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Tumor suppressor Parkin induces p53-mediated cell cycle arrest in human lung and colorectal cancer cells

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Dysregulation of the E3 ubiquitin ligase Parkin has been linked to various human cancers, indicating that Parkin is a tumor suppressor protein. However, the mechanisms of action of Parkin remain unclear to date. Thus, we aimed to elucidate the mechanisms of action of Parkin as a tumor suppressor in human lung and colorectal cancer cells. Results showed that Parkin overexpression reduced the viability of A549 human lung cancer cells by inducing G2/M cell cycle arrest. In addition, Parkin caused DNA damage and ATM (Ataxia telangiectasia mutated) activation, which subsequently led to p53 activation. It also induced the p53-mediated upregulation of p21 and downregulation of cyclin B1. Moreover, Parkin suppressed the proliferation of HCT-15 human colorectal cancer cells by a mechanism similar to that in A549 lung cancer cells. Taken together, our results suggest that the tumor-suppressive effects of Parkin on lung and colorectal cancer cells are mediated by DNA damage/p53 activation/cyclin B1 reduction/cell cycle arrest. [BMB Reports 2023; 56(10): 557-562]

INTRODUCTION

The Parkin gene (*PARK2*) is the causative gene of the autosomal recessive form of Parkinson's disease (1-3). This gene encodes an E3 ubiquitin ligase that catalyzes the formation of a polyubiquitin chain on substrate proteins, which initiates protein degradation via the ubiquitin-proteasome system (4-6). *PARK2* was mapped to the FRA6E region, a chromosomal fragile site frequently affected in the development of various cancers, and deletional mutations are the most common Parkin mutations (7-9). Since then, multiple lines of evidence have suggested that loss of *PARK2* heterozygosity and copy number can be implicated not only in Parkinson's disease but also in various cancers (10-12). Hence, the tumor-suppressive role of the Parkin protein (Parkin) has rapidly gained attention.

In the past two decades, studies directed at understanding the mechanisms underlying Parkin-mediated tumor suppression revealed that the tumor-suppressive effect of Parkin largely depends on the promotion of apoptosis and/or inhibition of cell cycle progression (13, 14). Parkin triggers the poly-ubiquitination and degradation of the anti-apoptotic molecule myeloid cell leukemia-1, thereby promoting the apoptosis of human cervical cancer cells (13). Parkin also ubiquitinates phosphoglycerate dehydrogenase (PHGDH), the first rate-limiting enzyme in the serine synthesis pathway, which is critical for the excessive proliferation of cancer cells, leading to the degradation of PHGDH to prevent tumor development in human Hs578T breast cancer and H1299 lung cancer cells (15). Another study showed that Parkin binds to microtubules and facilitates the interaction between anticancer chemicals and microtubules, increasing the sensitivity of HeLa cells to anticancer chemicals (16, 17). In addition, Parkin overexpression induces caspase-dependent apoptosis and cell cycle arrest at the G1 phase (10) in non-small cell lung cancer (NSCLC) cell lines. Similarly, Parkin overexpression impedes the proliferation of colorectal cancer cells, HCT116 and DLD1, by suppressing the entry of cells into the S phase (18). The doubling time of Parkin-overexpressing cells dramatically increases by two- to threefold (18). These studies show that Parkin suppresses tumor development via various molecular pathways.

The transcription factor p53 is a crucial molecule that is highly induced by diverse stresses, including DNA damage, which causes cell cycle arrest to maintain genomic integrity during cell division (19-21). Upon DNA damage, p53 becomes activated and elicits the transcriptional regulation of several cell cycle regulatory proteins (22). Among these proteins, p21 is the most well-studied transcriptional target of p53. It contributes to cell cycle arrest (23) by acting as a CDK (Cyclin-dependent kinase) inhibitor (24). Cyclin B1 is another important molecule regulated by the p53 cascade in response to DNA damage (25). The CDK1/cyclin B complex is responsible for G2/M phase

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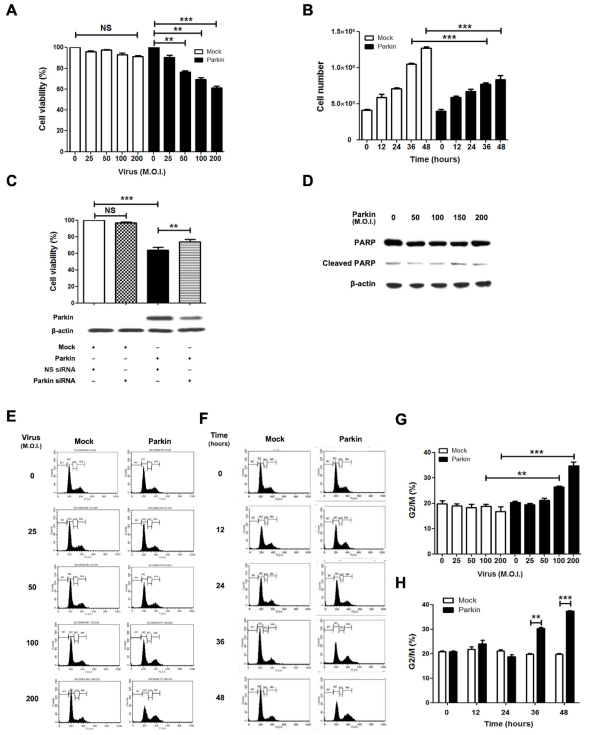

Fig. 1. Overexpression of Parkin decreases the viability of A549 lung cancer cells by inducing G2/M phase cell cycle arrest. (A) A549 cells were infected with the Parkin-expressing adenovirus (Parkin) or mock virus (Mock) at the indicated concentrations of for 48 h, (B) cells were infected with either the mock or Parkin virus for the indicated times, and (C) cells were infected with the mock or Parkin virus in the absence or presence of Parkin-specific siRNA (PK siRNA). Non-specific siRNA (NS siRNA) was used as a negative control. Then, viable cells were enumerated by a trypan blue dye exclusion assay. The number of viable cells in the non-infected group was set as 100%. Parkin was detected using western blot analysis using a specific antibody against Parkin. β-actin was used as a loading control. (D) Cells were infected with the Parkin virus at the indicated concentrations. Cell lysates were harvested and subjected to western blot analysis to detect the cleaved PARP. PARP was detected using a specific antibody against PARP. (E, F) Cells were treated as in (A) and (B). Then, cell cycle analysis was performed using propidium iodide staining and flow cytometry. (G, H) Percentage of cells in the G2/M phase was analyzed with CellQuestPro software and graphically presented. Data are expressed as the mean ± SEM from three independent experiments. $^{**}P < 0.01$, $^{***}P < 0.001$ or NS (non-significant).

transition (26). In response to DNA damage, activated p53 induces the transcriptional downregulation of cyclin B, which consequently inhibits the activity of the CDK1/cyclin B complex and results in cell cycle arrest at the G2/M phase (27).

In the present study, we aimed to examine the tumor-suppressive role of Parkin in lung and colorectal cancer cells.

RESULTS AND DISCUSSION

Parkin expression reduced the viability of A549 lung cancer cells by inducing G2/M cell cycle arrest

Parkin acts as a tumor suppressor in various cancer cells, including lung cancer cells (11). The large-scale datasets from cBioportal revealed that *PARK2* alterations can be observed in 4.83% out of 3,622 lung adenocarcinoma cases (28, 29). However, the mechanisms underlying the tumor-suppressive role of Parkin in lung cancer cells remain to be elucidated. In the present study, we examined whether Parkin affects the viability of A549 lung cancer cells. Parkin was overexpressed in A549 lung cancer cells, and the number of viable cells was counted. Parkin overexpression reduced the number of viable cells in a dose- and time-dependent manner (Fig. 1A, B). In addition, the Parkin-induced reduction in cell viability was partly rescued when Parkin overexpression was partially reduced by the introduction of Parkin-specific small-interfering RNA (siRNA, Fig. 1C). These results imply that Parkin can suppress the viability of lung cancer cells. To elucidate the mechanisms by which Parkin reduces cell viability, we investigated whether this protein promotes the apoptosis and/or suppresses the proliferation of lung cancer cells. As shown in Fig. 1D, no significant cleavage of PARP, a hallmark of apoptosis, was observed when Parkin was overexpressed in a dose-dependent manner. However, flow cytometry results showed Parkin overexpression induced G2/M cell cycle arrest in the A549 lung cancer cells in a dose- and time-dependent manner (Fig. 1E-H). Taken together, these results suggest that Parkin reduces the viability of A549 cells by decreasing their proliferation and not by promoting their apoptosis.

Parkin expression induced DNA damage leading to activation of p53

G2/M cell cycle arrest results from many causes, including DNA damage (30). A recent study has shown that ionizing radiation induces the upregulation of Parkin in lung cancer cells (31). In the present study, we investigated whether Parkin expression causes DNA damage. Parkin was overexpressed in A549 cells, and a comet assay was performed. Comet tails, which consist of broken DNA strands indicating DNA damage, were clearly observed in the Parkin-overexpressing group, whereas no comet tails were observed in the control group (Fig. 2A). In addition, the phosphorylation of ATM, one of the molecules associated with DNA damage response in cells, was increased in the Parkin-overexpressing cells in a time-dependent manner (Fig. 2B). We also found that the Parkin-induced reduction in cell viability was partially recovered by ATM inhibition (Fig. 2C). p53 is involved in DNA damage response (32) and phosphorylated in response to DNA damage, regulating various downstream molecules to facilitate cell cycle arrest (33). Therefore, we explored whether Parkin expression influences p53 expression. We found that Parkin expression increased the protein expression and phosphorylation of p53

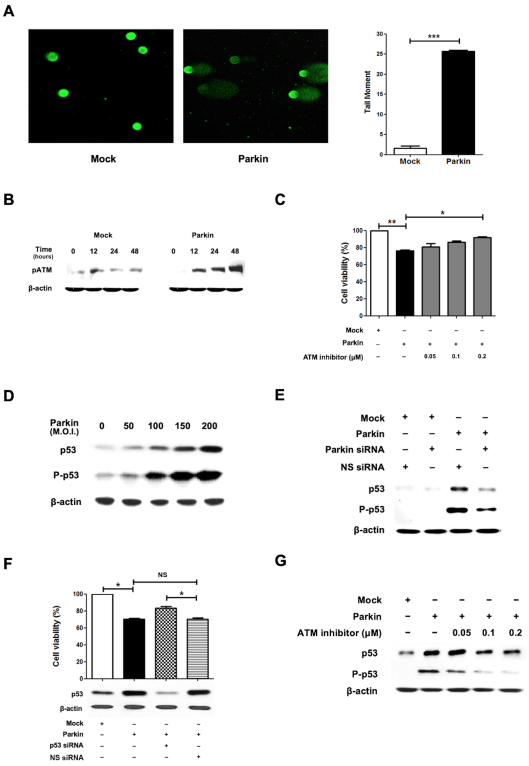

Fig. 2. Parkin-induced decrease of A549 cell viability is mediated by DNA damage and activation of p53. (A) Mock or Parkin virus-infected A549 cells were used for comet assays. Quantified tail moment (tail length × % of DNA in the tail) was displayed on the right panel. (B) Mock or Parkin virus-infected cells were harvested after the indicated time points post infection. Phosphorylated ATM was visualized using western blot analysis. β-actin was used as a loading control. (C) Cells were infected with the mock or Parkin virus in the absence or presence of the indicated concentrations of ATM inhibitor. Then, viable cells were enumerated via a trypan blue dye exclusion assay. The number of viable cells in the Mock-infected group was set as 100%. (D) Cells were infected with the Parkin virus at the indicated concentrations for 48 h, and p53 and phosphorylated p53 were visualized using western blot analysis. (E) Cells were infected with the mock or Parkin virus (100 M.O.I.) in the presence of either NS siRNA or PK siRNA. Cell lysates were subjected to western blot analysis to detect p53 and phosphorylated p53. (F) Cells were infected with the mock or Parkin virus in the absence or presence of p53-specific siRNA (p53 siRNA). NS siRNA was used as a negative control. Then, viable cells were enumerated. The number of viable cells in the Mock-infected group was set as 100%. p53 was detected via western blot analysis using a specific antibody against p53. (G) Cells were infected with the mock or Parkin virus in the absence or presence of the indicated concentrations of ATM inhibitor. Phosphorylated p53 and p53 were visualized using western blot analysis. Data are expressed as the mean ± SEM from three independent experiments. *P < 0.05, **P < 0.01, ***P < 0.001, NS (non-significant).

in a dose-dependent manner (Fig. 2D). Moreover, the Parkin-induced increase in the amount and phosphorylation of p53 was partly restored when Parkin overexpression was partially reduced after introducing Parkin-specific siRNA (Fig. 2E). The Parkin-induced decrease in cell viability was partly recovered when p53 was partially downregulated after introducing p53-specific siRNA, indicating that the Parkin-induced reduction in cell viability was mediated by p53 (Fig. 2F). We also found that ATM inhibition reversed Parkin-induced p53 activation in an ATM inhibitor dose-dependent manner (Fig. 2G), implying that ATM was an upstream molecule of p53. Collectively, these results suggest that Parkin induces DNA damage and ATM phosphorylation, which consequently activate p53 and decrease the viability of lung cancer cells. Previous studies have demonstrated the protective role of Parkin on DNA damage. After exposure to various DNA-damaging agents, Parkin translocates to the nucleus to promote DNA repair and reduce DNA damage in SH-SY5Y cells (34). Similarly, Parkin protects cells against reactive oxygen species-induced mitochondrial DNA damage by binding to DNA to facilitate DNA repair in SH-SY5Y cells (35). However, whether Parkin itself induces DNA damage remains unclear. In the present study, we demonstrated that Parkin induced DNA damage in the lung and colorectal cancer cells. Parkin seems to function differently depending on the proliferative capacity of cells. Parkin may decrease DNA damage in fully differentiated cells that are incapable of proliferation, such as neuronal cells. By contrast, Parkin may cause DNA damage in proliferating cells, such as lung and colorectal cells.

Parkin expression induced p53-dependent regulation of p21 and cyclin B1

The DNA damage-induced activation of p53 leads to the transcriptional regulation of genes associated with the cell cycle, such as p21, a cyclin-dependent kinase inhibitor (36). In the current study, we examined whether Parkin regulates p21 expression. We found that Parkin induced the upregulation of p21 at the transcriptional and translational levels in a dose-dependent manner (Fig. 3A, B). Cyclins are important molecules involved in cell cycle regulation, and decreased cyclin A2 and/or cyclin B1 levels cause cell cycle arrest at the G2/M phase in several cancer cell models (37-39). Therefore, we examined whether Parkin regulates the expression of cyclin A2 and cyclin B1. In our A549 cell model, Parkin expression elicited the transcriptional and translational downregulation of cyclin B1 but not cyclin A2 (Fig. 3C, D). The Parkin-induced upregulation of p21 and downregulation of cyclin B1 were restored when the Parkin-induced activation of p53 was reversed after introducing p53-specific siRNA (Fig. 3E, F). This result indicates that the Parkin-induced regulation of p21 and cyclin B1 is mediated by p53. A previous report showed that Parkin overexpression induces cell cycle arrest at the G1 phase in H1299 and H460 NSCLC cell lines (10). This study suggested that the G1 arrest is mediated by the upregulation of p21 and p18, potent inhibitors of the G1/S cell cycle transition, and downregulation of cyclin D1/CDK4, an inducer of cell cycle progression from the G1 to S phase. Further studies are warranted to elucidate the mechanisms by which Parkin influences

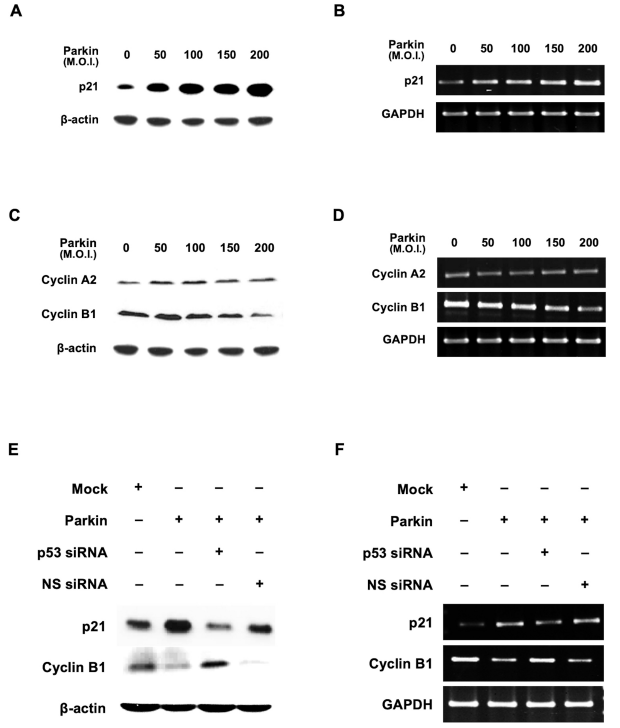

Fig. 3. Parkin overexpression induces the p53-mediated upregulation of p21 and downregulation of cyclin B1. A549 cells were infected with the indicated concentrations of the Parkin virus. The protein (A) and mRNA levels (B) of p21 and the protein (C) and mRNA levels (D) of cyclin A2 and cyclin B1 were detected using western blot analysis and RT-PCR, respectively. A549 cells were infected with the mock or Parkin virus in the absence or presence of p53 siRNA. The protein (E) and mRNA levels (F) of p21 and cyclin B1 were visualized using western blot analysis and RT-PCR, respectively. NS siRNA was used as a negative control.

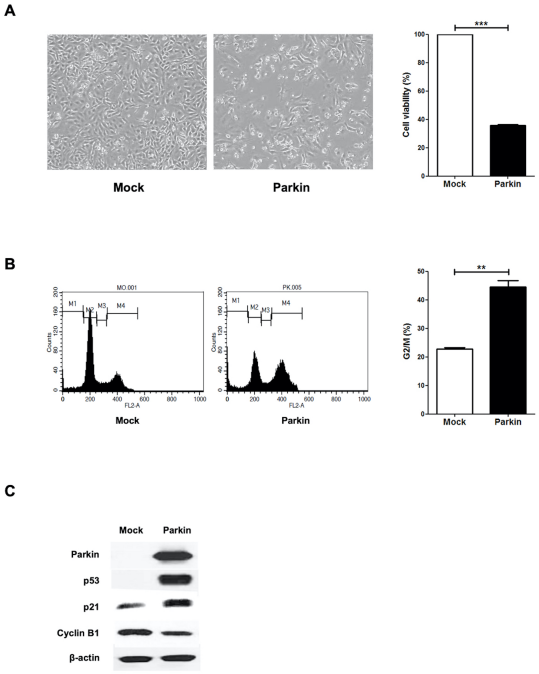

Fig. 4. Parkin exerts anti-proliferative effect on HCT-15 colorectal cancer cells. HCT-15 cells were infected with the Parkin or mock virus for 72 h. (A) Images of cells were taken using an inverted microscope (200×) (left panel), and viable cells were enumerated using a trypan blue dye exclusion assay (right panel). The number of viable cells in the Mock-infected group was set as 100%. (B) Cell cycle was analyzed using propidium iodide staining and flow cytometry, and G2/M population was displayed as a percentage relative to total cells. (C) Protein levels of Parkin, p53, p21, and cyclin B1 were measured using western blot analysis. Data are expressed as the mean ± SEM from three independent experiments. $^{**}P < 0.01$, $^{***}P < 0.001$.

the proliferation of lung cancer cells, which may vary depending on the cell type.

Parkin acted as a tumor suppressor in colorectal cancer cells via a mechanism similar to that in lung cancer cells

Parkin overexpression impedes cell proliferation in colorectal cancer cells, and the large-scale datasets from cBioportal show *PARK2* alterations in 7.83% out of 1,482 colorectal cancer cases (28, 29). To investigate whether the Parkin-associated anti-proliferative mechanism elucidated above is limited to lung cancer cells, we examined the anti-proliferative effect of Parkin in HCT-15 human colorectal cancer cells. We observed that Parkin overexpression dramatically reduced the viability of HCT-15 cells (Fig. 4A). In accordance with the results obtained in A549 lung cancer cells, Parkin expression induced G2/M cell cycle arrest in HCT-15 colorectal cancer cells (Fig. 4B). In addition, Parkin expression induced the upregulation of p53 and p21 and downregulation of cyclin B1 in colorectal cancer cells, similar to that in lung cancer cells (Fig. 4C). These results suggest that the suppressive effects of Parkin on cancer cell proliferation are not limited to lung cancer cells.

Parkin is a tumor suppressor that has been actively investigated. However, the mechanisms by which Parkin prevents tumorigenesis are not completely understood. In this study, we explored the mechanisms underlying Parkin-mediated tumor suppression in lung and colorectal cancer cells. Our findings clearly showed that 1) Parkin expression induces DNA damage, 2) Parkin-mediated DNA damage elicits the ATM-dependent activation of p53, and 3) activated p53 induces the upregulation of p21 and downregulation of cyclin B1, which consequently halt the cell cycle at the G2/M phase and inhibit cancer cell proliferation (Supplementary Fig. 1). In conclusion, we report the tumor-suppressive role of Parkin in lung and colorectal cancer cells. The findings of this study highlight the potential of Parkin as a target molecule for gene therapy to manipulate cancers derived from the loss of *PARK2* heterozygosity.

MATERIALS AND METHODS

RNA interference-based gene knockdown experiment

siRNA transfection was performed as previously described (40). Briefly, cells were seeded in a six-well plate at a density of 2×10^5 cells/well. After 24 h, the cells were infected with the mock or Parkin virus and treated with siRNA simultaneously and then incubated for another 48 h. Prior to transfection, siRNAs (200 pmol) were mixed with liposomes in serum-free RPMI 1640 medium and then incubated for 30 min at room temperature. The mixture and the virus were added to the cells. After 4 h incubation, the cells were supplemented with fresh RPMI 1640 medium containing FBS (to set a final concentration of 10%) and then incubated at 37°C in a CO_2 incubator for a given time. The siRNA sequences were as follows: siRNA specific for Parkin, sense 5′-GCA CCU GAU CGC AAC AAA UTT-3′ and antisense 5′-AUU UGU UGC GAU CAG GUG CTT-3′; p53, sense 5′-GCG UGU GGA GUA UUU GGA UTT-3′ and antisense 5′-AUC CAA AUA CUC CAC ACG CTT-3′; non-specific siRNA, sense 5′-AUG AAC GUG AAU UGC UCA ATT-3′ and antisense 5′-UUG AGC AAU UCA CGU UCA UTT-3′. Non-specific siRNA was used as a universal control.

Comet assay

The comet assay was performed as previously described (41). Briefly, cells were centrifuged, washed with ice-cold PBS, resuspended in a 0.5% (w/v) solution of low temperature-melting agarose in PBS at 37°C, and then layered onto Comet slides (Trevigen, Gaithersburg, USA). The agarose-cell mixture was incubated at 4°C for 30 min and then placed in a lysis buffer for 30 min at 4°C in the dark. Subsequently, the slides were immersed in an alkaline unwinding solution. Electrophoresis was performed in an alkaline buffer at 1 V/cm for 25 min at 4°C, and the gel was washed twice in distilled water. After washing, the slides were dried at 45°C for 20 min and then stained with SYBR Green. Images were captured using a laser confocal scanning microscope (LSM 710; Zeiss, Heidenheim, Germany).

CONFLICTS OF INTEREST

The authors have no conflicting interests.

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