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ORIGINAL ARTICLE

Heat shock protein 60 manipulates Foot-and-Mouth disease virus replication by regulating mitophagy

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Abstract

Mitochondria serve as the hubs of cellular signaling, energetics, and redox balance under physiological conditions. Mitochondria play an essential role in defending against pathogenic infections upon virus invasion. As a critical intracellular physiological process, mitophagy is crucial for maintaining mitochondrial homeostasis. Accumulating evidence suggests that mitophagy contributes to modulating viral infection. In our previous study, we reported that heat shock protein 60 (HSP60) is involved in orchestrating autophagy; however, the underlying mechanisms remain elusive. Here, we examined the role of HSP60 in priming mitophagy to regulate foot-and-mouth disease virus (FMDV) replication. We first reported that mitophagy was elicited post-FMDV infection and further restricted FMDV replication. Regarding HSP60, our results showed that HSP60 depletion triggered Parkin-dependent mitophagy via activating dynamin-related protein 1 (Drp1) phosphorylation at Ser616 and promoting Drp1 translocation to mitochondria. Furthermore, calmodulin-dependent protein kinase II (CaMKII) was essential for phosphorylating Drp1 at Ser616 in HSP60-depleted cells. Taken together, HSP60 manipulates FMDV replication by governing mitophagy. Importantly, HSP60 could be a promising antiviral target for controlling FMDV infection.

Keywords Heat shock protein 60 · Foot-and-Mouth disease virus · Mitophagy · Dynamin-related protein 1 · Parkin

Introduction

Autophagy is a highly conserved metabolic process essential for maintaining cellular homeostasis, in which damaged proteins or organelles are captured by autophagosomes and further degraded in lysosomes [1]. Autophagy can selectively clear damaged or dysfunctional organelles and thus maintain quality control [2]. Mitophagy is a mitochondria-specific autophagy pathway that can be triggered by various stimuli, such as hypoxia, mitochondrial depolarization, and viral infection [3]. The best-understood pathway of mitophagy is driven by the ubiquitin ligase Parkin, which is required for labeling damaged mitochondria. Subsequently, autophagy receptor proteins, such as p62, recognize and bind to ubiquitinated outer mitochondrial membrane (OMM) proteins and subsequently interact with LC3B to initiate autophagosome formation. Ultimately, damaged mitochondria are eliminated through the lysosomal degradative pathway [4].

As a conserved molecular chaperone, heat shock protein 60 (HSP60) plays a critical role in folding or refolding target proteins [5]. Furthermore, HSP60 maintains cellular homeostasis by regulating autophagy and immune responses. HSP60 depletion markedly reduced the expression of the autophagy-related proteins Atg4, Atg12, and LC3-II in osteoblasts. In contrast, forced HSP60 level mitigated the levels of autophagic marker proteins and reduced the abundance of LC3-II, suggesting that HSP60 promoted autophagy in osteoblasts under glucocorticoid stress [6]. Findings from other studies suggested that a point mutation in HSP60 (Thr320Ala) caused the accumulation of reactive oxygen species (ROS) and mitophagy through mitochondrial dysfunction [7]. HSP60 (residues 401 to 573) interacted with the cellular repressor of E1A-stimulated genes 1 (CREG1) to ablate its degradation and further suppress mitophagy [8]. The role and details of the mechanisms

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through which HSP60 manipulates mitophagy have not yet been fully elucidated.

Here, we first report that FMDV infection induces mitophagy. HSP60 depletion provokes Parkin-dependent mitophagy by enhancing mitochondrial translocation of Drp1 and CaMKII-mediated Drp1 phosphorylation at Ser616.

Materials and methods

Cells and viruses

PK-15 (porcine kidney; ATCC CCL-33) cells were maintained in Dulbecco's modified Eagle's medium (DMEM) (Gibco, CA, USA) supplemented with 10% fetal bovine serum (FBS) (Gibco), penicillin (100 U/ml), and streptomycin (100 mg/ml) (Gibco) at 37 °C under 5% CO2. The FMDV serotype O strain O/CHINA/99 (GenBank accession no. AF506822.2) was maintained by the OIE/National Foot-and-Mouth Disease Reference Laboratory (Lanzhou, China).

Antibodies and reagents

Mouse anti-HSP60 (Cat. No. 66041-1-Ig, Dilution: 1:2000), anti-COXIV (Cat. No. 66110-1-Ig, Dilution: 1:2000), and anti-P62 (Cat. No. 66184-1-Ig, Dilution: 1:2000) monoclonal antibodies were purchased from Proteintech (Wuhan, China). A mouse anti-actin monoclonal antibody (Cat. No. CW0096, Dilution: 1:2000) was purchased from CWBIO (Beijing, China). Rabbit anti-Beclin-1 (Cat. No. 3495 S, Dilution: 1:2000), anti-VDAC1 (Cat. No. 4661 S, Dilution: 1:2000), anti-LC3 (Cat. No. 3868 S, Dilution: 1:2000), anti-Drp1 (Cat. No. 8570 S, Dilution: 1:2000), anti-Drp1-Ser616 (Cat. No. 3455 S, Dilution: 1:2000), anti-Parkin (Cat. No. 2132 S, Dilution: 1:2000), anti-CaMKII (Cat. No. 50049 S, Dilution: 1:2000), anti-p-CaMKII (Cat. No. 12716 S, Dilution: 1:2000), anti-ERK2 (Cat. No. 9108 S, Dilution: 1:2000), anti-p-ERK2 (Cat. No. 4370 S, Dilution: 1:2000) monoclonal antibodies were purchased from CST (Danvers, MA, USA). The anti-mouse secondary antibodies conjugated with horseradish peroxidase (HRP) (Cat. No. A0168-1ML, Dilution: 1:2500) and anti-rabbit secondary antibodies conjugated with HRP (Cat. No. 12–348, Dilution: 1:2500) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Lipofectamine RNAi MAX and Lipofectamine 2000 were purchased from Invitrogen (CA, USA). A mitochondria isolation kit was purchased from Thermo Fisher Scientific (Waltham, MA, USA).

RNA interference (RNAi)

The sequences of target siRNAs (GenePharma, China): 5'-GC-AGAUGCUCGAGCCUUAATT (HSP60); 5'-GUGGCUGUAUGCACAUGAATT (Parkin); 5'-GGGCUAAUGAACAAUAAUATT (Drp1); 5'-CAGCUUGCAUCGCCUAUTT (CaMKII); 5'-GUGCUCUGCUUAUGAU-AAUTT (ERK2); and 5'-UUCUCCGAACGUG-UCACGUTT (NC). Cells were grown to 80% confluence and were transfected with siRNA using Lipofectamine RNAi MAX according to the manufacturer's instructions. After 6 h, the medium was changed. Incubating cells for 48 h at 37 °C in a CO2 incubator before harvesting.

Western blotting (WB)

The cells were collected and lysed with 1 × SDS loading buffer. After SDS-PAGE, the samples were transferred to the NC membrane. The membranes were incubated with 5% skim milk for 1 h at room temperature, followed by overnight incubating with primary antibodies. Next, membranes were washed with TBST. Then, membranes were incubated with a secondary antibody which is conjugated to horseradish peroxidase for 1 h, and TBST was used to wash membranes. The bands on membranes were visualized by incubating with chemiluminescence kit (Thermo Fisher Scientific, USA).

Mitochondrial fractionation

A Mitochondria isolation kit (Cat. No. 89874, Thermo Fisher Scientific, USA) was used in this assay. Firstly, cells were centrifuged at 1000 × g for 5 min. After discarding the supernatant, Reagent A (added with protease inhibitor) was used to resuspend the cells, followed by incubating in ice for 2 min. Next, 10 mL of Reagent B was added to resuspend the cells and further kept on ice for 6 min. Adding 800 mL Reagent C (contains a protease inhibitor). Two times centrifuge (800 × g for 5 min at 4 °C, 15,000 × g for 10 min at 4 °C) were performed. The purified mitochondria were found in the pellet while the supernatant contained cytosolic fraction.

Statistical analysis

The data presented in this paper are expressed as means and standard deviations (SD) for at least two replicates and were evaluated with a two-way analysis of variance (ANOVA) in GraphPad Prism software version 9 (GraphPad, La Jolla, CA, USA).

Results

Parkin-dependent mitophagy is induced during FMDV infection and further suppresses FMDV replication

Our previous studies revealed that FMDV infection induces autophagy [9]. To explore whether FMDV infection triggers mitophagy, PK-15 cells were infected with FMDV for 2 h, 4 h, or 6 h. Mitophagy-related protein expression was determined via Western blotting (WB). As shown in Fig. 1A, the protein level of P62 was strongly decreased at 6 hpi, while the protein levels of Beclin-1 and LC3-II were greatly increased at 6 hpi. These findings confirmed that FMDV infection activated autophagy. Furthermore, our data showed that the protein levels of VDAC1, OMM protein, and COXIV, an inner mitochondrial membrane protein, were markedly decreased at 6 hpi. Moreover, the levels of autophagy or mitophagy marker proteins was altered in a time-dependent manner. Briefly, our results revealed that FMDV infection induced mitophagy. We validated our findings by transfecting PK-15 cells with a GFP-tagged LC3 overexpression plasmid (GFP-LC3) and subsequently infected them with FMDV. In agreement with the previous studies, strongly accumulation of punctate structures was observed in FMDV-infected PK-15 cells at 4 hpi and 6 hpi. Moreover, the fluorescent puncta colocalized with mitochondria (Fig. 1B). Parkin is known to translocate from the cytoplasm to mitochondria, where they initiate mitophagy [2]. Our data indicated that mitochondrial Parkin protein levels were strongly increased, whereas they were reduced in the cytoplasm (Fig. 1 C). To further explore the role of Parkin in FMDV-mediated mitophagy. We depleted Parkin by transfecting cells with siRNA targeting Parkin (siParkin),

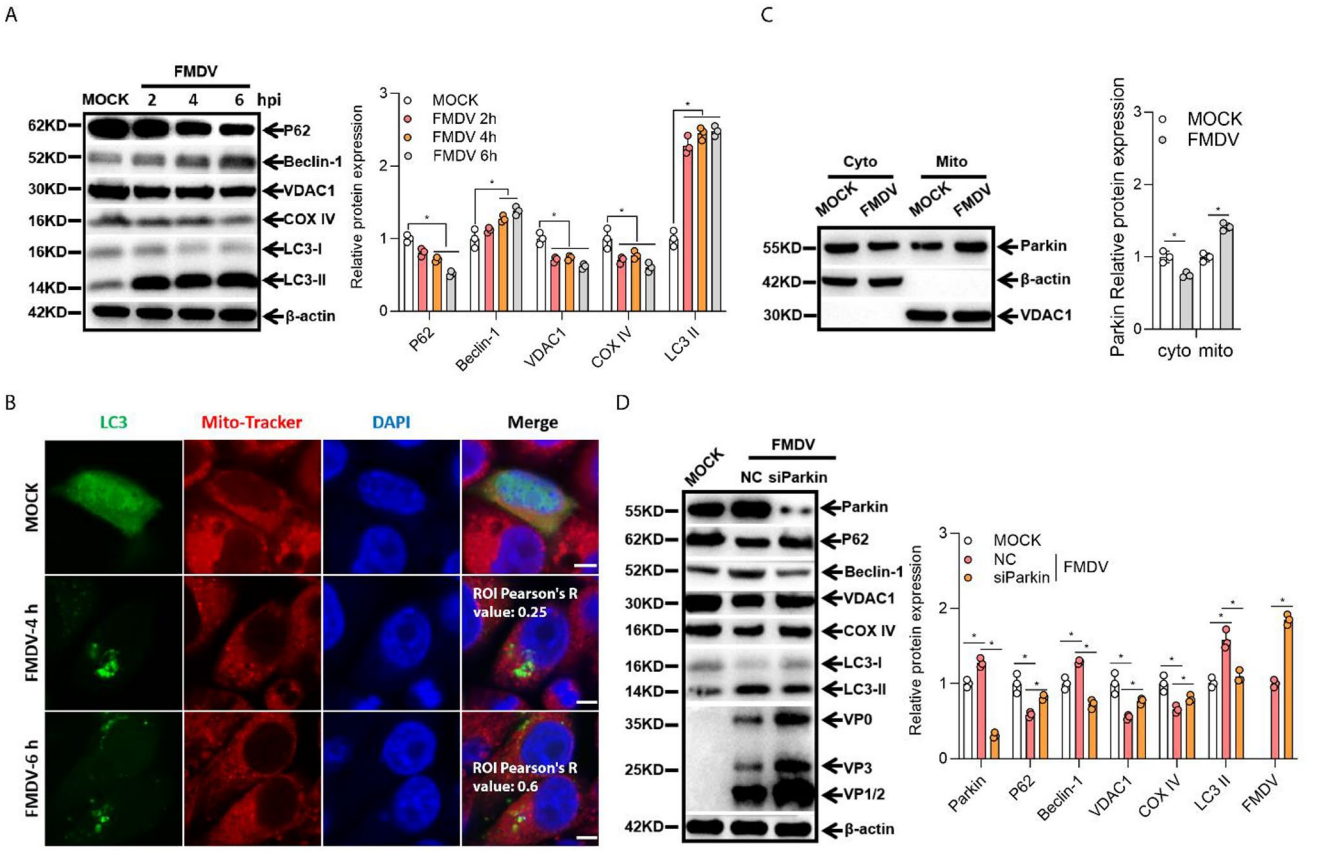

Fig. 1 Parkin-dependent mitophagy is induced during FMDV infection and further suppresses FMDV replication. (**A**) PK-15 cells were infected with FMDV type O at an MOI of 1. The samples were collected at different time points, and the indicated protein levels were determined via Western blotting. (**B**) GFP-LC3 colocalizes with mitochondria in PK-15 cells. Transfection of the GFP-LC3 plasmid was performed. After 20 h, the cells were infected with FMDV O for 4 h and 6 h. The cells were stained with MitoTracker and examined by confocal microscopy. Scale bars, 5 μm. (**C**) FMDV infection induced the mitochondrial translocation of Parkin. After infecting with FMDV O at an MOI of 1 for 6 h, the PK-15 cells were subjected to a mitochondria isolation assay. The mitochondrial or cytoplasmic levels of the indicated proteins were detected by Western blotting. (**D**) Parkin-dependent mitophagy suppressed FMDV replication. PK-15 cells were transfected with siRNA targeting Parkin (siParkin) or negative control (NC). At 36 h posttransfection, the PK-15 cells were infected with FMDV O at an MOI of 1. The samples were collected at 6 h postinfection, and the indicated protein levels were determined via Western blotting. Data are the means of results of three independent experiments, and error bars indicate standard deviations (SD). *, $P<0.05$

and the FMDV replication level was examined via WB. Our results indicated that Parkin depletion inhibited the mitophagy caused by FMDV infection; however, mitophagy suppression enhanced FMDV replication (Fig. 1D). Taken together, our results demonstrate that FMDV infection induces Parkin-dependent mitophagy; however, mitophagy suppresses FMDV replication.

HSP60 depletion activates Parkin-dependent mitophagy

First, we investigated the role of HSP60 in governing mitophagy in PK-15 cells. We downregulated HSP60 expression by transfecting cells with a small interfering RNA targeting HSP60 (siHSP60). We found that a reduction in HSP60 led to noticeably increased protein levels of Beclin-1 and LC3-II; however, the expression levels of P62, VDAC1, and COXIV were markedly decreased (Fig. 2A). To confirm the specific role of HSP60 in modulating mitophagy, PK-15 cells were treated with the autophagic phagophore formation inhibitor 3-MA. The 3-MA treatment reversed the change in mitophagy marker protein levels caused by depleting HSP60. We further investigated whether the Parkin-dependent pathway dominates the mitophagy in HSP60-depleted cells. Simultaneous depletion of HSP60 and Parkin markedly decreased the protein levels of Beclin-1 and LC3-II, while dramatically increasing the expression of P62, VDAC1, and COXIV compared to HSP60 knockdown cells (Fig. 2B). Next, a mitochondria isolation experiment was performed. As shown in Fig. 2 C, Parkin was significantly accumulated in the mitochondrial fraction after knocking down. Overall, our data suggested that HSP60 depletion activates Parkin-dependent mitophagy.

The phosphorylation of Drp1 at Ser616 and the mitochondrial translocation of Drp1 are crucial for HSP60 depletion-induced mitophagy

We next investigated whether Drp1 is involved in the mitophagy induced by HSP60 depletion. Mdivi-1, an inhibitor of Drp1 that suppresses its GTPase activity and prevents Drp1 mitochondrial translocation, was used to treat PK15 cells. As shown in Fig. 3A, HSP60 depletion facilitated the mitochondrial translocation of Parkin and Drp1. Further Mdivi-1 treatment markedly ablated the mitochondrial translocation of Parkin. To confirm our findings, we simultaneously depleted HSP60 and Drp1 expression. Next, a mitochondrial isolation experiment was performed. We found that HSP60 deficiency increased the level of p-Drp1-Ser616 both in the mitochondria and the

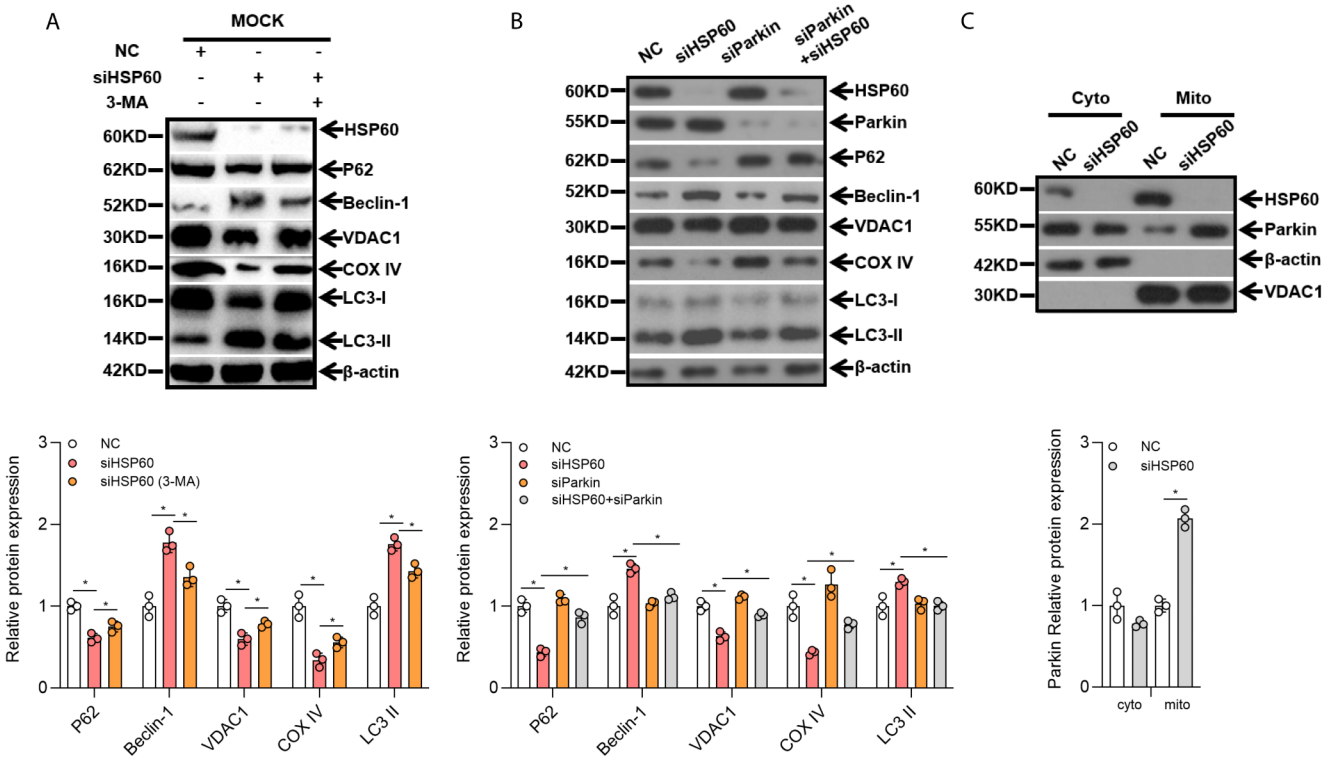

Fig. 2 Knocking down HSP60 activates Parkin-dependent mitophagy. (**A-B**) HSP60 depletion caused mitophagy. PK-15 cells were transfected with siRNA targeting HSP60 (siHSP60) or negative control (NC). After 48 h posttransfection, the samples were collected to assess the indicated protein levels via Western blotting. PK-15 cells were treated with 3-MA at 3 mM for 4 h. (**C**) HSP60 knockdown promoted Parkin translocation to mitochondria. PK-15 cells were transfected with an NC or siHSP60 for 48 h. Next, a mitochondria isolation assay was performed. The mitochondrial or cytoplasmic levels of the indicated proteins were detected via WB. Data are the means of results of three independent experiments, and error bars indicate standard deviations (SD). *, $P<0.05$

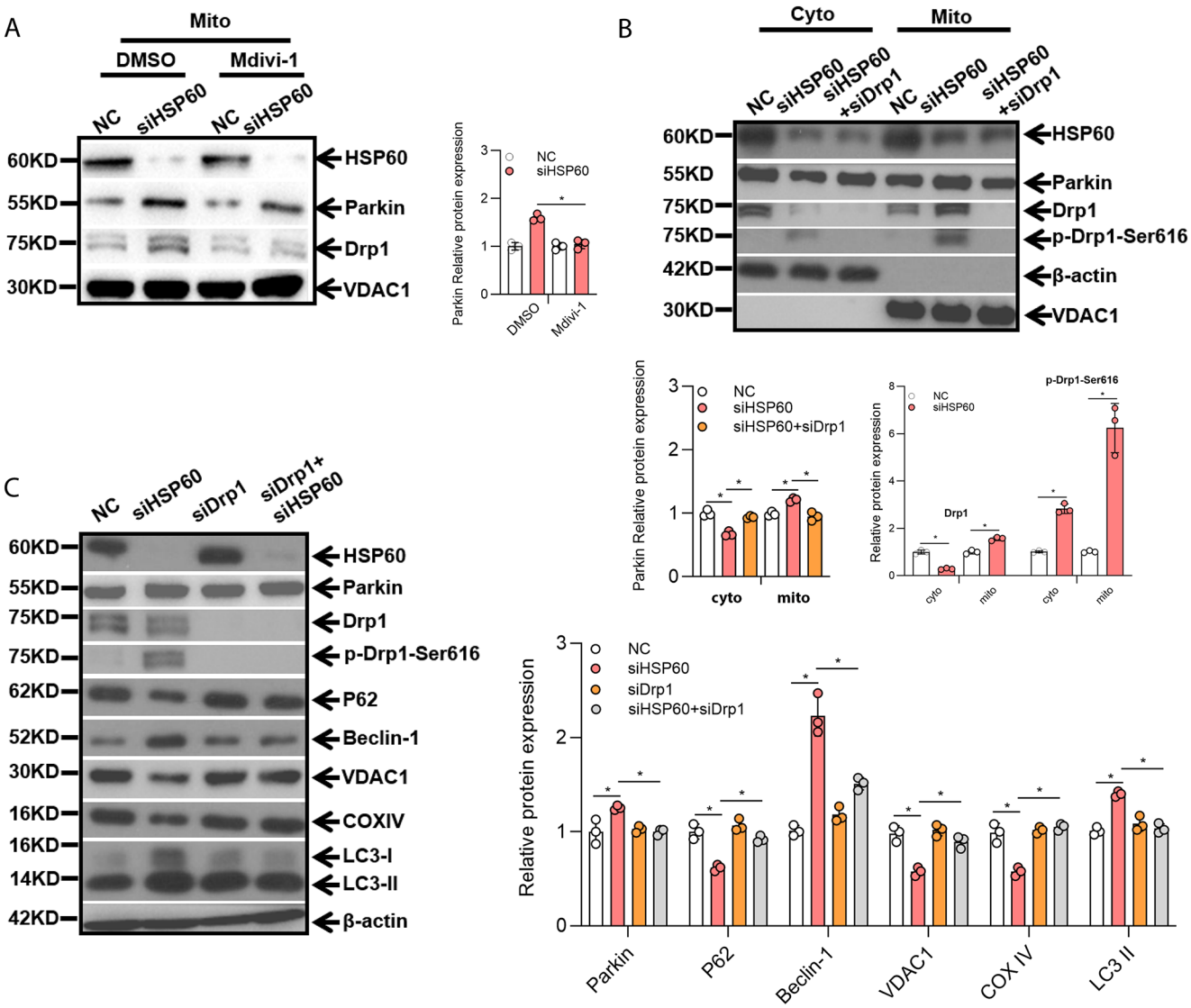

Fig. 3 HSP60 deficiency enhances the phosphorylation of Drp1 at Ser616 and promotes Drp1 translocation to mitochondria. (**A**) Mdivi-1 treatment abrogates the mitochondrial accumulation of Parkin in HSP60-depleted cells. PK-15 cells were transfected with NC or HSP60. Moreover, PK-15 cells were treated with Mdivi-1 or DMSO. Then, a mitochondria isolation assay was performed. The indicated protein levels were detected by WB. (**B**) The aggregation of Parkin at the mitochondrial membrane induced by HSP60 depletion was inhibited after Drp1 knockdown. PK-15 cells were transfected with NC, siHSP60, or siDrp1 for 48 h, mitochondria isolation assay was performed. The mitochondrial or cytoplasmic levels of the indicated proteins were detected. (**C**) Drp1 is essential for mitophagy induced by HSP60 depletion. PK-15 cells were transfected with NC, HSP60, or siRNA targeting Drp1 (siDrp1) for 48 h. The indicated protein levels were detected via WB. Data are the means of results of three independent experiments, and error bars indicate standard deviations (SD). *, $P<0.05$

cytosol (Fig. 3B). Importantly, further depletion of Drp1 suppressed the HSP60-induced mitochondrial accumulation of Parkin. Next, we transfected specific siRNAs to reduce HSP60 and Drp1 expression. Our data showed that the depletion of HSP60 increased the p-Drp1-Ser616 level (Fig. 3 C). Compared with those in HSP60-knockdown cells, the expression of Beclin-1 and LC3-II in HSP60 and Drp1 double depleted cells was markedly lower, and the expression of P62, VDAC1, and COXIV was dramatically greater. Therefore, our finding suggested that Drp1 are crucial for HSP60 depletion-induced mitophagy.

CaMKII phosphorylates Drp1 at Ser616 in HSP60 depleted PK-15 cells

We explored whether CaMKII or ERK2 mediates Drp1 Ser616 phosphorylation after depleting HSP60. As shown in Fig. 4A, HSP60 depletion did not change the protein levels of ERK2 or CaMKII. After activation, ERK2 and CaMKII undergo autophosphorylation to form active ERK2 (p-ERK2) and active CaMKII (p-CaMKII), which catalyze the target substrates. Our data showed that p-CaMKII was significantly

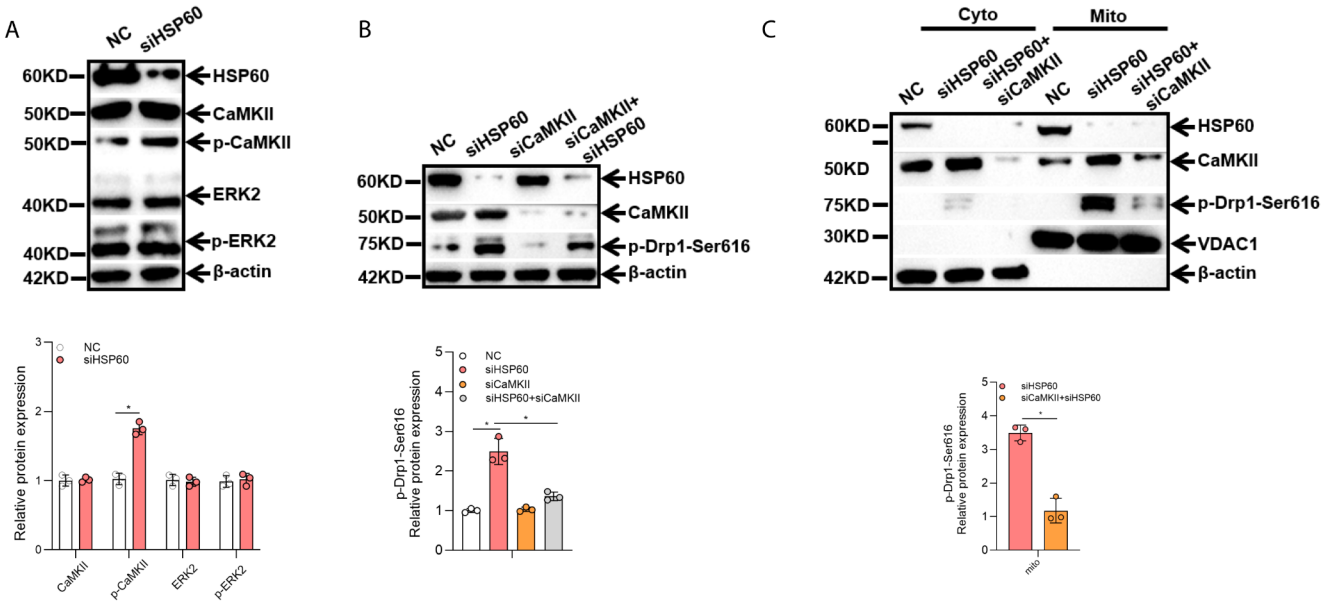

Fig. 4 HSP60 depletion induces Drp1 phosphorylation at Ser616 in a CaMKII-dependent manner. (**A**) The active CaMKII protein level is increased in HSP60-depleted PK-15 cells. (**B**) HSP60 depletion led to the phosphorylation of Drp1 at Ser616 in a CaMKII-dependent manner. PK-15 cells were transfected with NC, HSP60, or siRNA targeting CaMKII (siCaMKII) for 48 h. WB was used to detect the indicated protein levels. (**C**) HSP60 depletion induced the accumulation of Drp1 and p-Drp1-Ser616 in mitochondria in a CaMKII-dependent manner. PK-15 cells were transfected with NC, siHSP60, or siCaMKII for 48 h. A mitochondria isolation assay was performed. The mitochondrial or cytoplasmic levels of the indicated proteins were detected. Data are the means of results of three independent experiments, and error bars indicate standard deviations (SD). *, $P<0.05$

increased, whereas p-ERK2 was not altered after knocking down HSP60. These findings emphasized the potential role of CaMKII in mediating Drp1 Ser616 after HSP60 depletion. To confirm our hypothesis, we next depleted CaMKII by transfecting cells with a siRNA targeting CaMKII (siCaMKII). Our data showed that simultaneous depletion of HSP60 and CaMKII decreased the p-Drp1-Ser616 level compared to that observed following HSP60 depletion (Fig. 4B). Next, we performed a mitochondria separation assay to detect alteration of mitochondrial p-Drp1-Ser616 level. As shown in Fig. 4 C, the accumulation of mitochondrial p-Drp1-Ser616, caused by HSP60 depletion, was significantly decreased after simultaneously depleting HSP60 and CaMKII. Altogether, CaMKII is involved in regulating the phosphorylation of Drp1 at Ser616 in HSP60-depleted PK-15 cells.

Discussion

As the main energy source for multiple intracellular processes, mitochondria also play a crucial role in defending against pathogenic infections [10, 11]. Accumulating evidence shows that mitophagy regulates viral infection [12, 13]. Our previous study indicated that HSP60 promotes FMDV replication by stabilizing the viral nonstructural proteins 3 A and 2 C via apoptosis and autophagy-dependent pathways [9]. The role of the key mitochondrial protein HSP60 in modulating mitophagy, thereby orchestrating FMDV replication, has not been determined. This study revealed that HSP60 depletion induces Parkin-dependent mitophagy by triggering CaMKII mediated-Drp1-Ser616 phosphorylation, thereby suppressing FMDV replication.

We have reported that FMDV infection induces autophagy and further regulates viral replication [14, 15]. As a mechanism of mitochondrial quality control, mitophagy is involved in viral infection. However, whether FMDV infection causes mitophagy has not been determined. By detecting changes in mitophagy marker protein levels, we found that FMDV triggered mitophagy. We further confirmed these results by observing the colocalization of GFP-LC3 with mitochondria (Fig. 1A-B). Furthermore, we found that FMDV infection induces mitophagy via a Parkin-dependent pathway (Fig. 1 C-D). Next, we investigated the role of mitophagy in ensuring FMDV growth. siRNA experiments showed that mitophagy inhibited the viral replication of FMDV (Fig. 1D). The results above give rise to a hypothesis that mitophagy acts as a defense mechanism employed by host cells during pathogen infection.

HSP60 plays a key role in maintaining mitochondrial homeostasis [16]. Many reports have indicated that HSP60 modulates mitophagy [6–8]. However, further investigations are required to uncover the underlying molecular mechanism involved. First, the role of HSP60 in regulating mitophagy was determined in PK-15 cells. As shown in Fig. 2A, HSP60 depletion induced mitophagy. Furthermore,

the inhibition of mitophagy caused by 3-MA treatment further confirmed the role of HSP60 in driving mitophagy. The Parkin pathway functions as a crucial signaling pathway to maintain mitochondrial homeostasis by regulating mitophagy [17]. Our study uncovered that Parkin was markedly translocated to mitochondria in HSP60-depleted cells (Fig. 2 C). Moreover, Parkin deficiency significantly reduced mitophagy, which was induced by knocking down HSP60 (Fig. 2B). These results support the critical role of HSP60 in mediating mitophagy via a Parkin-dependent pathway. Drp1 is involved in regulating mitochondrial homeostasis [18]. During this process, Drp1 translocates to the OMM. Next, the phosphorylation of Drp1 at Ser616 activates mitophagy [19]. We proposed that Drp1 mediates the mitophagy caused by HSP60 depletion. As shown in Fig. 3, HSP60 depletion elicited Drp1 mitochondrial translocation and increased the level of p-Drp1-Ser616. Next, Mdivi-1 treatment and Drp1 depletion strongly abolished the mitochondrial translocation of Parkin. As expected, mitophagy was dramatically impaired when Drp1 was further depleted in HSP60-depleted cells. These results underscore the critical role of Drp1 in initiating mitophagy after HSP60 depletion. It has been reported that ERK2 and CaMKII, well-known protein kinases, are responsible for phosphorylating Drp1 at Ser616 [20–21]. Thus, further experiments were carried out to validate the potential key kinase involved in catalyzing Drp1 phosphorylation. First, the increased level of p-CaMKII suggested that CaMKI might be the critical enzyme (Fig. 4). Furthermore, our results showed that CaMKII depletion significantly reduced the phosphorylation of Drp1 at Ser616; however, ERK2 had a negligible effect on the p-Drp1-Ser616 level. Thus, we confirmed that HSP60 depletion activated CaMKII to phosphorylate Drp1 at Ser616. In conclusion, we show that FMDV infection triggers mitophagy to restrict viral replication, and that HSP60 depletion initiates Parkin-dependent mitophagy by promoting CaMKII-mediated Drp1 phosphorylation at Ser616 and its translocation to mitochondria. However, given HSP60's extensive involvement-whether directly or through innate immune responses such as endoplasmic reticulum stress-the role of HSP60 in modulating various pathogen infections and its potential as a broad-spectrum antiviral target requires further investigation.

Author contributions J.T. and H.G. designed the study. J.T. performed the experiments with technical support from S.W.A. J.T. performed data analysis. J.T. wrote the draft of the manuscript. H.G. and S. S. supervised the study and edited the manuscript. All authors discussed the results and approved the final manuscript.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare no conflicts of interest.

Disclosure The funders were not involved in study design, data collection, analysis, publishing decisions, manuscript preparation, editing, approval, or decision to publish.

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