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Tollip negatively regulates mitophagy by promoting the mitochondrial processing and cytoplasmic release of PINK1

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PTEN-induced putative kinase 1 (PINK1) is a serine/threonine kinase that phosphorylates several substrates and exerts neuroprotective effects against stress-induced apoptotic cell death. Mutations in PINK1 have been linked to autosomal recessive forms of Parkinson's disease (PD). Mitophagy is a type of autophagy that selectively promotes mitochondrial turnover and prevents the accumulation of dysfunctional mitochondria to maintain cellular homeostasis. Toll-interacting protein (Tollip) was initially identified as a negative regulator of IL-1β receptor signaling, suppressing inflammatory TLR signaling cascades. Recently, Tollip has been reported to play a role in autophagy and is implicated in neurodegeneration. In this study, we determined whether Tollip was functionally linked to PINK1-mediated mitophagy. Our results demonstrated that Tollip promoted the mitochondrial processing of PINK1 and altered the localization of PINK1, predominantly to the cytosol. This action was attributed to increased binding of PINK1 to mitochondrial processing peptidase β (MPPβ) and the subsequent increase in MPPβ-mediated mitochondrial PINK1 cleavage. Furthermore, Tollip suppressed mitophagy following carbonyl cyanide *m*-chlorophenylhydrazone-induced mitochondrial dysfunction. These findings suggest that Tollip inhibits mitophagy via the PINK1/parkin pathway upon mitochondrial damage, leading to the blockade of PINK1-mediated neuroprotection. [BMB Reports 2022; 55(10): 494-499]

INTRODUCTION

A hallmark of Parkinson's disease (PD) is the slow and gradual degeneration of dopaminergic neurons in the substantia nigra (1). Although the cause of neurological loss in PD was not well known, several genetic mutations related to familial PD have been discovered, including in *SNCA*, *PINK1*, *PARK2*, *LRRK2*, *PARK7*, and *FBXO7* (2). Recent findings suggest that inadequate mitochondrial quality control is implicated in the pathogenesis of PD and that PINK1 and E3 ligase parkin play an important role in mitophagy, which is a selective autophagy of mitochondria that eliminates damaged mitochondria (3). Since PINK1 has a mitochondrial targeting sequence, it migrates into the mitochondria through the TOM and TIM complex immediately after being synthesized in the cytosol (4). The translocated PINK1 is then consecutively processed by mitochondrial proteases like MPP and PARL (5, 6). The processed cytosolic PINK1 is then targeted to the N-end rule pathway (7) and ultimately degraded by the proteasome (8, 9).

Mitophagy is a complexly controlled process in which cells break down defective mitochondria to maintain a mitochondria population. When the mitochondrial membrane potential is depleted, PINK1 accumulates on the outer membrane (OMM) and forms a large complex with parkin on the OMM surface (10). Parkin phosphorylated by PINK1 (11, 12) links ubiquitin chains to various substrates on the mitochondria. These ubiquitinated proteins can act as adaptors to sequestosome-1 (SQSTM1 or p62) and facilitate the removal of defective mitochondria by autophagosome (13). The ubiquitination of substrates is delicately controlled by the ubiquitin proteasome system (UPS) and deubiquitin proteases (DUBs), and dysfuction of UPS and DUBs is directly related to PD (14).

Toll-like receptors (TLRs) are evolutionarily conserved receptor groups that induce interleukins and other inflammatory proteins to cause inflammatory reactions (15). In TLR signaling cascades, adaptor protein Tollip acts as an inhibitory factor (16-18). When stimulated by IL-1 or LPS, Tollip forms a complex with IL-1 receptor (IL-1R) and IRAK1 and suppresses the kinase activity of IRAK1 (19). We previously found a new mechanism for PINK1-mediated regulation of TAK1 and TRAF6 activation during sequential inflammatory signal cascades (20). In addition, we further clarified that PINK1 binds directly to Tollip and IRAK1 under IL-1β stimulation and accelerates the separation of Tollip from IRAK1, ultimately promoting IL-1β-mediated inflammatory signals (21). Interestingly, Tollip has recently been reported to play a role in autophagy and its alteration is implicated in neurodegeneration, such as in Alzheimer's disease (22, 23) and Huntington's disease (24). Tollip plays an important role in the autophagic clearance of cytotoxic protein aggregates by linking ubiquitin-modified protein aggregates to autophagosome (24). Based on these findings, it is probable that Tollip somehow

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affects PINK1 function within the mitochondria, possibly affecting PINK1-mediated mitophagy.

In the present study, we investigated the effect of Tollip on PINK1-mediated mitophagy following mitochondrial depolarization. We found that Tollip suppressed mitophagy by increasing mitochondrial processing of PINK1 and the release of cleaved PINK1 into the cytosol. These results suggest that Tollip negatively regulates mitophagy by affecting the PINK1 processing.

RESULTS

PINK1 binds to Tollip in mammalian cells

To investigate the regulatory role of Tollip in mitophagy, we examined whether PINK1 binds to Tollip in mammalian cells. Ectopically overexpressed PINK1 was bound to Tollip in HEK293 cells (Supplementary Fig. 1A), and the binding between endogenous PINK1 and Tollip in human neuroblastoma SH-SY5Y cells was also confirmed (Supplementary Fig. 1B). In addition, endogenous Tollip and PINK1 was colocalized primarily outside the nuclei of SH-SY5Y cells (Supplementary Fig. 1C). These data suggest that PINK1 binds to Tollip in a specific way, and this binding mainly occurs in the cytosolic area.

Tollip increases cytosolic processing of mitochondrial PINK1

As shown in Supplementary Fig. 1A, co-transfection of Tollip and PINK1 resulted in a noticeable increase in the level of cleaved PINK1 accompanied by a decrease of the larger precursor PINK1 form compared with that of cells transfected with PINK1 alone. Based on this finding, we hypothesized that Tollip may affect PINK1 processing, thereby enhancing the mitochondrial processing of PINK1 and consequently leading to the accumulation of cleaved PINK1 in the cytosol. The cleavage of exogenous PINK1 was significantly increased in a dose-dependent manner by exogenous Tollip (Supplementary Fig. 2A). Also, the increase in the extent of PINK1 cleavage induced by Tollip was not recovered by MG132 treatment (Supplementary Fig. 2B, C), indicating that Tollip affected the cleavage of PINK1, but not its degradation through the proteasome machinery. This finding was further confirmed by comparing the relative levels of PINK1 in *Tollip*-null and control MEFs (Supplementary Fig. 2D). When treated with CCCP, full-length PINK1 level was increased in both $Tollip^{+/+}$ MEF and $Tollip^{-/-}$ MEF cells (Supplementary Fig. 2D, E). However, the amount of full-length PINK1 in $Tollip^{+/+}$ MEFs was markedly reduced compared with that in $Tollip^{-/-}$ MEFs. These results indicate that Tollip increases the mitochondrial processing of PINK1 in mammalian cells.

Tollip alters PINK1 intracellular localization to the cytosol.

The cleavage of PINK1 is closely related to its subcellular localization (8). Co-expression of PINK1 and Tollip increased cleaved PINK1 levels in the cytosol fraction compared to PINK1 alone (Fig. 1A). In addition, Tollip overexpression in cells treated with MG132 also caused increased levels of cleaved endogenous PINK1 within the cytosol fraction (Fig. 1B). Moreover, the amount of full-length PINK1 was markedly increased in the cell fraction containing membrane organelles, whereas cleaved PINK1 level was reduced in the cytosol of cells transfected with *Tollip*-specific siRNA (Fig. 1C). We also compared the intracellular localization of PINK1 in $Tollip^{-/-}$ and control $Tollip^{+/+}$ MEFs. Tollip induced a marked increase in cytosolic PINK1 levels, which had an equivalent loss in mitochondrial PINK1 levels (Fig. 1D). Overall, these data indicate that Tollip played an important role in the modulation of PINK1 cleavage and localization.

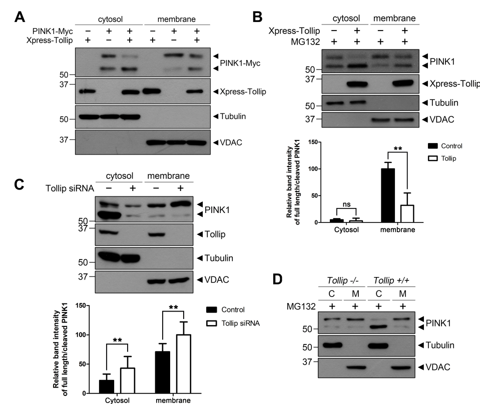

Fig. 1. Tollip alters the intracellular location of PINK1 to the cytosol. (A, B) HEK293 cells were transfected for 48 h with a plasmid encoding Xpress-Tollip (B) or/and Myc-PINK1 (A). The resulting cell lysates were separated into cytosolic and membrane organelle fractions. (C) HEK293 cells were mock-transfected or transfected for 48 h with *Tollip*-siRNA and treated with 10 μM MG132 for 4 h. Cell lysates were separated into cytosolic and the mitochondrial fractions. (D) $Tollip^{+/+}$ and $Tollip^{-/-}$ MEFs were treated with 10 μM MG132 and separated into cytosolic and the mitochondrial fractions. All data in the graphs are presented as the mean ± SEM of three independent experiments (**P ≤ 0.01; B, C).

Tollip promotes PINK1 binding to MPPβ, inducing PINK1 cleavage

It is widely known that MPP and PARL are involved in the mitochondrial processing of PINK1 through sequential proteolytic cleavage (5, 6). We previously reported that hTERT inhibits the processing of mitochondrial PINK1 and its cytoplasmic release, positively affecting mitophagy (25), which is in contrast to the role of Tollip. Based on these previous findings, we aimed to determine whether a similar mechanism may apply to the Tollip-mediated increase in PINK1 processing. Ectopically expressed MPPβ physically bound to Tollip (Supplementary Fig. 3A). In addition, Tollip overexpression markedly increased the binding affinity between PINK1 and MPPβ (Supplementary Fig. 3B). Conversely, the binding of PINK1 to MPPβ decreased in *Tollip* siRNA-transfected cells (Supplementary Fig. 3C). These data indicate that Tollip increases the processing of mitochondrial PINK1 by enhancing the interaction between PINK1 and MPPβ, which may consequently promote the MPP-mediated

cleavage of PINK1.

Tollip decreases autophagy and mitophagy marker levels

We investigated whether Tollip-mediated increases in mitochondrial PINK1 cleavage and its cytoplasmic release led to reduced mitophagy rates. CCCP treatment increased levels of LC3-II, the secondary form of autophagy marker LC3, while the accumulation of LC3-II was significantly decreased with Tollip overexpression (Fig. 2A). In addition, Tollip had a negative effect on the formation of endogenous LC3-II, similar to that observed when LC3 was added exogenously (Fig. 2B). CCCP treatment increased LC3-II formation in both *Tollip*$^{-/-}$ and *Tollip*$^{+/+}$ MEFs, but the band intensity of LC3-II in *Tollip*$^{+/+}$ MEFs was significantly lower than that in *Tollip*$^{-/-}$ MEFs (Fig. 2C). Furthermore, although the formation of LC3-II was considerably decreased by Tollip in *PINK1*$^{+/+}$ MEFs, there was no comparable change in *PINK1*$^{-/-}$ MEFs (Fig. 2D), suggesting an essential role in PINK1 triggering autophagy.

The protein BNIP3L is also commonly used as a marker of mitophagy (26). Tollip overexpression decreased endogenous BNIP3L levels, comparable to the outcome observed in LC3-II (Fig. 2E). Collectively, these data indicate that Tollip promotes PINK1 cleavage, thereby negatively modulating the levels of autophagy and mitophagy markers.

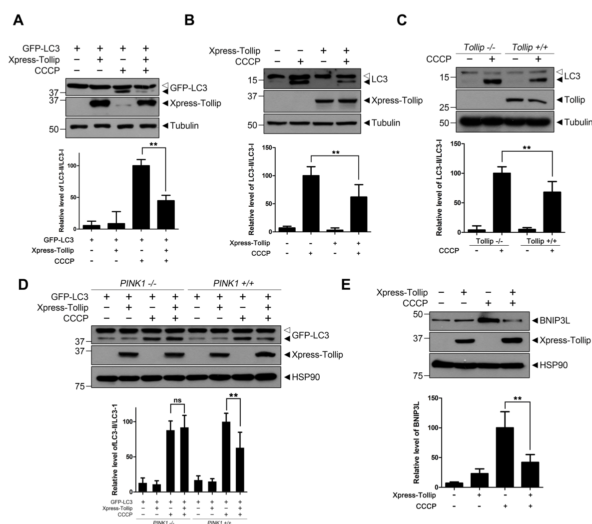

Fig. 2. Tollip decreases expression of the autophagy marker LC3 and mitophagy marker BNIP3L. (A, B) HEK293 cells were transfected for 48 h with a plasmid encoding GFP-LC3 alone or together with Xpress-Tollip. Cells were then treated with 10 μM CCCP for 4 h. (C) *Tollip*$^{+/+}$ and *Tollip*$^{-/-}$ MEFs were treated with vehicle or 10 μM CCCP for 4 h. (D) *PINK1*$^{+/+}$ and *PINK1*$^{-/-}$ MEFs were transfected for 48 h with a plasmid encoding GFP-LC3 alone or in combination with Xpress-Tollip, and treated 10 μM CCCP for 4 h. (E) HEK293 cells were transfected for 48 h with a plasmid encoding Xpress-Tollip. All data in the graphs are presented as the mean ± SEM of three independent experiments (**P ≤ 0.01; A-E).

Tollip decreases PINK1 interaction with TOM20 and parkin after CCCP treatment

We investigated whether the PINK1-binding to both TOM20 and parkin could be affected by Tollip. As shown in Fig. 3A and B, the interaction between PINK1 and TOM20/parkin were all increased under CCCP treatment. The binding affinity of PINK1 to these two proteins was significantly decreased by the co-expression of Tollip. Under CCCP treatment the binding of PINK1 to TOM20 was also significantly increased by knockdown of endogenous Tollip (Fig. 3C). Moreover, PINK1 binding to TOM20 was stronger in *Tollip*$^{-/-}$ MEFs compared with that in *Tollip*$^{+/+}$ MEFs (Fig. 3D). These data indicate that Tollip decreases the tight binding of PINK1 to parkin, as well as to TOM20, following CCCP treatment.

Tollip suppresses CCCP-induced mitophagy and disrupts mitochondrial functions

Finally, we investigated whether Tollip would inhibit mitophagy and eliminate damaged mitochondria. As shown in Fig. 4A, Tollip overexpression resulted in reduced rates of mitophagy,

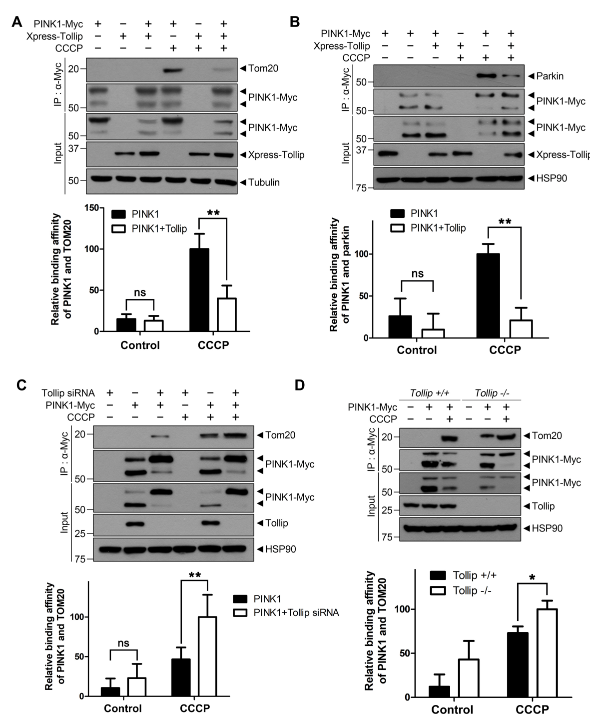

Fig. 3. Tollip decreases the interaction of PINK1 with TOM20 and parkin after treatment with CCCP. (A-C) HEK293 cells were transfected for 48 h with a plasmid encoding Myc-PINK1 or Xpress-Tollip (A, B), Myc-PINK1, or *Tollip*-siRNA, alone or in combination (C). Cells were then treated for 4 h with 10 μM CCCP. (D) *Tollip*$^{+/+}$ and *Tollip*$^{-/-}$ MEFs were transfected for 48 h with a plasmid encoding Myc-PINK1 and treated for an additional 4 h with 10 μM CCCP. All data in the graphs are presented as the mean ± SEM of three independent experiments (**P ≤ 0.01; A-C, *P ≤ 0.05; D).

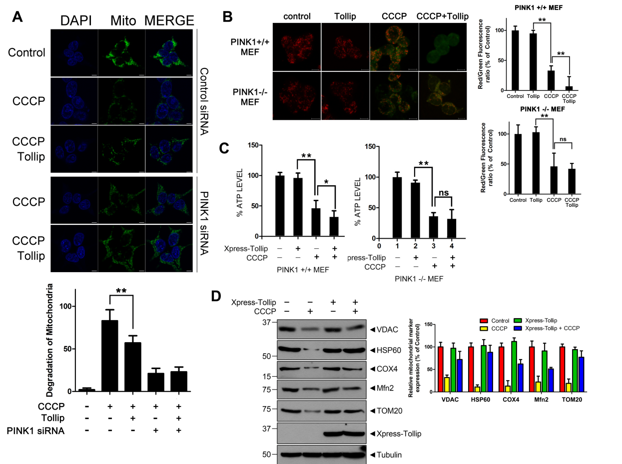

Fig. 4. Tollip suppress CCCP-induced mitophagy. (A) HeLa cells overexpressing wild-type parkin were transfected with wild-type Tollip, scrambled siRNA (control siRNA), and/or *PINK1*-siRNA for 24 h and then treated with either DMSO (control) or 20 μM CCCP for an additional 24 h. Scale bar = 10 μm. Mitochondrial loss in each cell type was quantified (bottom graph, $^{**}P \leq 0.01$). (B) $PINK1^{+/+}$ and $PINK1^{-/-}$ MEFs were mock-transfected or transfected for 24 h with Xpress-Tollip and treated with DMSO or 20 μM CCCP for 4 h. Mitochondrial membrane potential of each sample was then evaluated using JC-1 staining. Scale bar = 10 μm. (C) $PINK1^{+/+}$ and $PINK1^{-/-}$ MEFs were mock-transfected or transfected with Xpress-Tollip for 24 h, followed by treatment with DMSO or 20 μM CCCP for 72 h. The level of ATP in each sample was then measured using an ATP Determination Kit. (D) SH-SY5Y cells were either mock-transfected or transfected with Xpress-Tollip for 24 h and then treated with 10 μM CCCP for 4 h.

but it was not shown in *PINK1*-knockdown cells. CCCP treatment triggered mitochondrial depolarization, while Tollip overexpression exacerbated the CCCP-induced loss of ΔΨm in $PINK1^{+/+}$ MEFs (Fig. 4B). Further, reduction of intracellular ATP induced by CCCP was exacerbated by Tollip 72 h after CCCP treatment (Fig. 4C). Because mitochondrial biogenesis is closely associated with the process of proper mitophagy and the removal of damaged mitochondria, it was expected that Tollip could also suppress mitophagy, resulting in a decrease in mitochondrial biogenesis and ATP production. Finally, we investigated whether Tollip affected the levels of typical mitochondrial proteins under CCCP treatment and its potential mechanism. Overexpression of Tollip followed by CCCP treatment rescued the decreased mitochondrial protein levels, restoring them to that of cells undergoing CCCP treatment alone. (Fig. 4D). In conclusion, the present study proposes that Tollip acts as a novel regulator of PINK1 processing and decreases mitophagy in response to mitochondrial damage caused by CCCP.

DISCUSSION

Mitophagy plays an important role in the quality control of mitochondria and serves as the major process for maintaining mitochondrial network homeostasis (3). Mitochondrial dysfunction can induce autophagy-dependent cell death (27), and mitophagy protects cells from mitotoxicity by removing damaged mitochondria. Various mutations in *PINK1* gene are associated with autosomal recessive early onset PD, and mitochondrial dysfunction has been observed in PINK1-null animal model (28). PINK1, along with parkin, plays an important role in the execution and regulation of mitophagy (29). Although the sequential events of PINK1 activation and its regulatory function in mitophagy are well known, the regulators controlling the binding between PINK1 and these targets are unclear.

PINK1 is also involved in the inflammatory signaling pathway of IL-1β by upregulating the components of TRAF6 and TAK1 (20). Furthermore, PINK1 positively modulates the interaction between Tollip and IRAK1, promoting IL-1β-mediated signaling (21). The modulatory function of PINK1 in the mitochondria is also associated with the components of the neuroinflammatory signaling cascade, such as TRAF6. PINK1 stabilization on damaged mitochondria requires TRAF6-mediated and Lys63-linked ubiquitination of PINK1 and the complex formation with SARM1 and TRAF6 (30).

Many recent studies have demonstrated a crucial role of Tollip in the progression and control of autophagy. Tollip also acts as a core regulator of endosomal compartment and regulates cargo trafficking by interacting with the TOM1 (31). Closely associated with these functions, Tollip has been implicated in many neurodegenerative diseases. For example, Tollip is associated with autophagic dysfunction in Alzheimer's disease (22, 23). Moreover, autophagic clearance of Huntington's disease-related polyQ protein is regulated by Tollip (24) and Tollip mediates parkin-dependent trafficking of mitochondrial-derived vesicles (MDV) (32). Based on these findings, we explored the possible effects of Tollip on mitophagy. Our findings displayed that Tollip increases the cleavage of mitochondrial PINK1 and its cytosolic release, resulting in the negative regulation of mitophagy.

MPP and PARL are two mitochondrial proteases involved in sequential processing of PINK1 (5). Mutations in MPP and PARL result in dysfunction of proper processing of many mitochondrial proteins, consequently resulting in various mitochondria-related diseases (33). Here, we demonstrated that Tollip directly binds to MPPβ and promotes the interaction of PINK1 and MPPβ, facilitating the cytosolic release of cleaved PINK1.

As described previously, the cleavage status of PINK1 is important for activation of the PINK1/parkin pathway. Since only full-length PINK1 can induce parkin recruitment and subsequent recruitment of autophagy adapters and LC3-II, we hypothesized that enhanced cleavage of PINK1 by Tollip may be linked with a decrease in mitophagy levels. Our hypothesis was supported by the finding that Tollip markedly reduces the formation of LC3-II and the amount of BNIP3L.

Considering the role of PINK1 in mitophagy, elucidation of the underlying mechanisms of PINK1 cleavage and stability

are very important. Although many studies have investigated the subcellular localization of PINK1 (34-36), little is known regarding the mechanisms regulating these processes and the specific factors involved. One of our findings is that CHIP, is an E3 ligase of PINK1, which promotes PINK1 ubiquitination and degradation (37). Moreover, we previously demonstrated that hTERT decreases the processing of PINK1 and regulates mitophagy (25). In the present study, we proposed an additional regulator for the PINK1 processing and localization. We also demonstrated that Tollip-mediated processing and cytosolic release of PINK1 reduced mitophagy, suggesting that Tollip may act as a novel factor involved in PD progression.

In conclusion, based on the results from the present study, we propose a novel regulatory pathway for PINK1 processing and localization. Furthermore, our findings demonstrated that Tollip-mediated increase of mitochondrial PINK1 cleavage and its cytoplasmic release could reduce mitophagy, and defect in those modulation of PINK1 activity might contribute to the progression of PD.

MATERIALS AND METHODS

DNA constructs and RNA interference

The mammalian construct encoding Myc-tagged human wild-type PINK1 (pBOS-3X-Myc-hPINK1-WT) was kindly provided by J. Chung (Seoul National University, Seoul, Korea). The plasmid encoding Xpress-tagged Tollip and FLAG-tagged MPPβ were generated by PCR amplification using PrimeSTAR HS DNA polymerase (TAKARA, Shiga, Japan) and subcloned into a pcDNA3 or pRK5 vector. Small interfering RNAs (siRNAs) targeting human Tollip and control scrambled siRNAs were designed and synthesized by Thermo Fisher Scientific (Waltham, Massachusetts, USA).

Cell culture and preparation of cell lysates

Mouse embryonic fibroblasts (MEFs) derived from *PINK1*-null ($PINK1^{-/-}$) and control ($PINK1^{+/+}$) mice were provided by J. Shen (Harvard Medical School, Boston, MA, USA). Human embryonic kidney 293 (HEK293) cells and human neuroblastoma SH-SY5Y cells were purchased from the American Type Culture Collection (ATCC, Manassas, VA, USA). Cells were maintained in Dulbecco's Modified Eagle Medium (DMEM) containing 10% fetal bovine serum and 100 U/ml penicillin-streptomycin (Invitrogen, Carlsbad, CA, USA) and grown at 37°C in 5% CO_2. All DNA transfections were performed using Lipofectamine and PLUS™ Reagent (Invitrogen), according to the manufacturer's protocol. The cells were rinsed twice with ice-cold PBS and lysed in lysis buffer containing 50 mM Tris (pH 7.4), 1.0% Nonidet P-40, 150 mM NaCl, 10% glycerol, and a protease inhibitor cocktail.

Co-immunoprecipitation and immunoblot analysis

Cell lysates containing 1 mg protein were incubated with 0.5 μg of appropriate antibody overnight at 4°C, and then with an equal volume of Protein A-Sepharose beads for 2 h at 4°C with gentle rotation. The beads were pelleted by centrifugation and washed five times with lysis buffer. The immunocomplexes were dissociated by boiling in sample buffer, resolved by SDS-PAGE, and transferred to nitrocellulose membranes. The membranes were blocked in Tris-buffered saline with Tween 20 (TBST) buffer containing 5% nonfat dry milk, and then incubated with the primary antibodies overnight at 4°C in 3% nonfat dry milk. The membranes were then washed with TBST, incubated for 1 h with HRP-conjugated secondary IgG, washed again with TBST, and visualized using ECL reagent (Abclon, Seoul, Korea).

Statistical analysis

All statistical analyses were performed using an unpaired Student's t-test and IBM SPSS statistical analysis software (version 23.0). All values are expressed as the mean ± standard error of the mean (SEM).

Supplementary methods

Immunocytochemistry analysis, analysis of mitochondrial membrane potential, and determination of intracellular ATP level are described in the supplementary information.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

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