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# High Expression of Rab13 is Associated with Poor Survival of Patients with Non-Small Cell Lung Cancer via Repression of MAPK8/9/10-Mediated Autophagy

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Data Interpretation D  
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**Background:** Rab-like 3 (Rab13) is a member of the Rab subfamily of small GTPases which are involved in controlling proliferation and vesicular trafficking. Recent studies suggest that Rab proteins might play a critical role in regulating cancer cell survival, but the underlying mechanisms remain largely unknown.

**Material/Methods:** We performed a bioinformatics analysis to examine the correlation between the expression level of Rab13 and survival of non-small cell lung cancer (NSCLC) patients in three independent cohorts containing 484 patients. The function of Rab13 was examined in NSCLC cell line A549 *in vitro*. Following Rab13 knockdown, cells were stained with propidium iodine (PI) and Annexin V, followed by flow cytometry analysis (FACS) for cell death and autophagy induction. The activity of the MAPK signaling pathway was assessed by Western blotting of different MAPK phosphorylations, and modulated with different chemical inhibitors.

**Results:** High expression of Rab13 was significantly correlated with poor survival in all three independent NSCLC cohorts. In line with this result, Rab13 was frequently overexpressed in lung cancer cell lines as compared with normal lung fibroblast cell lines. Knockdown of Rab13 in lung cancer cells significantly enhanced cell death accompanied with autophagy induction, as evidenced by an increased level of autophagy marker LC3-II. Interestingly, Rab13 knockdown was associated with enhanced activation of MAPK8/9/10 but not MAPK11/12/13/14. Treatment of MAPK8/9/10-specific inhibitor SP600125, but not MAPK11/12/13/14-specific inhibitor SB203580, largely abolished Rab13 knockdown-induced LC3-I/LC3-II conversion and autophagic cell death.

**Conclusions:** Together, these results suggest that high expression of Rab13 might inhibit cell death in NSCLCs via repression of MAPK8/9/10-mediated autophagy.

**MeSH Keywords:** **Autophagy • Carcinoma, Non-Small-Cell Lung • Mitogen-Activated Protein Kinase Kinases**

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## Background

NSCLC is the most commonly diagnosed subtype of lung cancer and one of the most aggressive human malignancies, with poor survival [1,2]. Recent efforts in genetic studies have identified several reproducible genetic alterations underlying the pathogenesis of the disease, such as mutations in TP53, KRAS, and EGFR genes, which have already been proven successful in facilitating clinical decision-making in NSCLC [3–9]. In addition to genetic alterations, altered expression and activity of numerous signaling transductions have also been identified, and these are likely playing important roles in tumorigenesis and chemoresistance of lung cancer [4,6,7,10,11]. However, it is also well known that NSCLC is a disease with high genetic/cellular heterogeneity and diverse pathological features [10]. As a result, pinpointing a particular gene or biological process that is causally linked to the pathogenesis of the disease is rarely straightforward. In an attempt to identify genes putatively associated with NSCLC survival, we performed an integrative bioinformatics analysis using publically available transcriptome datasets of three independent NSCLC cohorts (n=484) using the DRUGSURV Database [12]. This initial screen allowed us to identify the RABL3 gene as one of the most sensitive predictors for poor prognosis of patients in all three cohorts.

The RABL3 gene belongs to the Rab subfamily, the largest group in the Ras superfamily of small GTPases, which contains over 70 putative members in the human genome [13]. Similar to other Ras superfamily proteins, Rab proteins may bind to GTP or GDP and possess intrinsic GTPase activity to control GDP/GTP conversion [13,14]. Genetic and functional studies on these Rab proteins, together with their associated regulators and effectors, have supported their putative roles in endosome formation, intracellular vesicular transport, and cytoskeleton formation [14–18]. Of note, the important role of the Ras subfamily in tumorigenesis has been well established, and emerging evidence indicates a link between alterations in the Rab small GTPases and tumorigenesis [19]. For example, recent studies showed that Rab25, another Rab protein, is frequently amplified and overexpressed in ovarian and breast cancer [19,20]. Overexpression of Rab25 decreased apoptosis and increased proliferation and aggressiveness in both breast and ovarian cancer cells [21]. In addition, it has also been shown that knockdown of Rabl3 impairs proliferation and motility in breast cancer cells *in vitro* [22]. We thus hypothesize that high expression of Rabl3 might be causally linked to proliferation and survival of lung cancer cells.

The MAPK signaling pathway is an evolutionarily conserved pathway that mediates the extracellular signals to the cellular machinery that controls a number of critical cellular processes, such as cell survival, proliferation, differentiation, and migration. Deregulation of the signaling has been frequently

observed in various cancers and is causally linked to tumorigenesis. Recently, there is growing evidence supporting the role of this pathway in autophagy regulation [23,24]. In the current study, we investigated the effects and putative mechanisms of Rabl3 on lung cancer cell viability. We found that Rabl3 is frequently overexpressed in lung cancer cell lines and knockdown of Rabl3 induced cell death accompanied with autophagy induction, and the mechanism may involve activation of MAPK8/9/10 signaling. These results support the hypothesis that Rabl3 functions as an oncogene in NSCLC and provide a novel potential therapeutic target for disease treatment.

## Material and Methods

### Cancer gene expression and survival

Gene expression profiles from three independent cohorts of NSCLC patients, annotated with survival information, were downloaded from the DRUGSURV database [12]. The GEO numbers of these datasets are GSE13213, GSE11969, and GSE31210, which included 116, 149, and 219 patients respectively. In each independent cohort, for each individual gene, patients with expression of that gene higher than the average of all patients were grouped into “high expression” while patients with expression lower than average were grouped into “low expression.” The probability that up/downregulation of a certain gene is associated ( $p$  value  $<0.01$ ) with patient survival was calculated using the log-rank test. Genes associated with significant differences in outcome were selected as a cancer gene signature in the dataset.

### Cell lines and culture conditions

Lung cancer cell lines A427, A549, HCC44, and normal lung fibroblast cell lines WI-26 VA4 and MRC-5, were obtained from the American Type Culture Collection (ATCC). All cells were cultured in DMEM (Gibco, USA), 10% (v/v) fetal bovine serum and with 100 Upenicillin and streptomycin, and were maintained in a humidified atmosphere, 95% air, 5% CO<sub>2</sub> at 37°C.

### Rabl3 siRNA

The sequence of siRNA used to knock down Rabl3 in A549 lung cancer cells was: si-Rabl3, 5'-CAAGAGCAUAUCUACAATT-3'. The sequence of the scrambled control siRNA was: scrambled, 5'-UUCUCCGAACGUGUCACGUTT-3'.

5×10<sup>5</sup> cancer cells were seeded in six-well plates for 24 hours, and then were transfected with 4 μL RNAi Max (Invitrogen, USA) and 6 μL siRNAs (20 μM). After 24 hours, cells were collected for protein Western blotting or FACS analysis.

## Western blotting

The cells transfected with different siRNAs were harvested following 24 hours of transfection and washed once with cold PBS. Cells were then suspended in an appropriate volume of lysis buffer (20 mM Tris HCl, pH 7.4, 150 mM NaCl, 1 mM EDTA, 1 mM EGTA, 1 mM PMSF and 1% Triton X-100) and incubated for 30 minutes at 4 °C. Cells were then centrifuged at the highest speed for 15 minutes and the supernatant was collected for quantification using the BCA protein quantification kit (Pierce, USA). 20 µg of proteins were separated by 4–12% SDS-PAGE and then transferred onto nitrocellulose membranes (Amersham Pharmacia, UK). Rab13 antibody (Proteintech, USA, 1:1000), LC3 antibody (Cell Signaling, USA, 1:1000), MAPK8 (Cell Signaling, USA, 1:2000), MAPK14 (Proteintech, USA, 1:2000), p-MAPK8/9/10 (Cell Signaling, USA, 1:1000) and p-MAPK11/12/13/14 (Cell Signaling, USA, 1:1000) and Actin Beta Antibody (Sigma, USA, 1:5000) were used.

## FACS analysis

Annexin V-PI staining (Thermo Fisher, USA) was performed to measure phosphatidylserine externalization in A549 cells transfected with different siRNAs for cell death detection. Briefly, trypsinized cells were collected and washed twice with ice-cold PBS, and resuspended in 200 µL of binding buffer containing 10 µL FITC-conjugated Annexin V and 5 µL of PI (propidium iodide). The staining sample was incubated at room temperature for 20 minutes and 10,000 cells were immediately analyzed using a FACSCalibur flow cytometer (Becton-Dickinson, USA).

## Results

### High expression of Rab13 is associated with poor survival of NSCLC patients

The availability of a vast amount of transcriptome datasets has allowed integrative analysis of data from different clinical studies and identification of gene signatures associated with a specific cancer type. To investigate gene signatures associated with NSCLC survival, we obtained three independent cancer expression datasets from the DRUGSURV database [12], including GSE13213 (relapse-related molecular signature in lung adenocarcinomas identifying patients with dismal prognosis), GSE11969 (expression profile-defined classification of lung adenocarcinoma) as well as GSE31210 (gene expression data for pathological stage i-ii lung adenocarcinomas). These datasets contain 116, 149, and 219 patients annotated with survival information, respectively. For each individual gene, patients were grouped with respect to expression rank of the gene in the same cohort, and the difference in survival outcome between the “low expression” and “high expression”

patient groups was determined using the log-rank test. This allowed us to identify Rab13 as one of the strongest predictors for survival of NSCLC patients. As shown in Figure 1A–1C, high expression of Rab13 was significantly associated with poor survival in all three cancer expression datasets tested (GSE13213,  $p=0.004$ ; GSE11969,  $p=0.005$ ; GSE31210,  $p=1.1e-6$ ).

Furthermore, we examined Rab13 expression in several lung cancer cell lines (A427, A549, and HCC44) and two normal lung fibroblast cell lines (WI-26 VA4 and MRC-5). Consistently, we observed that Rab13 expression was highly elevated in lung cancer cells as compared with normal lung fibroblast cells. These results suggested that RAB13 might function as an oncogene and elevated expression of Rab13 might facilitate tumorigenesis of NSCLC cells.

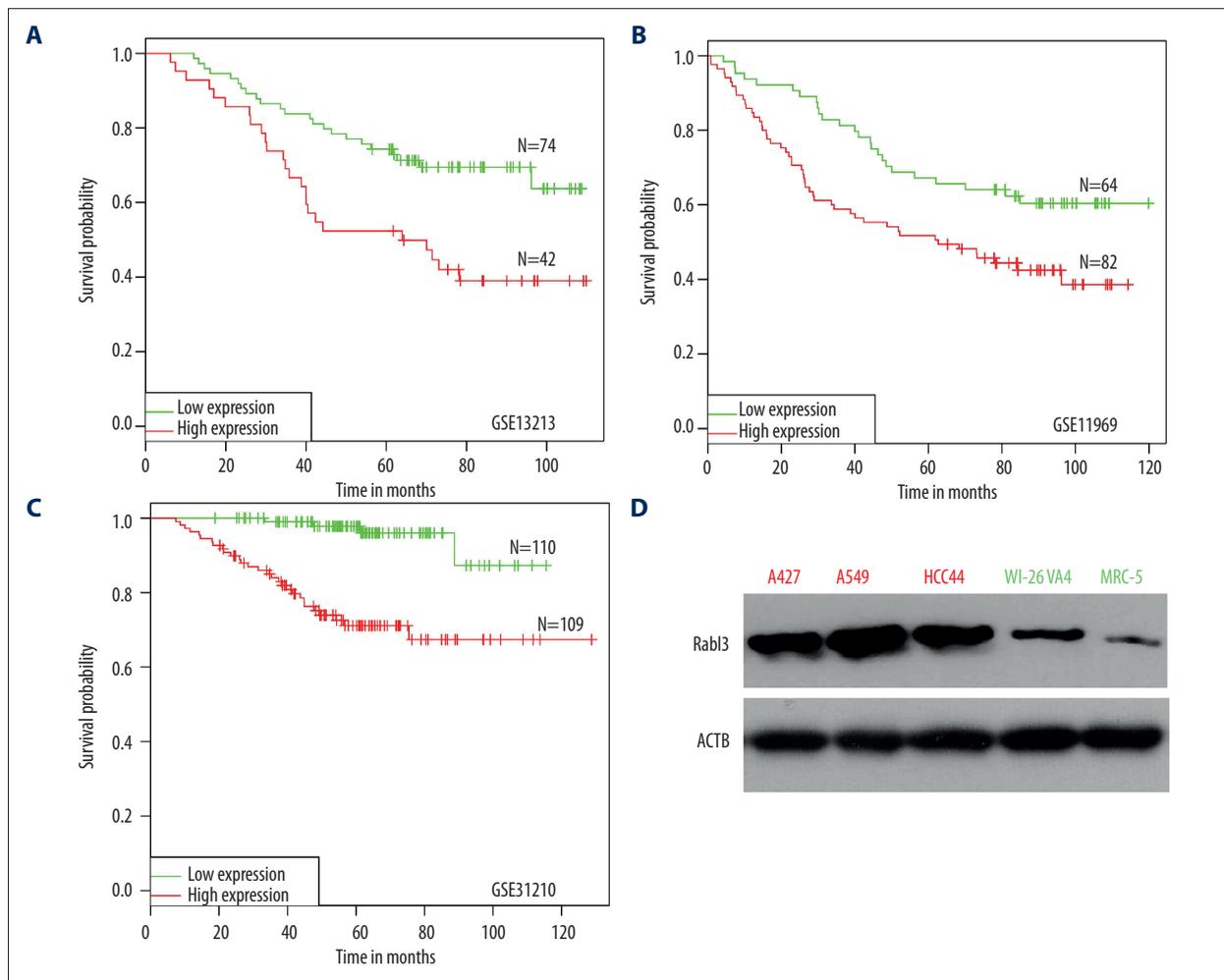
### Knockdown of Rab13 resulted in enhanced cell death accompanied by autophagy induction

To investigate the role of Rab13 in regulating lung cancer cell survival, we used siRNA to knock down Rab13 expression in A549 cells. As shown in Figure 2A, following siRNA transfection for 24 hours, we obtained robust knockdown of Rab13. Cells were then stained with PI and Annexin V and cell death was analyzed using FACS. As shown in Figure 2B and 2C, Rab13 knockdown resulted in significantly enhanced number of Annexin V positive cells, indicating enhanced apoptosis and cell death. Of note, we observed a large proportion of cells with positive signals for both PI and Annexin V, indicating induction of autophagic cell death.

This is consistent with a recent finding that knockdown of Rab25, which is another Rab protein, could robustly induce autophagy in ovarian cancer cells. To determine whether autophagy was activated by Rab13 knockdown, we used Western blotting to examine the conversion of LC3-I to LC3-II in these cells. LC3 functions in microtubule assembly and is involved in autophagy. In response to autophagy induction, LC3-I is lipidated and processed to LC3-II, which is targeted to the autophagosomal membrane and regarded as a sensitive marker for autophagy [25]. As expected, our results showed that Rab13 knockdown resulted in a robust increase in LC3-II level (Figure 2D), supporting enhanced autophagic cell death in these cells.

### Rab13 knockdown induces MAPK8/9/10-mediated autophagy

Previous studies have provided a putative link between the MAPK/ERK pathway and autophagy [26]. It has also been shown that Rab25 knockdown results in activation of MAPK/ERK signaling and enhanced autophagy in ovarian cancer cells [27]. However, there are a number of different protein kinase MAPKs that are activated and function as critical regulators



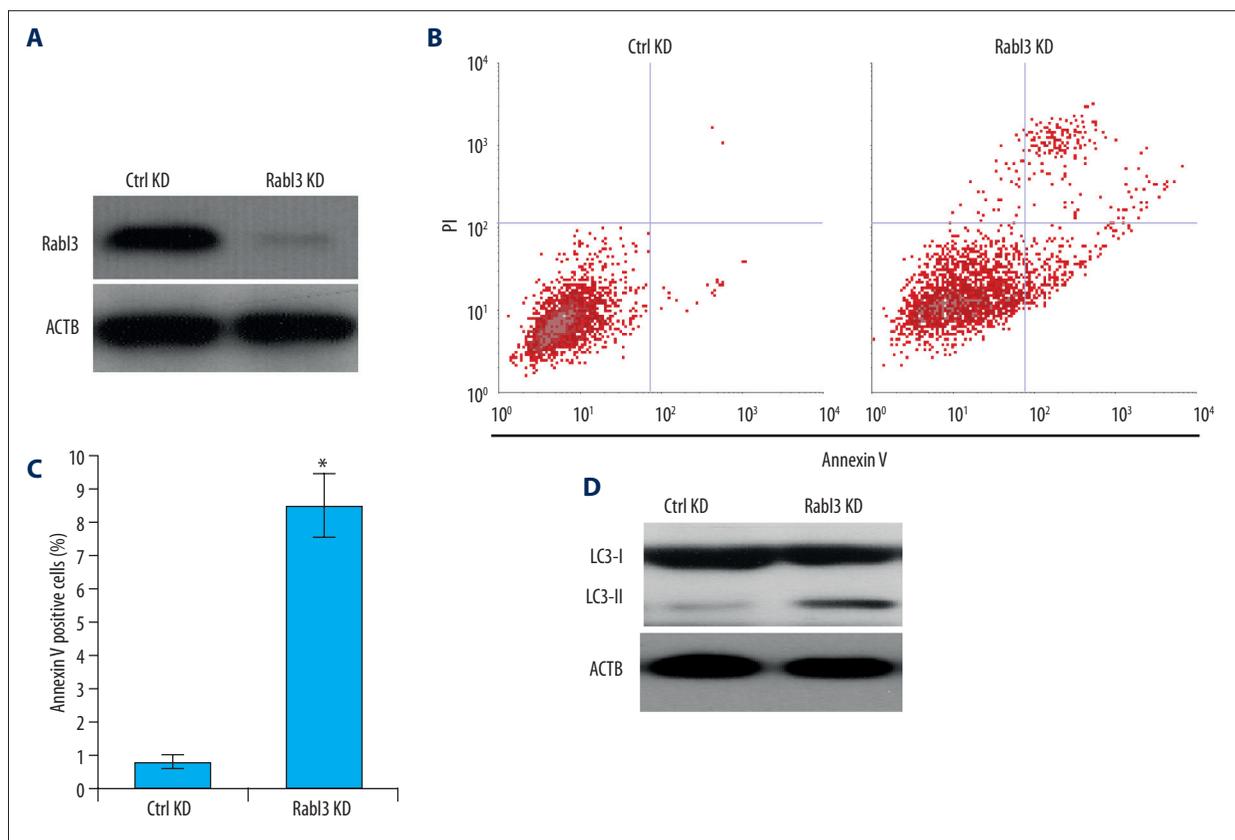
**Figure 1.** High expression of Rabl3 is associated with poor survival of NSCLC patients. (A) A plot of survival curves for patients with high expression of Rabl3 (n=42) and low expression of Rabl3 (n=74) in cancer gene expression dataset GSE13213. (B) A plot of survival curves for patients with high expression of Rabl3 (n=85) and low expression of Rabl3 (n=64) in cancer gene expression dataset GSE11969. (C) A plot of survival curves for patients with high expression of Rabl3 (n=109) and low expression of Rabl3 (n=110) in cancer gene expression dataset GSE31210. (D) Western blotting analysis of Rabl3 expression from different lung cancer cell lines in red (A427, A549, and HCC44) and normal lung fibroblast cell lines in green (WI-26 VA4 and MRC-5).

of autophagy under certain conditions. We thus examined the role of MAPK8/9/10 and MAPK11/12/13/14, the two major groups of MAPKs, in Rabl3 knockdown-induced autophagy. As shown in Figure 3A, Rabl3 knockdown resulted in a potent increase in MAPK8/9/10 phosphorylation, whereas only a small increase in MAPK11/12/13/14 phosphorylation was observed. A slight decrease in MAPK8 and MAPK14 expression was observed in Rabl3 knockdown cells. This result indicates that MAPK8/9/10, but not MAPK11/12/13/14, might be critical downstream regulators of autophagy following Rabl3 knockdown. To test this hypothesis, a MAPK8/9/10-specific inhibitor, SP600125, and a MAPK11/12/13/14-specific inhibitor, SB203580, were used to examine the effect of these MAPK kinases on Rabl3 knockdown-induced autophagy. Treatment

of both inhibitors did not significantly induce the conversion of LC3-I to LC3-II (Figure 3B). Of note, treatment of SP600125, but not SB203580, largely impaired Rabl3 knockdown-induced LC3-II production (Figure 3B). Consistent with this result, treatment of SP600125 could largely rescue autophagic cell death induced by Rabl3 depletion (Figure 3C). Together, these data suggest that Rabl3 knockdown-induced autophagy and cell death requires activation of MAPK8/9/10 signaling.

## Discussion

Lung cancer is the leading cause of cancer-related mortality worldwide, responsible for over 1.3 million deaths annually [2].



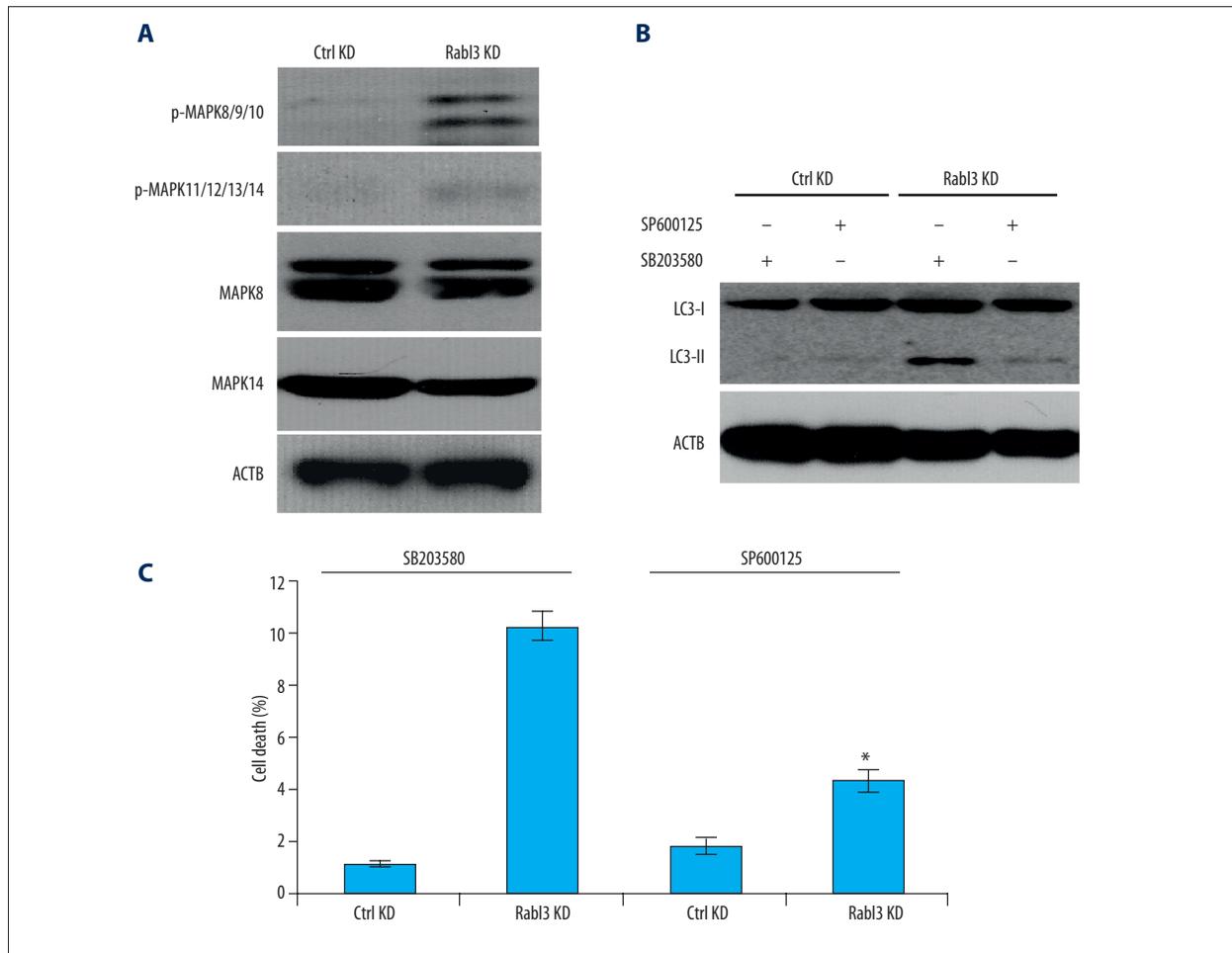
**Figure 2.** Knockdown of Rab13 induces autophagic cell death in A549 cells. **(A)** Western blotting analysis of Rab13 expression in cells transfected with control or Rab13 siRNAs. **(B)** FACS analysis of cells transfected with control or Rab13 siRNAs and stained with propidium iodide (PI) and Annexin V. **(C)** The percentage of Annexin V positive cells in cells transfected with control or Rab13 siRNAs. **(D)** Western blotting of LC3-I/LC3-II conversion in cells transfected with control or Rab13 siRNAs.

Identification of novel genes associated with patient survival is critical to developing new diagnostic and therapeutic methods for the disease. In this study, we performed an integrative bioinformatic analysis of cancer gene expression from several independent cohorts of NSCLC patients, and identified a robust correlation between high expression of Rab13 and poor survival of patients. We also provided evidence that elevated expression of Rab13 might facilitate cancer cell survival by reducing autophagic cell death.

Rab13 is a member of the Rab group of proteins, which form the largest subfamily of small GTPases involved in cellular transportation and cytoskeleton organization. Accumulating evidence supports the critical role of different Rab proteins in tumorigenesis. For example, it has been observed that Rab25 is overexpressed in ovarian cancer and is associated with enhanced proliferation and reduced cell death [20,27]. Similarly, previous results support the role of Rab13 in regulating proliferation and motility of breast cancer cells [22]. Another Rab family member, Rab20, is highly expressed in exocrine pancreatic carcinoma and has close relationships with tumor progression and aggressiveness [28]. These results are consistent with our

findings that Rab13 knockdown resulted in cell death accompanied by autophagy induction. As decline in autophagic activity is immediately linked to tumorigenesis, we thus suggest that reduced survival of patients with high Rab13 expression is at least partially caused by inhibition of cancer cell autophagy.

There are several possible mechanisms that might link Rab13 protein to autophagy. First, as Rab small GTPases are key regulators of the formation, transport, and infusion of transport vesicles [16], insufficiency of Rab13 might compromise protein transport and result in accumulation of unfolded or misfolded proteins in the ER lumen, leading to ER stress [29]. In response to ER stress, cells activate several integrated signaling pathways to restore homeostasis and normal ER function [30]. However, when overall cellular homeostasis is irreversibly perturbed, programmed cell death and autophagy signaling would be activated. Secondly, it is well known that autophagy is closely linked to vesicular formation and transport, while recent studies have suggested the critical role of Rab small GTPases in regulating autophagosome maturation. Deregulation of Rab13 might disturb the formation and function of autophagosomes and lead to abnormally activated



**Figure 3.** Involvement of MAPK8/9/10 activation in siRab13-induced autophagic cell death. **(A)** Western blotting of total protein and phosphorylation levels of MAPKs, MAPK8/9/10, and MAPK11/12/13/14 in cells transfected with control or Rab13 siRNAs. **(B)** Cells were transfected with different siRNAs and treated with MAPK8/9/10-specific inhibitor SP600125 or MAPK11/12/13/14-specific inhibitor SB203580, and LC3-I/LC3-II conversion was analyzed by Western blotting. **(C)** Percentage of cell death following Rab13 knockdown and treatment with SP600125 or SB203580.

autophagy. Meanwhile, under pathological conditions where Rab13 is highly expressed, autophagy might be compromised as a result of the crosstalk between Rab13 and the interacting proteins involved in autophagosome formation. Nevertheless, although further studies are required to clarify the underlying mechanisms of how Rab13 might participate in the autophagic process, our results provided robust evidence that depletion of Rab13 could trigger autophagy via activation of MAPK8/9/10 signaling. Although the role of Rab proteins and autophagy in the pathogenesis of NSCLC and other cancers still remains to be established, the possibility that autophagy could be induced in cancer cells via targeting Rab small GTPases is intriguing and merits further studies.

## Conclusions

Our results provided a putative role for Rab13 in repressing autophagy in NSCLC cells via inhibiting the activity of MAPK8/9/10. Further studies are required to characterize more comprehensively the Rab-associated network, and translate the findings into effective clinical treatment of NSCLC patients. Comprehensive understanding of the role of Rab proteins in regulating autophagic signaling pathways will provide knowledge regarding the mechanisms underlying tumorigenesis and metastasis. As the underlying mechanism comes to light, it is certain that these proteins and their regulators/ effectors will represent novel targets for therapeutic intervention in the future.

## Conflicts of interest

There are no conflicts of interest.

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