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Ribosomal protein S3 interacts with TRADD to induce apoptosis through caspase dependent JNK activation

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ABSTRACT

It has been reported that ribosomal protein S3 (rpS3) functions as a ribosomal protein, a DNA repair endonuclease, a proapoptotic protein, and an essential subunit of the native NF-κB complex. However, it is unknown how rpS3 induces apoptosis in response to extracellular stresses. We report here that rpS3 sensitizes genotoxic stress-induced apoptosis by activating JNK through a caspase dependent manner. This apoptotic effect was shown to result from the physical interaction between rpS3 and TRADD, as assessed by coimmunoprecipitation. Moreover, GFP-rpS3 colocalized with TRADD around the plasma membrane and in the cytoplasm during apoptosis. Thus, rpS3 appears to be recruited to the death-inducing signaling complex (DISC) to induce apoptosis by interacting TRADD in response to extracellular stresses. Based on the findings of this study, we concluded that rpS3 is recruited to the DISC and plays a critical role in both genotoxic stress and cytokine induced apoptosis.

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1. Introduction

Mammalian cells defend against extra-cellular stresses by activating corresponding pathways that arrest the cell cycle and induce signals to facilitate repair or cell death. The failure of these processes results in severe genomic instability, which can cause cells to eventually become cancerous. In the event of irreversible DNA damage, cells respond by the induction of apoptosis. In most cells, triggering of apoptosis directly activates caspase-8, which leads to the activation of other caspases, such as caspase-3 [1]. An alternative pathway that performs the downstream events of apoptosis is the MAP kinase cascade, which involves JNK/SAPK [2]. Also, cell cycle arrest after DNA damage allows time for the cell to repair DNA lesions [3]; thus, DNA damage-induced apoptosis seems to protect organisms from cancer generation.

Apoptosis also plays a central role both in development and in immune responses. In the case of necessity, an organism eliminates individual cells that threaten its survival using death signals. Cytokines, such as Fas ligand and TNFα, can be used as death signals and bind to death receptors at the surface of a target cell, which transmits apoptosis signals [4]. Subsequently, the adaptor protein TNFR-associated death domain (TRADD) binds to the receptor death domain and recruits signal molecules, such as Fas-associated death domain (FADD), TNFR-associated factor-2 (TRAF2), and receptor-interacting protein (RIP). TRAF2 and RIP stimulate the activation of NF-κB and JNK, whereas FADD activates the caspases pathway [5].

The ribosome is a large ribonucleoprotein complex responsible for translation of the transcribed mRNA. It is well known that ribosomes consist of a large and a small subunit and the small subunit mediates the association between mRNA and tRNAs [6]. Several ribosomal proteins have also been found to play various extraribosomal functions, including induction of apoptosis [7–9], suppression of tumors [10], and DNA repair [11,12]. Interestingly, rpS3 was identified in the NF-κB complex by a proteomic screen and was shown to be an integral subunit of NF-κB [13]. rpS3 interacts with Rel dimers to form the NF-κB complex through its heterogeneous nuclear protein K (hnRNP K) homology (KH) domain and subsequently regulates NF-κB DNA-binding affinity and specificity of target gene transcription. In addition, rpS3 is also involved in cytokine induced apoptosis [14]. Several post-translational modifications, such as phosphorylation [15–17], methylation [18], and SUMOylation [19], regulate the extraribosomal functions of rpS3 under different conditions. However, at present, the mechanism by which rpS3 function is regulated in DNA repair, apoptosis and immune response is still unknown.

In this study, we demonstrate that rpS3 sensitizes apoptosis under stress conditions by activating JNK/SAPK, which is dependent on caspase activation. Mechanistically, rpS3 associates with TRADD in TNFR1 DISC to induce apoptosis. These data suggest that pS3 is a new component in DISC and is involved in the stress induced apoptosis pathway.

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2. Materials and methods

2.1. Plasmids

rpS3 was subcloned into the pEGFP-C1 vector (CLONTECH) in frame with GFP (green fluorescence protein), generating GFP-rpS3 fused with the GFP gene. The pRK5 and pcDNA3 vector (Invitrogen) were used for expression of TRADD and FADD, respectively.

2.2. Cell culture and transfection

293T cells were cultured on 10 cm plates in Dulbecco's modified Eagle's media (DMEM), supplemented with 10% fetal bovine serum (GIBCO-BRL). Jurkat human T cells were cultured in RPMI, supplemented with 10% fetal bovine serum (GIBCO-BRL). Cells were transfected using SuperFect Transfection Reagent (Quiagen), and lysed in lysis buffer containing 50 mM Tris–HCl (pH 7.5), 150 mM NaCl, 1% Nonidet P-40, 0.5% sodium deoxycholate and protease inhibitors (1 μg/ml pepstatin, 1 μg/ml PMSF, 5 μg/ml leupeptin, 10 μg/ml aprotinin) and sonicated briefly, followed by immunoblotting.

2.3. Antibodies and immunoblot analysis

Monoclonal antibodies against GFP-epitope (Roche), FADD (Stressgene), TRADD (Santa Cruz Biotechnology) and caspase-3 (Santa Cruz Biotechnology) were used for immunoblot analysis. Polyclonal antibodies against human rpS3 were purchased from BioInstitute, Korea University.

Cell extracts were lysed in the lysis buffer containing 50 mM Tris–HCl (pH 7.5), 150 mM NaCl, 1% Nonidet P-40, 0.5% sodium deoxycholate and protease inhibitors (1 μg/ml pepstatin, 1 μg/ml PMSF, 5 μg/ml leupeptin, 10 μg/ml aprotinin). Lysates were sonicated briefly and cleared by centrifugation. Proteins from total cell lysate were electrophoresed on 12% SDS–PAGE and transferred to a nitrocellulose membrane (Bio-Rad). Immunoblotting was performed using a chemiluminescence blotting substrate (Roche). Horseradish peroxidase conjugated anti-mouse IgG and anti-rabbit IgG (Roche) were used as secondary antibodies.

2.4. Immunocytochemistry

Jurkat cells were transfected with GFP or GFP-rpS3. Twenty-six hours later, the cells were fixed with 3.7% paraformaldehyde in PBS for 30 min and permeabilized with 0.1% Triton X-100 in PBS for 10 min at room temperature. The cells were then incubated with rabbit anti-TRADD or mouse anti-FADD antibodies for 1 h at room temperature. The cells, which were plated on slides (Beckton Dickinson), were then stained with goat anti-rabbit or anti-mouse secondary antibodies conjugated with Texas Red (Jackson). Images were acquired using a Zeiss LSM510 confocal microscope (Carl Zeiss) with a 40× objective.

2.5. Detection of apoptosis

For microscopic observation of apoptotic cells, Jurkat cells plated on 6 cm plates were transiently transfected with pEGFP-C1 and other GFP fusion vectors using SuperFect (Quiagen). Twenty-eight hours after transfection, apoptotic cells were counted under a fluorescence microscope (Carl Zeiss).

3. Results and discussion

3.1. rpS3 is involved in DNA damage induced apoptosis

Transcriptional activation of p53 has been demonstrated to play a key role in the early responses induced by DNA damage [20]. Previous studies on rpS3 have indicated existence of alternative defense responses against DNA damage, since rpS3 itself was shown to display DNA repair activity. Thus, we examined the effect of rpS3 on apoptosis induced by adriamycin or UV-irradiation. Interestingly, rpS3 overexpression increased apoptosis even under low dose UV-irradiation, which did not trigger apoptosis in normal cells (Fig. 1A). These findings indicate that rpS3 overexpression increases sensitivity to DNA damage and implies that rpS3-induced apoptosis involves not only cytokine-induced apoptosis [14] but also DNA damage-induced apoptosis. An enhanced sensitivity similar to that found in UV-irradiation was observed when cells were treated with adriamycin (Fig. 1A). In addition to its involvement in the repair of single-strand DNA breaks at AP sites [11], rpS3 is also likely to be involved in apoptosis triggered by single- or double-strand DNA breaks.

In response to UV radiation or other DNA damage, ATR triggers the JNK pathway, which plays a central role in extrinsic apoptotic pathways initiated by death receptors and intrinsic apoptotic pathways initiated by mitochondrial events [21]. To determine whether the proapoptotic ability of rpS3 is related to the JNK pathway, cells were transfected with GFP-rpS3 and then the kinase activity of anti-JNK immunoprecipitate was analyzed using an *in vitro* kinase assay. As shown in Fig. 1B, rpS3 expression enhanced the JNK activity by 10-fold, indicating that rpS3 uses JNK, in addition to caspase, as a downstream executor in rpS3-induced apoptosis. Taken together, rpS3 was shown to be a pivotal protein for JNK activation and subsequent apoptosis during DNA damage-induced apoptosis.

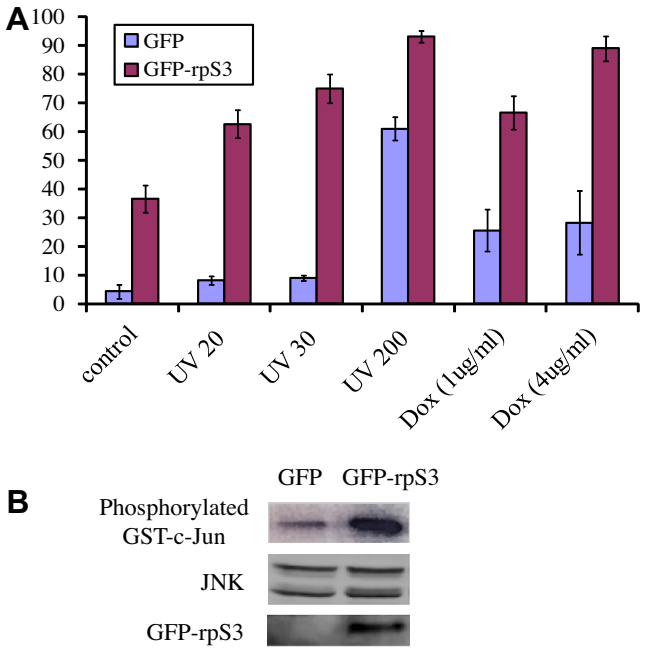

Fig. 1. rpS3 sensitizes genotoxic stress induced apoptosis through JNK activation. (A) Jurkat cells were transfected with the GFP-rpS3 or control plasmid (pEGFP-C1) and treated with UV or adriamycin. Twenty-four hours after UV radiation, cells were fixed, stained with DAPI and apoptotic cells were counted under a fluorescence microscope. Cells were treated with adriamycin for 4 h. The data shown are the average of three independent experiments. (B) Jurkat cells were transiently transfected with the GFP-rpS3 or control plasmid (pEGFP-C1). After 26 h, the kinase activities of immunoprecipitated endogenous JNKs were measured using appropriate exogenous substrates (GST-junN79) as indicated.

3.2. Caspase cascade is linked to JNK pathway in rpS3-induced apoptosis

It was proposed that the cleavage of MEKK-1 by caspase is required for its activation, which can stimulate the JNK pathway and apoptosis [22], and that Fas-induced JNK activation id needed for the activation of caspases [23,24]. Previously, we reported that rpS3 activates the caspase cascade for induction of apoptosis [14]. Consistent with this previous work, rpS3 overexpression reduced the level of inactive caspase-3, while the inactive form was recovered by zDEAD-fmk and zIETD-fmk, which are caspase-3 and caspase-8 inhibitors, indicating that rpS3 acts upstream of the caspase-8/caspase-3 pathway (Fig. 2A). To further analyze the relationship between the caspase cascade and JNK pathway during rpS3-induced apoptosis, we performed an *in vitro* kinase assay after treatment with caspase inhibitors. As shown in Fig. 2B, rpS3-induced JNK activation was diminished by pretreatment with zDEVD-fmk and zIETD-fmk. This indicates that there is cross-talk between the caspase cascade and JNK pathway, and JNK appears to act as a downstream effector when rpS3 induces apoptosis. Taken together, these results suggest that rpS3 acts upstream of caspase-8, followed by activation of caspase-3 and JNK, which conveys the apoptotic signal to downstream molecules.

3.3. rpS3 colocalizes with proteins in DISC

It was previously reported that rpS3 also sensitizes cytokine-induced apoptosis [14,25]. Therefore, we tested whether rpS3 is involved in the signal transduction of cytokine-mediated apoptosis, which has been extensively investigated as a model of programmed cell death mediated by caspases-8 and -3. Fas ligand or TNFα triggers downstream death signals by trimerization of TNFR, which induces the association of death domains and recruitment of TNFR-binding molecules, including TRADD, TRAF2, RIP, FADD/MORT1, caspase-8 and caspase-3 [26,27]. To examine the subcellular localization of rpS3 and death effecter proteins, cells were transfected with plasmids containing GFP or GFP-rpS3. As previously reported, FADD and TRADD were mainly detected in the cytoplasm. Interestingly, GFP-rpS3 was colocalized with TRADD and FADD around the plasma membrane (Fig. 3A and B). Furthermore, in apoptotic cells, GFP-rpS3 was colocalized with FADD and TRADD in the cytoplasm (Fig. 3A and B, lower panels), suggesting that rpS3 is recruited to DISC and seems to induce apoptosis by activating the caspase and JNK pathway.

3.4. rpS3 interacts with TRADD under UV radiation

To determine whether rpS3 interacts with TRADD, 293T cells were transfected with plasmids containing GFP-rpS3 and TRADD. In the immunoprecipitation experiment with anti-TRADD or anti-FADD antibody, we demonstrated that GFP-rpS3 binds strongly to TRADD (Fig. 4A), whereas only low levels of GFP-rpS3 bound to FADD (Fig. 4B). We then performed immunoprecipitation experiments using an antibody against TRADD in UV-irradiated cells to verify that rpS3 plays a role in the TNFR1 DISC by activating downstream molecules under UV-irradiation. Immunoprecipitation of endogenous TRADD revealed that TRADD and rpS3 interacted under UV-irradiation (Fig. 4C), suggesting that rpS3 is recruited to TNFR1 DISC for induction of apoptosis after exposure to extracellular stresses. These results indicate that rpS3 is a new component of TNFR1 DISC and the interaction between rpS3 with TRADD

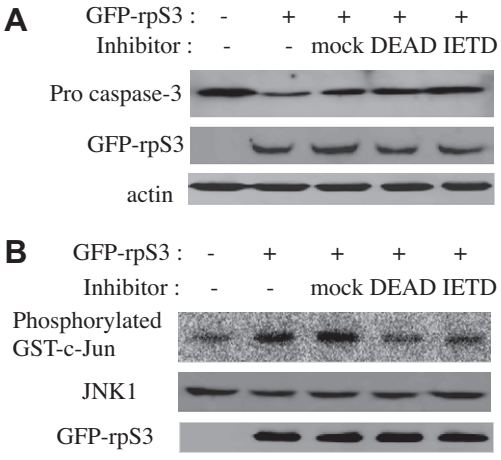

Fig. 2. rpS3 activates JNK in caspase dependent manner. Jurkat cells were transfected with pEGFP-rpS3 (GFP-rpS3). Three hours after transfection, cells were treated with DMSO carrier (mock) or Z-DEVD or Z-IETD. (A) Following inhibition of caspase-3 and caspase-8 for 23 h, Jurkat cell lysates were subjected to immunoblotting (IB) with antibodies to the indicated proteins. The position of the 32-kDa pro-caspase-3 precursor is indicated. (B) Twenty-six hours after transfection, the kinase activity of endogenous immunoprecipitated JNK was measured as described in Fig. 1A. The expression level of JNK was monitored by anti-JNK immunoblotting.

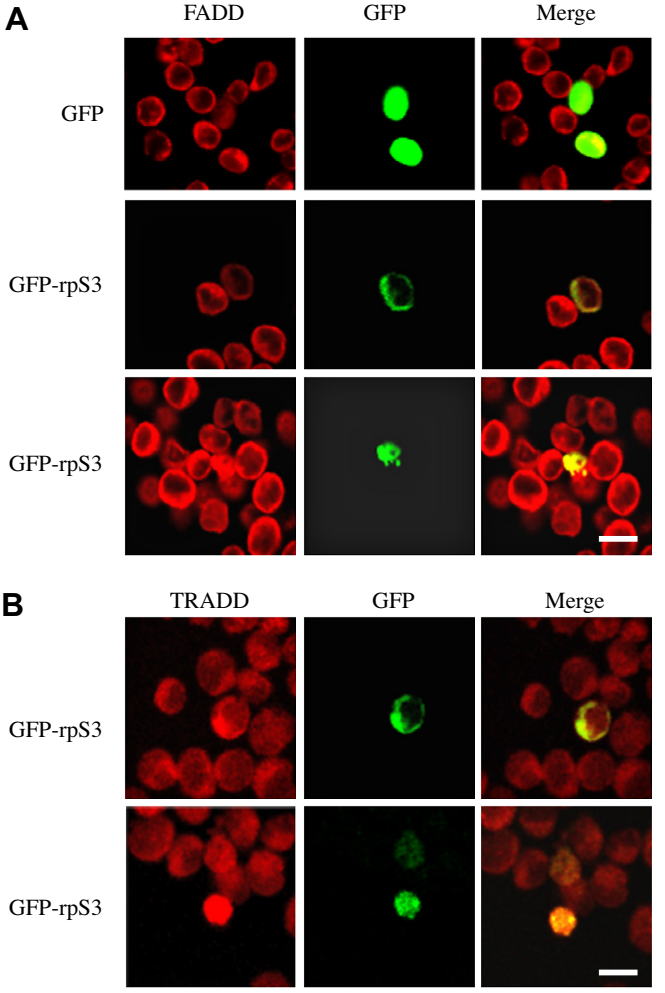

Fig. 3. rpS3 colocalizes with FADD and TRADD. (A and B) Jurkat cells were transfected with GFP alone or GFP-fused rpS3 protein expression vectors. Twenty-four hours after transfection, cells were fixed with paraformaldehyde and subjected to immunofluorescence analysis using anti-TRADD polyclonal antibodies (A) and anti-FADD monoclonal antibodies (B). Images show representative cells that were detected by GFP (green) and stained for TRADD or FADD (red). Scale bars, 10 μm. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this paper.)

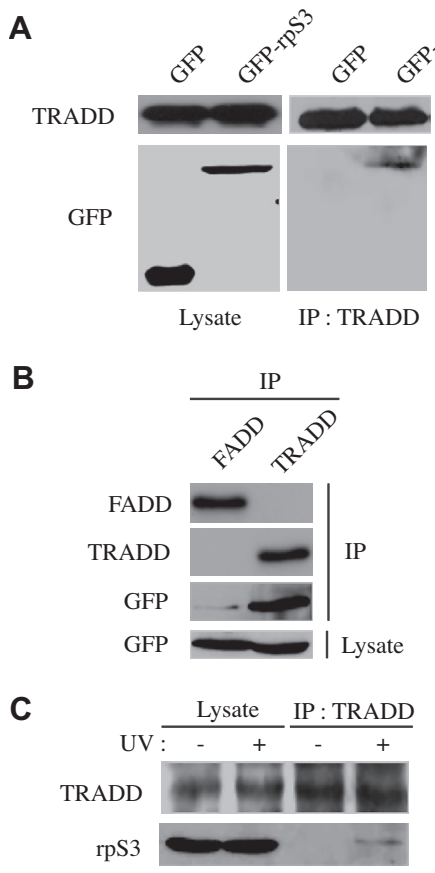

Fig. 4. rpS3 is associated with TRADD under UV-irradiation. (A) 293T cells were cotransfected with GFP-rpS3 and TRADD. After 24 h, cell lysates were immunoprecipitated with anti-TRADD antibody and subjected to immunoblot analysis using the indicated antibodies. (B) Twenty-four hours after cotransfection of GFP-rpS3 with TRADD or FADD, the cell lysates were immunoprecipitated with antibodies to TRADD or FADD and subjected to immunoblotting with the indicated antibodies. (C) 293T cells were exposed to UV (200 J/m^2). Four hours after UV-irradiation, cell lysates were immunoprecipitated with anti-TRADD antibody and subjected to immunoblot analysis using the indicated antibodies.

followed by recruitment of FADD appears to activate the downstream apoptosis pathway.

Apoptosis and DNA repair are the major mechanisms used to protect eukaryotic cells from intrinsic and extrinsic stresses. In addition, cell cycle arrest in response to DNA damage gives cells the time to repair the damage [3]. These pathways are modulated to maximize cellular and organismic survival, while minimizing the chance of carcinogenesis. Death receptors, which transmit apoptotic signals induced by specific death ligands, play a central role in the extrinsic apoptotic pathway. These receptors can activate caspases through trimerization of the intracellular death domain, which is critical for the recruitment of adaptor molecules, including TRADD, FADD, RIP, and TRAF2 to initiate caspase activation [4]. When cells are exposed to genotoxic stress, the DNA damage response is initiated and propagated by DNA-PK, p53 and other kinases, including p38 MAPK, c-jun N-terminal kinase (JNK), PKA, PKB and Akt [2]. Here, we provide evidence that rpS3 is indispensable for JNK activation under genotoxic stress. We also demonstrate that rpS3 interacts with TRADD. Thus, the apoptotic signal caused by DNA damage or cytokines might lead rpS3 to the TNFR1 DISC by interacting with TRADD, and then sequentially activate caspases and JNK pathways. These findings indicate that rpS3 plays a pivotal role in both genotoxic stress and cytokine induced apoptosis. However, the correlation of rpS3 in DISC and NF-κB complex is still unknown.

Recent studies have reported that a mismatch repair system is involved in the signaling of DNA damage triggered apoptosis induced by alkylating agents and chemical carcinogens [28,29]. Furthermore, it has also been reported that histone acetylase TIP60 functions as a signaling mediator, informing the apoptotic machinery about the existence of damaged DNA [30]. Even-though it has been proposed that the DNA repair machinery is responsible for DNA damage-induced apoptosis [31], the precise mechanism behind this response has not yet been established. Our finding that rpS3 induces apoptosis by interacting with TRADD directly links two pathways that were previously thought to be indirectly related: DNA damage processing and DNA damage-induced apoptosis. Our study also showed that the rpS3 protein induces programmed cell death through activation of caspase-8 and caspase-3 as well as the JNK pathway, indicating that a DNA repair enzyme itself is the major determinant of cell fate in response to DNA damage. In conclusion, this study demonstrates that translation, DNA repair and apoptosis are interrelated by a common denominator, rpS3, which is likely to determine the fate of a damaged cell.

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