fluoride, 10 μg/mL aprotinin). After centrifugation at 16 000×g for 10 min, nuclear extracts were obtained and stored at –80°C until use. The protein concentration of these extracts was determined by the Bradford assay.

### 1.5 Co-immunoprecipitation Assay

Immunoprecipitation assays were performed as described previously[11]. Briefly, 500 μg of nuclear extracts were incubated with indicated antibodies or nonspecific IgG at 4°C for 1 h, and protein-G agarose at 4°C for 12 h. The immunoprecipitates were pelleted by centrifugation at 5000×g for 1 min and washed 4 times with lysis buffer. The pellets were suspended in SDS gel loading buffer, boiled for 10 min, and subjected to Western blotting analysis. Nonspecific IgG was used as the negative control.

### 1.6 RNA Interference and Transfection

Small interfering RNAs (siRNAs) for IRF1 were designed and synthesized by RiBoBio Co. Ltd (China). The sequences of siRNA are listed in table 2. The

**Table 2 The sequences of IRF1 siRNA**

| siRNA | Sequence sence (5′-3′) |
|---|---|
| IRF1 | AAGTAATTTCCCTTCCTCATCTATAGTGAGTCGTATTAGGATCC |
| | AAGATGAGGAAGGGAAATTACTATAGTGAGTCGTATTAGGATCC |

cultured cells were transfected in 6-well plates at 70% confluence. Transfection of siRNA was performed at a final concentration of 50 nmol/L using Lipofectamine 2000 (Invitrogen, USA) according to the manufacture's protocol.

**1.7 Western Blotting Assay**

Total protein was quantified with the BCA protein assay kit (Pierce, USA). After denaturation and SDS-PAGE electrophoresis, separated proteins were transferred to nitrocellulose membranes. After incubation with primary antibodies in TBS at 4°C overnight, membranes were incubated with a HRP-conjugated secondary antibody in TBS at room temperature for 2 h. Specific bands were detected using the ECL detection system (Pierce). Protein expression levels were quantified and normalized to histone H1 as a loading control.

**1.8 Luciferase Activity Assay**

A total of 1 mg ISRE-luc constructions or control pGL3-basic plasmids were cotransfected with 10 ng of pRL-SV40 plasmid into Jurkat cells using lipofectamine 2000 (Invitrogen, USA). The luciferase activity was determined with Dual Luciferase-reporter Assay Kit (Promega, USA) according to the manufacturer's instruction.

**1.9 Statistical Analysis**

Values are shown as mean ± standard deviations (SD) of at least three independent experiments. The significance of differences was estimated by one-way ANOVA, followed by Student-Newmann-Keuls multiple comparison tests. $P<0.05$ was considered significant. All statistical analyses were performed with SPSS software (version 11.0, SPSS Inc., USA).

## 2 RESULTS

**2.1 Inhibition of PARP1 Promotes IRF1-targeted Genes Transcription in Jurkat Cells**

To identify whether PARP1 was involved in the immune responses, which is characterized by variation of the IRF1 targeted genes, we used Jurkat cells, a human T lymphocyte cell line. Realtime-qPCR assays showed that treatment with 10 μmol/L Dex significantly suppressed the mRNA expression of the IRF1-targeted genes, including IL-12β, LMP2, OAS1 and PKR, while pretreating with PARP inhibitor PJ34 could significantly reverse the suppressive effect of Dex (fig. 1).

Then IRF1 was knocked down by siRNA transfection. We found that knockdown of IRF1 abolished the suppression of IL-12β, OAS1 and PKR induced by Dex, and the restoration by PJ34 also disappeared (fig. 2A–2D). However, the mRNA expression of LMP2 was slightly suppressed by Dex when IRF1 was knocked down, and treatment with PJ34 could not reverse the down-regulation of LMP2, suggesting the down-regulation of LMP2 expression caused by Dex might be partially mediated through the PARP1/IRF1 pathway.

Meanwhile, the expression of IL-12β, LMP2, OAS1, and PKR was examined in Jurkat cells which were transfected with IRF1 siRNA and subsequently stimulated by Dex, or co-transfected with PARP1 siRNA. The similar results were observed (fig. 2E–2H). All the results suggested that PARP1 was involved in the regulation of IRF1-mediated transcriptional activation.

**2.2 Interaction between IRF1 and PARP1**

The finding that PARP1 was involved in the regulation of IRF1-mediated transcriptional activation led us to explore the interaction between PARP1 and IRF1. IRFs consist of many transcription factors in mammals. We aimed to find which one could interact with PARP1. We constructed HA-tagged IRF1, 3, 4, 7, 8, and 9, and transfected them into Jurkat cells respectively. The nuclear extracts were then subjected to co-immunoprecipitation (co-IP) assays with anti-HA antibody. Western blotting analysis revealed that

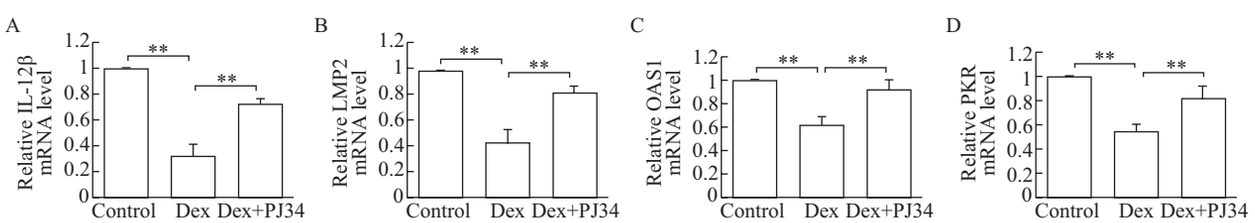


**Fig. 1** Pharmacological inhibition of PARP1 promotes IRF1-targeted genes transcription in Jurkat cells
Real-time RT-PCR analysis of IRF1 target genes IL-12β (A), LMP2 (B), OAS1 (C) and PKR (D) in Jurkat cells treated with Dex (10 μmol/L) or Dex plus PJ34 (10 μmol/L). Data represent mean±standard deviation. $^{**}P<0.01$

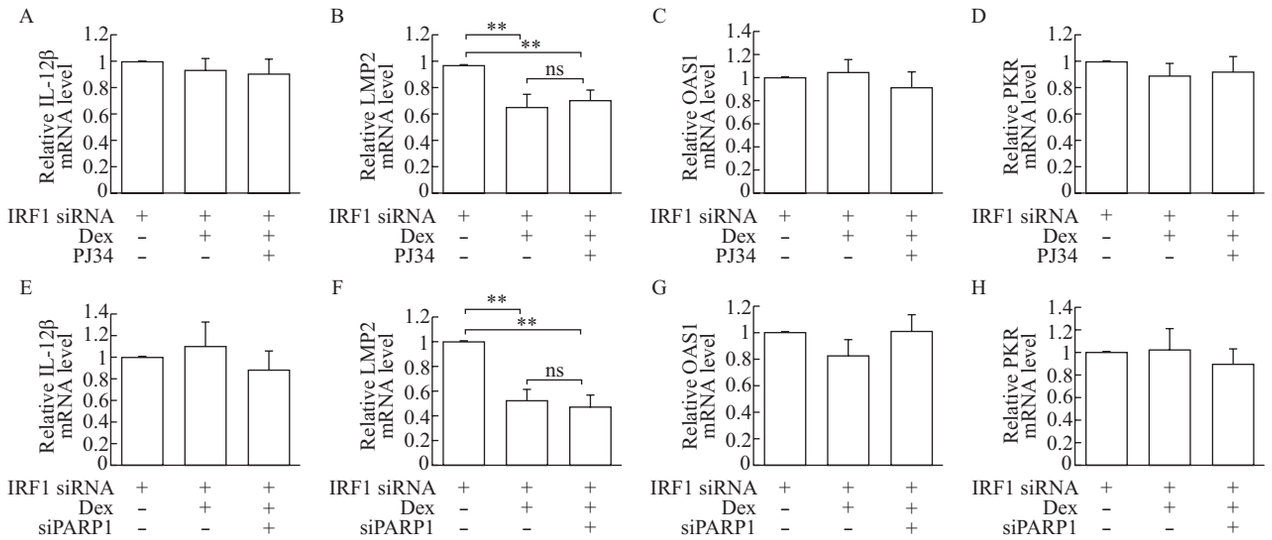


**Fig. 2** Knock-down of IRF1 restrains the increase of IRF1 target genes transcription induced by inhibition of PARP1 in Jurkat cells
Real-time RT-PCR analysis of IRF1 target genes IL-12β (A, E), LMP2 (B, F), OAS1 (C, G) and PKR (D, H) in Jurkat cells which were transfected with IRF1 siRNA, and followed by treatment of Dex (10 μmol/L), Dex plus PJ34 (10 μmol/L) or co-transfected with PARP1 siRNA. Data represent mean±standard error. $^{**}P<0.01$

PARP1 could be specifically co-immunoprecipitated with IRF1, rather than IRF3, 4, 7, 8 or 9 (fig. 3A and 3B).

Then, endogenous IRF1 was immunoprecipitated by anti-IRF1 antibody, and subsequently underwent Western blotting assay using anti-PARP1 antibody. Results showed that PARP1 was co-immunoprecipitated with IRF1 in the nuclear extracts (fig. 3C), which further verified the specificity of the interaction between PARP1 and IRF1. Additionally, Jurkat cells were transfected to express exogenous Flag-tagged PARP1 and HA-tagged IRF1. Then the cells were lysed and subjected to IP assay with anti-HA antibody and subsequently underwent Western blotting assay with anti-Flag antibody (fig. 3D). The result showed evidence of the PARP1-IRF1 interaction once again. These data demonstrated that PARP1 could directly interact with IRF1.

**2.3 Poly(ADP-ribosyl)ation of IRF1 by PARP1**

Poly(ADP-ribosyl)ation is an important post-transcriptional modification to proteins. We detected whether IRF1 was poly(ADP-ribosyl)ated with IP assay using the poly(ADP-ribose) polymer (PAR) specific antibody. The molecular weight of IRF1 was approximately 48 kD (fig. 4A), and a band near 48 kD could be detected in the immunoprecipitation

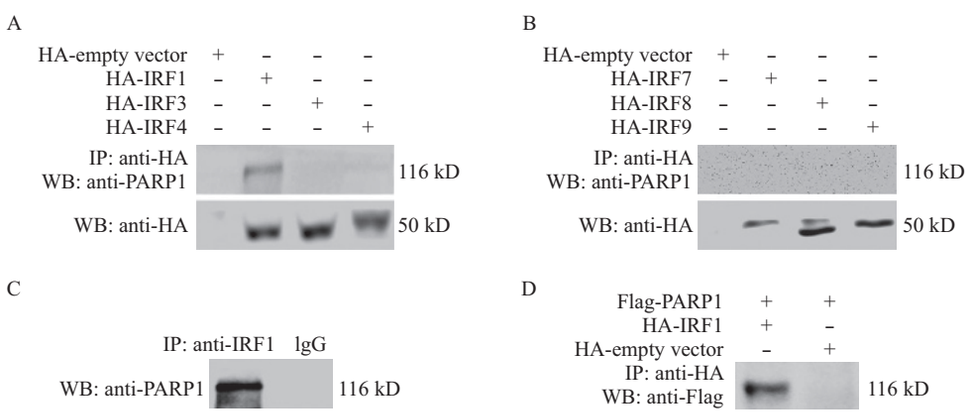


**Fig. 3** The interaction between PARP1 and IRF
A and B: HA-tagged IRF1, 3, 4, 7, 8 and 9 plasmids were transfected into Jurkat cells respectively, then the nuclear extracts were subjected to co-IP assay with anti-HA antibody, and the eluted proteins were submitted to Western blotting with anti-PARP1 antibody. C: After co-IP of nuclear extracts with anti-IRF1 antibody or unspecific IgG respectively, the eluted proteins were subjected to Western blotting with anti-PARP1 antibody. D: Flag-tagged PARP1 plasmids, HA-tagged IRF1 plasmids or empty vectors were transfected into Jurkat cells respectively, followed by co-IP assay of nuclear extracts with anti-HA antibody, and the eluted proteins were subjected to Western blotting with anti-flag antibody.

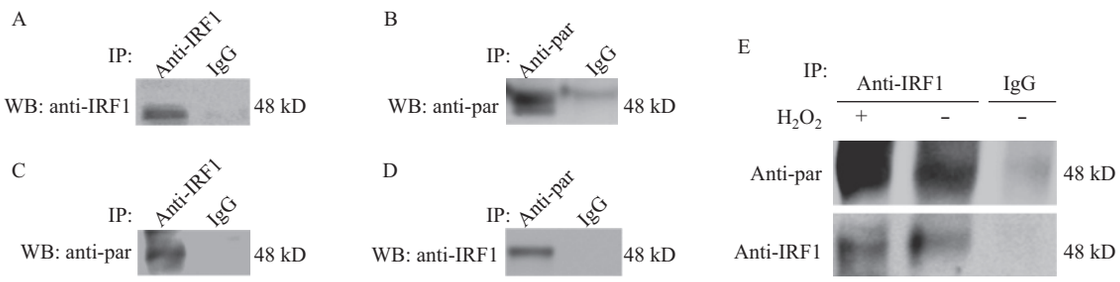


**Fig. 4** Poly(ADP-ribosyl)ation of IRF1 by PARP1

A–D: After co-IP of nuclear extracts with anti-IRF1 antibody, anti-par antibody or unspecific IgG respectively, the eluted proteins were subjected to Western blotting with anti-IRF1 or anti-par antibody as indicated. E: The Jurkat cells were stimulated with $H_2O_2$ (0.3 mmol/L), then the nuclear extracts were submitted to co-IP assay with anti-IRF1 antibody or unspecific IgG antibody, followed by Western blotting with anti-par antibody.

assay with PAR-specific antibody (fig. 4B). Then nuclear extracts from Jurkat cells were subjected to immunoprecipitation assay with anti-IRF1 antibody, subsequently underwent Western bloting assay using PAR-specific antibody. Results revealed that IRF1 could be immunoprecipitated with PAR-specific antibody, and vice versa (fig. 4C and 4D).

Then Jurkat cells were stimulated by $H_2O_2$, a well-known PARP1 activator. The poly(ADP-ribosly)ation levels of IRF1 in Jurkat cells were promoted by $H_2O_2$ (fig. 4E). All the evidence showed that IRF1 could be poly(ADP-ribosyl)ated by PARP1.

### 2.4 Inhibition of PARP1 Increased ISRE-directed Reporter Expression

In the nucleus, IRF1 directly binds to the interferon stimulated response elements (ISRE) in the promoters of target genes to regulate their transcription[12–15]. To explore the influence of PARP1 on IRF1-dependent transcriptional activities, ISRE-driven luciferase reporter was constructed. Jurkat cells were treated with PJ34 or transfected with IRF1 plasmids, and the transcriptional output of the ISRE-driven luciferase reporters was significantly promoted. $H_2O_2$ treatment or PARP1 plasmids transfection to Jurkat cells resulted in attenuated transcriptional output of ISRE-driven luciferase activity. Treatment with PJ34 could reverse the attenuation of luciferase activity in $H_2O_2$-stimulated cells (fig. 5). The data indicated that inhibition of PARP1 could increase IRF1-dependent transcriptional activities.

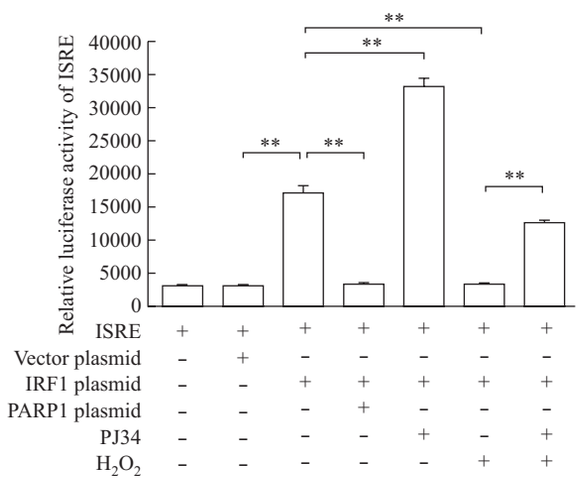


**Fig. 5** Inhibition of PARP1 increases ISRE directed reporter expression

ISRE-driven luciferase activity in Jurkat cells. Jurkat cells were treated with $H_2O_2$ (0.3 mmol/L) or PJ34 (10 μmol/L), or were transfected with empty vectors, IRF1 plasmids or PARP1 plasmids. Data represent mean±standard error. $^{**}P<0.01$

## 3 DISCUSSION

PARP1 is the dominant member of PARP family. It has been reported to interact with a variety of nuclear-located transcription factors and thereby alter their regulatory function[11, 16, 17]. IRF1 contains a highly conserved N-terminal DNA-binding domain and a carboxy-terminal portion of an IRF-association domain, which regulates the transcriptional activity of IRFs by mediating protein-protein interactions[18, 19]. In this study, we first examined the interaction between PARP1 and IRF1, and it was found that IRF1 could bind to PARP1 directly. Like many other nuclear proteins, IRF1 serves as integrating platforms for a variety of stimuli and is the target for post-translational modification, such as ubiquitination, sumoylation, acetylation and phosphorylation[20–23]. In the present study, we demonstrated that IRF1 could be poly(ADP-ribosyl)ated by PARP1. Poly(ADP-ribosyl)ation is an important post-transcriptional modification of protein catalyzed by PAPR enzymes, mainly by PARP1. Moreover, poly(ADP-ribosyl)ation decreased the DNA binding capacity of IRF1 and thus inhibited the transcription of its target genes in Jurkat cells. All our results illustrated that activation of PARP1 was critical

for Dex-induced IRF1 transcriptional repression in Jurkat cells.

IRFs constitute a family of regulator factors comprising 9 members (IRF1–9) in mammalian cells. IRF1, a member of the IRFs family, was originally identified as a regulator of the IFNβ promoter, but later recognized as also able to regulate gene transcription by binding to ISRE[24, 25]. Intensive functional analyses have revealed on this transcription factor a remarkable functional diversity. Once activated, IRF1 shaped the appropriate response by stimulating an overlapping but distinct set of target genes with antiviral functions, including PKR, but also immunomodulatory cytokines, such as IL-12, and genes that are important for antigen presentation, such as LMP2, could be regulated by IRF1. Inhibition of IRF1 by Dex may trigger a cascade of events that affect a wide range of immune responses via direct or indirect mechanisms. It has been reported that psychological and physical stressors could impair humoral and cell-mediated immunity by modulating the hypothalamic-pituitary-adrenal (HPA) axis and leading to increased glucocorticoid release, and subsequently inhibiting specific gene products directly on immune cells[19]. Our results showed that inhibition of PARP1 reversed Dex-induced repression of IRF1 target genes, indicating that the influence of Dex on IRF1 transactivation was mediated through the PARP1 pathway.

Interestingly, we observed that LMP2 mRNA level was still influenced by Dex slightly when IRF1 was knocked down, which was different from the expression of IL-12, OAS1 and PKR. LMP2 is a subunit of immunoproteasomes, which plays a prominent role in mediating the antimicrobial activity linked to IRF1[26, 27]. Recent studies revealed that LMP2 expression is dependent on the binding of a complex of signal transducer and activator of transcription 1 (STAT1) and IRF1 to the ISRE present in the LMP2 promoter[3, 28]. Whether PARP1 is involved in the function of STAT1 is currently unknown, so the mechanisms of regulation of LMP2 expression still need further investigations.

In summary, the data revealed a novel mechanism underlying IRF1 transactivation in Jurkat cells. PARP1 could bind to and poly(ADP-ribosyl)ate IRF1 in the nucleus. Poly(ADP-ribosly)ation of IRF1 by PARP1 decreases the DNA binding capacity of IRF1, and thereby inhibits IRF-dependent gene transcription. Inhibition of PARP1 reversed the Dex-induced suppression of IRF1 targeted genes. As a whole, these findings indicated that PAPR1 is a crucial regulator of IRF1-dependent gene transcription and modulation of IRF1 poly(ADP-ribosyl)ation might be exploited as an innovative immunomodulatory strategy. This study provides experimental evidence for the possible application of PARP1 inhibitors in the treatment of IRF1-related immune anergy.

**Conflict of Interest Statement**

The authors declare no conflict of interest.

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