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Research article

Exploring the molecular mechanism of resveratrol for the treatment of lung adenocarcinoma based on molecular docking ☆

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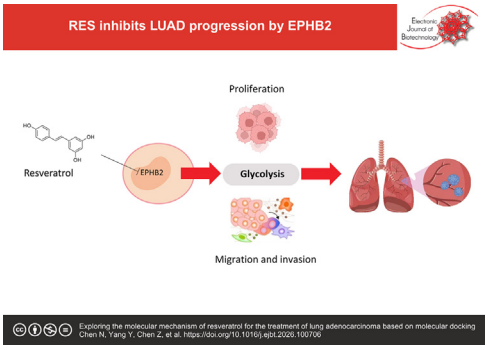
GRAPHICAL ABSTRACT

Exploring the molecular mechanism of resveratrol for the treatment of lung adenocarcinoma based on molecular docking.



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ABSTRACT

Background: Resveratrol (RES) has been found to inhibit the progression of lung cancer. Our study aims to explore the molecular mechanisms by which RES regulates lung adenocarcinoma (LUAD) progression.
Results: Our study unveils two key novel findings: First, our study demonstrates that EPHB2 is a direct functional target of RES in LUAD. Molecular docking and CETSA confirmed the binding, and crucially, EPHB2 overexpression reversed the anti-tumor effects of RES. Second, our study reveals a previously unrecognized role for EPHB2 in promoting glycolysis in LUAD, which is effectively suppressed by RES. Specifically, RES potently inhibited LUAD tumor growth *in vivo* and suppressed cell proliferation, migration, invasion, and glycolysis *in vitro*. These inhibitory effects were consistently abolished upon EPHB2 overexpression.
Conclusions: Collectively, our findings suggest that RES inhibits LUAD cell proliferation, migration, invasion, and glycolysis, with EPHB2 downregulation appearing to contribute to these effects. Further studies are needed to determine whether RES directly targets EPHB2 and to evaluate the translational potential of these findings.
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1. Introduction

Lung adenocarcinoma (LUAD), belongs to non-small cell lung cancer (NSCLC), is mainly caused by malignant lesions of the mucosal epithelium or mucous glands [1,2]. The early cure rate of LUAD is high, while patients with middle and advanced stage are mostly treated with comprehensive treatment [3,4]. Despite advances in standard therapies, a significant clinical challenge persists in overcoming tumor progression and treatment resistance. This underscores the critical need to explore effective adjuvant agents and elucidate their precise molecular mechanisms of action, which may lead to novel therapeutic strategies for LUAD.

Resveratrol (RES) is a natural polyphenol with strong biological properties, which has anti-inflammatory, antiviral, antioxidant and neuroprotective effects [5,6,7]. Notably, RES is a phytoalexin, a class of compounds produced by plants in response to stress, injury, or pathogen attack. This intrinsic role in plant defense mechanisms may underlie its broad-spectrum biological activities in mammals, including its observed anti-cancer effects. Importantly, more and more studies have confirmed that RES has anti-cancer effects [8]. For example, RES repressed breast cancer cell proliferation and increased chemosensitivity [9]. The development of nanoparticles provides a promising strategy for targeted delivery [10]. Nano-formulated RES inhibited cancer-stem-like-cell proliferation, metastasis and angiogenesis in oral cancer [11]. Xie et al. [12] suggested that RES suppressed the properties of lung cancer stem-like cells, thus inhibiting lung cancer malignancy progression. Besides, RES could activate NSCLC cell autophagy and apoptosis [13]. However, the underlying molecular mechanisms by which RES exerts its anti-cancer effects in LUAD remain to be further revealed.

It is important to introduce new molecular insights into cancer research to complement existing diagnostic and therapeutic approaches [14]. Eph receptor B2 (EPHB2) is an important member of the Eph receptor family and has been shown to mediate tumorigenesis as a cancer-promoting factor, such as gastric cancer [15] and hepatocellular carcinoma [16]. In lung cancer, the androgen receptor enhanced cell invasion by increasing EPHB2 protein expression [17]. EPHB2 was found to promote the glutamine pathway to accelerate LUAD cell proliferation and metastasis [18]. Notably, among the Eph receptor family members, EPHB2 has been consistently associated with aggressive tumor phenotypes and poor prognosis in multiple cancer types, making it a compelling candidate for investigating RES-mediated anti-cancer effects. However, whether RES mediates LUAD malignant behavior through regulating EPHB2 has not been explored.

Based on these findings, our study hypothesized that RES might exert its anti-tumor effects in LUAD by targeting EPHB2. To test this hypothesis, our study selected a RES concentration of 100 μM for *in vitro* experiments and 40 mg/kg for *in vivo* studies, which are consistent with concentrations previously shown to elicit significant anti-cancer effects in preclinical models [19,20,21,22,23,24]. This study aims to elucidate the molecular mechanisms by which RES regulates LUAD progression, with a focus on the role of EPHB2, thereby providing new insights for LUAD treatment.

2. Materials and methods

2.1. Database download

TIMER database was used to analyze EPHB2 expression in pan-cancer tissues and normal tissues. Besides, GEPIA and TCGA databases were used to assess EPHB2 expression in LUAD and lung squamous cell carcinoma (LUSC) tissues. Following the methodology of previous studies [25], the expression of differentially expressed genes (DEGs) was analyzed by genomic expression profiling. The DEGs in NSCLC tissues and normal tissues were downloaded from the GEO database (accession number: GSE268175), and the DEGs in RES-treated and untreated A549 cells were downloaded from GSE9008. Limma method was used to analyze the DEGs, with the screening criteria as adj. $p < 0.05$ and $|\log2FC| < -1$ or $|\log2FC| > 1$. The results were displayed as a volcano map.

2.2. Cell culture and transfection

Human LUAD cell lines (A549 and H1299) and airway epithelial cells (16HBE) were purchased from Biovector (Beijing, China) and cultured in RPMI-1640 medium. LUAD cells were treated with 100 μM RES [19,20] (Sigma-Aldrich, St. Louis, MO, USA) to explore the effect of RES on LUAD progression. At 24 h before RES treatment, LUAD cells were transfected with the EPHB2 overexpression vector and a negative control (vector) by Lipofectamine 3000 (Invitrogen, Carlsbad, CA, USA).

2.3. Molecular docking and dynamic investigation

The crystal structure of human EPHB2 (PDB ID: 3ZFM) was used for docking analysis. The docking results of RES and EPHB2 were evaluated using the normal mode analysis (NMA) of iMOD server. The binding energies were preprocessed with PyMOL software and calculated by AutoDock Vina 1.1.2 with central coordinates (x: −12.129, y: −4.214, z: −19.761) and box size (x: 44 Å, y: 66 Å, z: 56 Å), as the transparent reporting provided in previous studies [10]. Besides, molecular deformability and B factor were analyzed to assess the stability of proteins.

2.4. CCK8 assay

A549 and H1299 cells were treated with different concentrations (25, 50 and 100 μM) of RES for 24 h. After that, cells were incubated with CCK8 reagent (Beyotime, Shanghai, China) for 2 h, and cell viability was detected at 450 nm using a microplate reader.

2.5. Cellular thermal shift assay (CETSA)

CETSA was employed to assess alterations in the stability of the EPHB2 protein. A549 cells were treated with 100 μM RES or DMSO for 12 h at various temperatures (42, 47, 52, 57, and 62°C). Western blot (WB) was conducted to determine any changes in EPHB2 protein levels.

2.6. Animal models

BALB/c nude mice (SPF Biotechnology Co., Ltd., Beijing, China) were injected with A549 cells (1×10^6 cells) at the right flanks subcutaneously. At the 7th day, mice were administered intraperitoneally injected with RES (40 mg/kg) or the same volume of DMSO once daily (n = 6/group). Tumor volumes were monitored weekly, and tumor tissues were collected after the animals were sacrificed at 4 weeks. Animal studies were approved by the Animal Ethics Committee of ShunDe Hospital GuangZhou University of Chinese Medicine (ShunDe District Hospital of Chinese Medicine of Foshan City).

2.7. Immunohistochemistry (IHC) staining

The tumor tissues of mice were fixed with 4% paraformaldehyde and then embedded to prepare paraffin sections. Sections

were treated with blocking buffer and incubated with anti-Ki-67 (ab16667, Abcam, Cambridge, MA, USA), anti-EPHB2 (ab252935, Abcam), anti-GLUT1 (ab115730, Abcam), anti-HK2 (ab209847, Abcam) and secondary antibody (ab6720, Abcam). After sections were stained with DAB, Ki-67/EPHB2/GLUT1/HK2-positive cells were visualized under a microscope with ImageJ software. Five randomly selected fields of view were captured at 200x magnification using a light microscope. The entire process of image acquisition and analysis was performed in a blinded manner. The person who captured the images and performed the counting was unaware of the group assignment of the samples. The quantitative data from the five fields per sample were averaged to represent a single biological replicate. This approach helps to account for intra-tumor heterogeneity.

2.8. Western blot

Extracted proteins were transferred to PVDF membranes after being separated by SDS-PAGE gels. Membrane was treated with anti-EPHB2 (1:1000, ab252935, Abcam), anti-β-actin (1:1000, ab8227, Abcam), and Goat anti-Rabbit IgG (1:20000, ab97051, Abcam). Protein bands were visualized using ECL reagent and analyzed by ImageJ software.

2.9. Colony formation assay

LUAD cells seeded into 6-well plates were cultured for 14 d. Then, the colonies were stained with crystal violet, and colony numbers were analyzed under a microscope.

2.10. Transwell assay

LUAD cells were suspended with serum-free medium and seeded into the upper of the transwell chamber (Corning Inc., Corning, NY, USA), which was pre-coated with Matrigel (Corning Inc.) for testing cell invasion. After cultured for 24 h with complete medium as an inducer in the lower chamber, migrated and invaded cells were stained with crystal violet, followed by counting under a microscope.

2.11. Detection of cell glycolysis

Glucose uptake, lactate production and ATP level in LUAD cells were determined according to the instructions of Glucose Uptake Assay Kit (ab136955, Abcam), Lactate Assay Kit (ab65330, Abcam) and ATP Detection Assay Kit (ab113849, Abcam), respectively. The number of cells was used as a reference.

2.12. Statistical analysis

All experiments were performed in triplicate, with each independent experiment set 3 times to generate an average value. Data were analyzed as mean ± SD, and comparisons were analyzed using Student's *t*-test (for two groups) or ANOVA with Tukey post-hoc test (for multiple groups) by GraphPad 8.0 software. $p < 0.05$ denotes a statistically significant result.

3. Results

3.1. EPHB2 expression in LUAD cells and RES-treated A549 cells by bioinformatics

TIMER, GEPIA and TCGA databases analyzed that EPHB2 was higher expressed in LUAD and LUSC tissues (Fig. 1A–C). Also, GEO database (GSE268175 and GSE9008) showed that EPHB2 was a significantly overexpressed gene in NSCLC tissues (Fig. 1D), and it was a downregulated gene in RES-treated A549 cells (Fig. 1E).

3.2. Molecular docking and dynamic simulation analyzed the binding of RES and EPHB2

To explore the binding affinity of active ingredients of RES and EPHB2, molecular docking analysis was performed. The chemical construction of RES is shown in Fig. 2A. The molecular docking results indicated that the critical active ingredients of RES exhibited excellent binding affinity (−6.9 kcal/mol) for EPHB2 (Fig. 2B). The key interaction residues between RES and EPHB2 included ILE-697, THR-699, VAL-635, PHE-701, MET-702, and LEU-753. Among them, RES forms 2.7 Å proximity interaction with ILE-697, 3.9 Å interaction with THR-699, 3.4 Å interaction with VAL-635, and 3.6 Å interaction with PHE-701, 3.9 Å interaction with MET-702 and 3.4 Å interaction with LEU-753. These residues jointly stabilize the conformation of resveratrol in the EPHB2 binding pocket through hydrophobic interactions and van der Waals forces, providing a molecular basis for its regulation of cell proliferation and migration. By analyzing the deformability and B factor, our study determined that the amino acid residue deformation was reasonable (Fig. 2C), and the protein structure was in the natural motion mode (Fig. 2D). In addition, under the treatment of different concentrations of RES, the present study found that LUAD cell viability was gradually decreased with the increase of RES concentration (Fig. 2E). Furthermore, CETSA analysis demonstrated that RES augmented the thermal stability of EPHB2 (Fig. 2F). Therefore, the molecular docking and CETSA results suggest a potential binding interaction between RES and EPHB2.

3.3. RES reduced LUAD tumor growth in vivo

To further explore the role of RES on LUAD tumorigenesis, animal models were constructed. Compared with the CON group, tumor size, weight and volume were markedly reduced in the RES group (Fig. 3A–C). Besides, the positive cells of Ki-67, EPHB2, GLUT1 and HK2 were significantly decreased in the tumor tissues of RES group (Fig. 3D–E). Thus, our study believed that RES played antitumor activity by decreasing EPHB2 expression.

3.4. RES inhibited LUAD cell proliferation and metastasis by downregulating EPHB2 in vitro

As shown in Fig. 4A, EPHB2 protein level was markedly enhanced in LUAD cells (A549 and H1299). To investigate the role of EPHB2 in LUAD progression and whether it was involved in the regulation of RES, rescue experiments were performed. The transfection of EPHB2 overexpression vector markedly increased EPHB2 protein expression in A549 and H1299 cells (Fig. 4B). RES treatment reduced EPHB2 level in LUAD cells, and RES + EPHB2 group markedly enhanced EPHB2 level compared to the RES + Vector group (Fig. 4C). RES reduced cell colony numbers, and migration/invasive cell numbers, while RES + EPHB2 group increased cell colony numbers, and migration/invasive cell numbers compared to the RES + Vector group (Fig. 4D–F). All data indicated that RES suppressed EPHB2 expression to restrain LUAD cell progression.

3.5. RES inhibited LUAD cell glycolysis by EPHB2 in vitro

GEPIA database analyzed that EPHB2 expression was positively correlated with glycolysis-related markers (SLC2A1, HK2 and LDHA) (Fig. 5A). To further explore whether the RES/EPHB2 axis regulated cell glycolysis to mediate LUAD progression, the effect of RES/EPHB2 axis on LUAD cell glycolysis was explored. Our

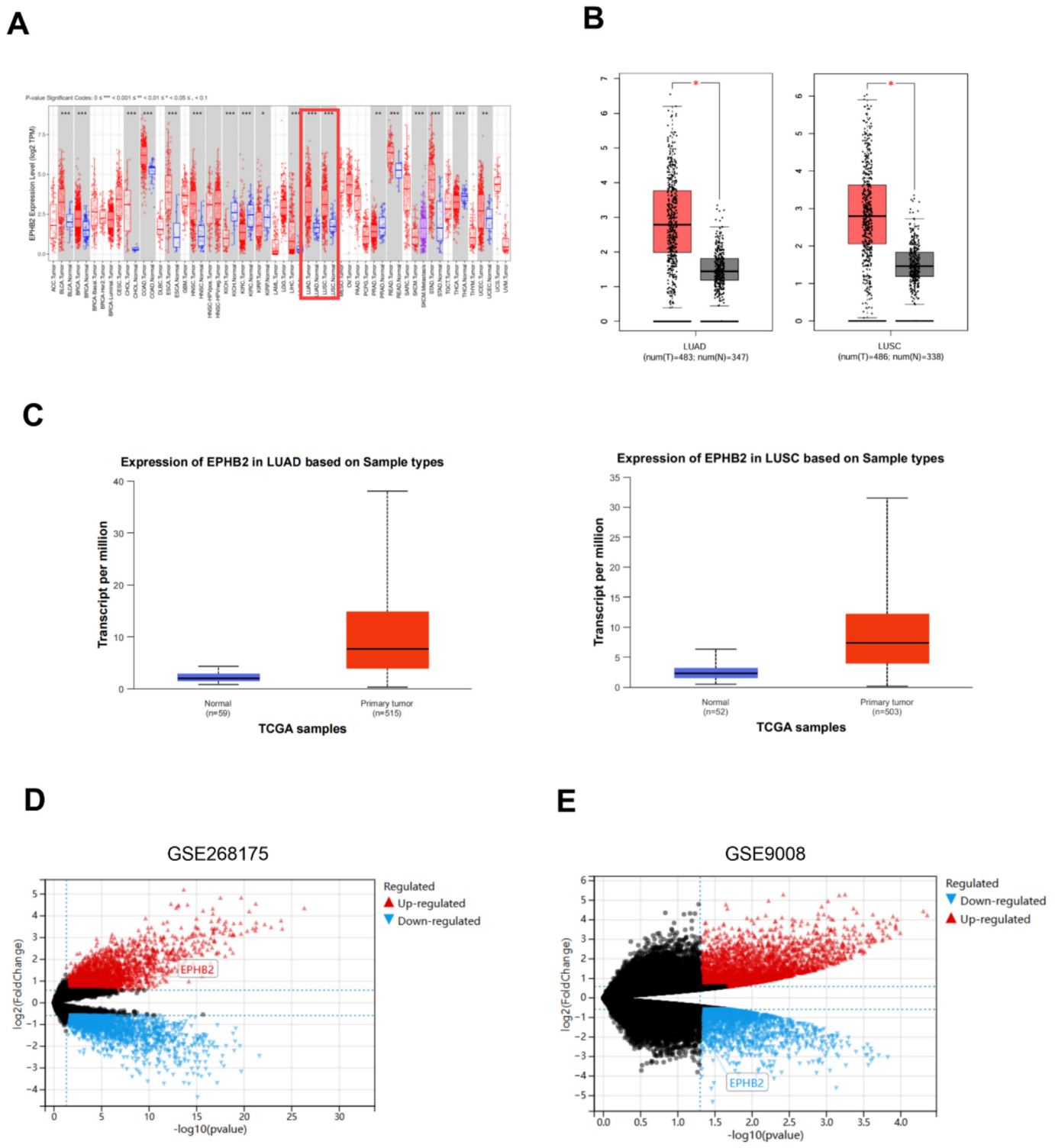

Fig. 1. Effect of RES on EPHB2 expression in LUAD cells. (A) TIMER database, (B) GEPIA database and (C) TCGA database were used to analyze EPHB2 expression in LUAD and LUSC tissues. (D–E) Volcano map showed the differentially expressed genes in NSCLC tissues by GEO database (GSE268175), and the differentially expressed genes in A549 cells treated with or without RES by GEO database (GSE9008).

results showed that EPHB2 overexpression markedly enhanced glucose uptake, lactate production and ATP level in A549 and H1299 cells (Fig. 5B). Besides, RES treatment significantly decreased glucose uptake, lactate production and ATP level in A549 and H1299 cells, while RES + EPHB2 group markedly enhanced these levels in this effect compared to the RES + Vector group (Fig. 5C). All data indicated that RES reduced EPHB2 expression to repress LUAD cell glycolysis.

4. Discussion

It has been found that many natural extracts may mediate cancer progression. For example, triptolide restrained colon cancer cell migration by decreasing macrophage infiltration and M2 polarization [26]. Curcumin suppressed the progression of LUAD [27], as well as paclitaxel chemoresistance of breast cancer [28]. Astragaloside IV inhibited ovarian cancer cell proliferation and metastasis via antago-

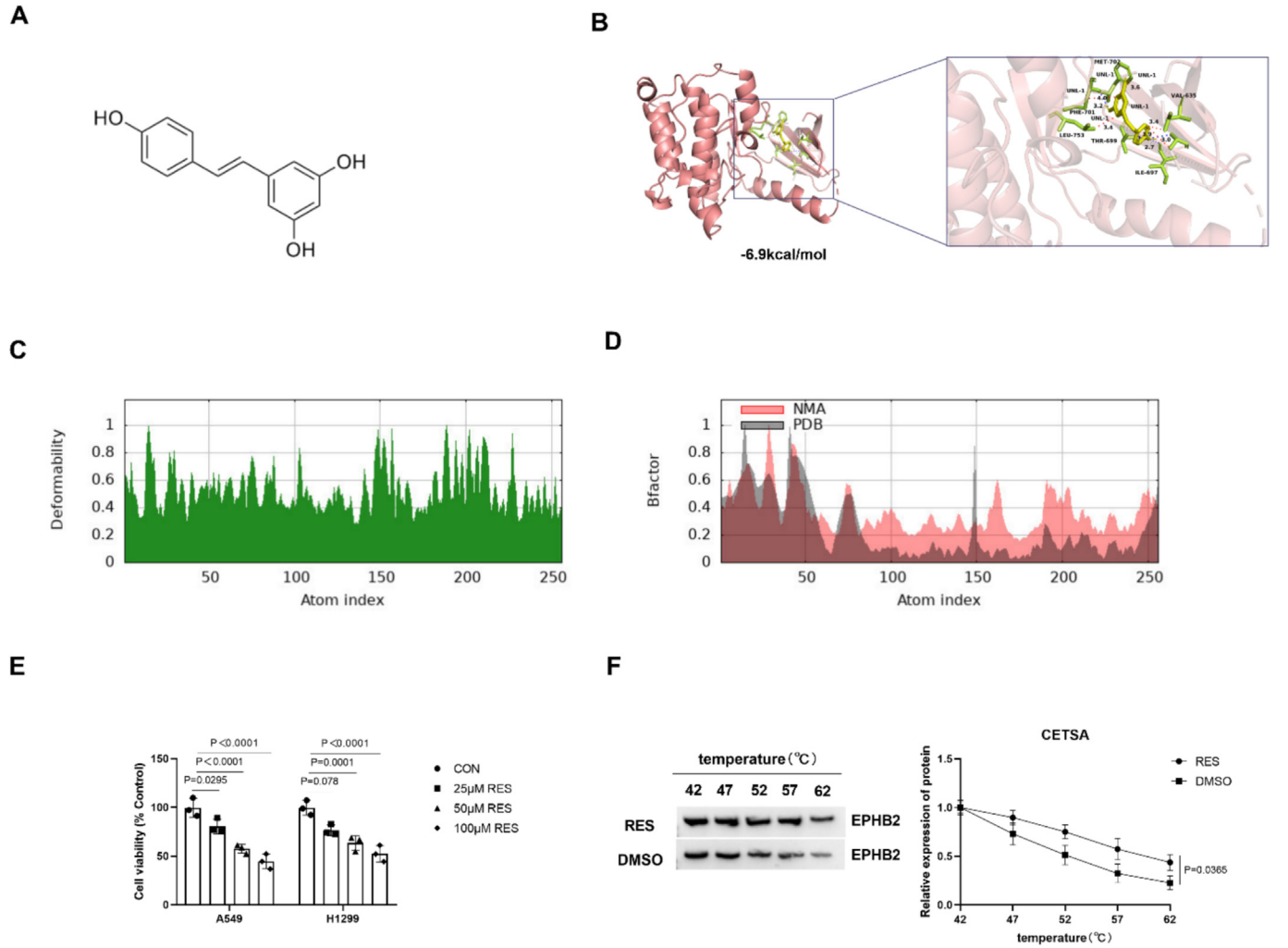

Fig. 2. Molecular docking results. (A) The chemical construction of RES. (B) Docking complex of RES with EPHB2. (C–D) Molecular fluctuation plot of RES indicated by NMA. (E) LUAD cell viability was examined using CCK8 assay under the treatment of different concentrations (25, 50 and 100 μM) of RES (n = 3). (F) CETSA analysis was used to assess the regulation of RES on the thermal stability of EPHB2 (n = 3). E–F, two-way ANOVA with Tukey post-hoc test.

nizing macrophage polarization [29]. The above studies confirmed the important functions of natural extracts in anti-tumorigenesis. Here, this study found that RES had a repressing effect on LUAD cell proliferation, metastasis and glycolysis by downregulating EPHB2, which provided new ideas for an in-depth understanding of the anti-cancer effect of RES in LUAD.

RES, a polyphenolic compound, is considered as a natural chemopreventive agent for cardiovascular/cerebrovascular diseases and cancers [30]. RES protected against myocardial ischemia/reperfusion injury via inhibiting cell oxidative stress and ferroptosis [31]. RES reduced excessive ROS production and elevated antioxidant enzyme activity to alleviate cerebrovascular diseases [32]. RES has more significant cytotoxicity in cancer cells, which may induce cell apoptosis and inhibit cell cycle to restrain cancer malignancy progression [33]. Previous studies confirmed the anti-tumor role of RES on lung cancer [12,13]. Besides, RES derivatives could suppress NSCLC cell growth via inhibiting the activity of Akt/mTOR pathway [20]. Here, this study found that RES reduced LUAD tumorigenesis *in vivo*, and inhibited LUAD cell proliferation, migration, invasion and glycolysis *in vitro*. The above evidence suggests that RES can inhibit the malignant progression of LUAD.

EPHB2 belongs to the tyrosine protein kinase receptor family and has been shown to regulate dermal fibrosis [34], nonalcoholic steatohepatitis [35], and neurogenic inflammation [36]. EPHB2 may be a novel independent prognostic marker for gastric cancer, whose knockdown suppresses cancer cell invasion and migration [37,38]. EPHB2 was overexpressed in colorectal cancer, and it might promote proinflammatory cytokine production in colorectal epithelial cells [39]. The above results confirm the positive role of EPHB2 in cancer progression. According to a previous study, EPHB2 has been found to enhance lung cancer development [17], and it may regulate M2 macrophages polarization to accelerate LUAD cell metastasis [18]. Through database analysis and experimental detection, EPHB2 was confirmed to be highly expressed in LUAD tissues and cells. Besides, molecular docking was used to confirm the potential binding interaction between RES and EPHB2. Functional experiments revealed that RES decreased EPHB2 expression, and EPHB2 ectopic expression could reverse the inhibitory effect of RES on LUAD cell proliferation, metastasis and glycolysis, suggesting that RES might contribute to LUAD malignancy progression by reducing EPHB2 expression. Our study reveals a novel link between EPHB2 and glycolysis in LUAD, extending its known tumor-promoting function. Our study hypothesized that EPHB2, as a receptor tyrosine kinase, may affect glycolytic processes by regulating downstream signaling cascades (such as the PI3K/Akt or MAPK pathways, which are well-established master regulators of glycolytic enzymes, including HK2 and GLUT1). Elucidating the exact molecular bridge between EPHB2 signaling and metabolic reprogramming will be a key focus of our future work.

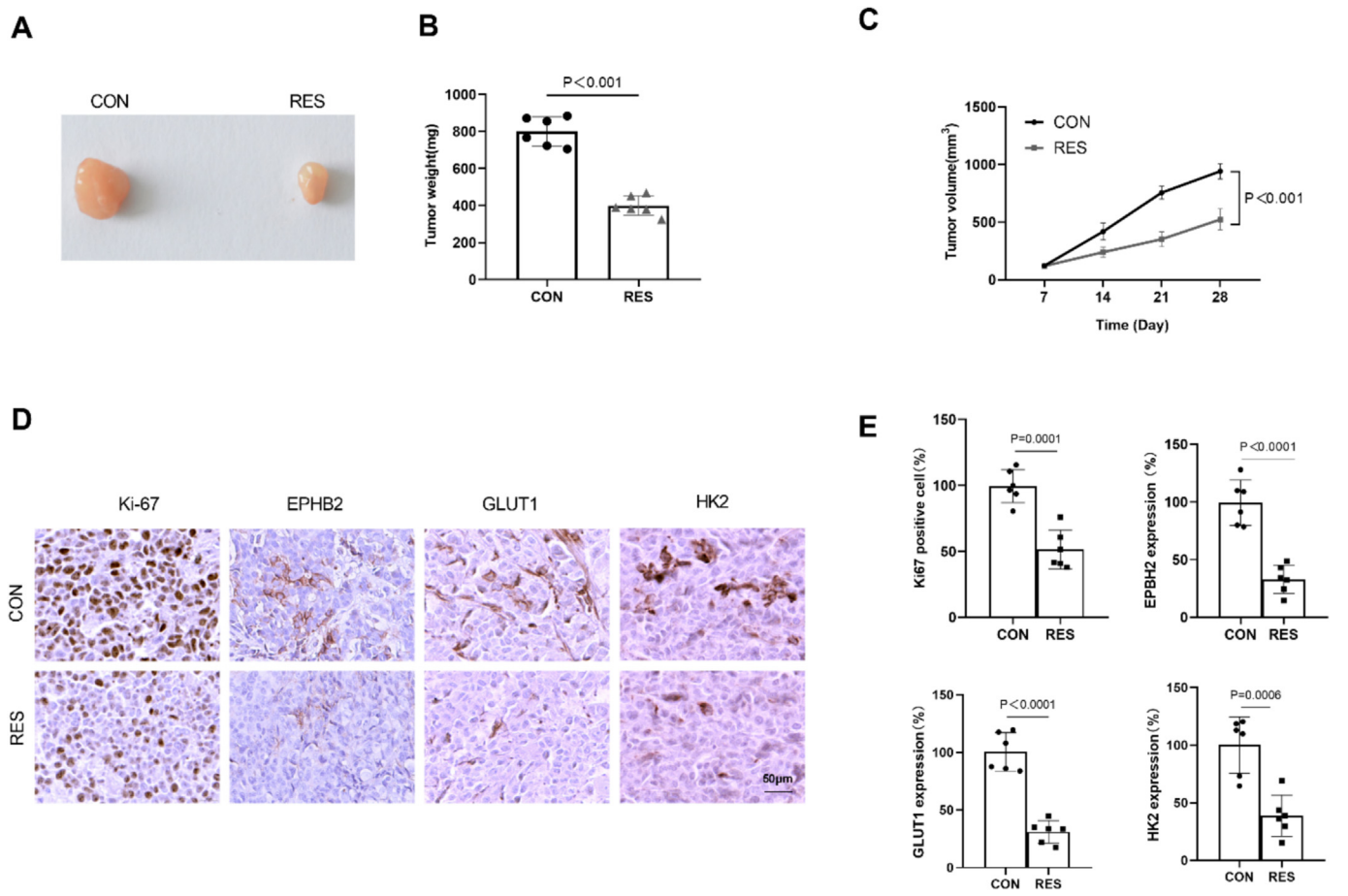

Fig. 3. Effect of RES on LUAD tumor growth *in vivo*. Mice were injected with A549 cells and RES (n = 6). (A–C) Tumor picture, weight and volume were shown. (D–E) IHC staining was used to measure Ki-67, EPHB2, GLUT1 and HK2 positive cells in mice tumor tissues. A and E, Student's t-test; C, two-way ANOVA with Tukey post-hoc test.

For the use of 100 μM concentration of RES *in vitro*, although it is higher than human plasma levels achievable with regular dietary intake, it is widely used in cancer cell line studies [40,41]. This is because cancer cells are more metabolically active and drug resistant than normal cells, and relatively high concentrations are required to observe significant biological effects (e.g., inhibition of proliferation, induction of cell death). In addition, 100 μM is within the concentration range that can be achieved in local tissues (e.g., tumor microenvironment) by targeted delivery strategies (e.g., nanocapsules, prodrugs) or high-dose supplements, which have been actively explored in both preclinical and clinical studies [19,20]. In addition, the dose of 40 mg/kg for RES *in vivo* experiments is consistent with the concentration commonly used in mouse models of breast cancer [21,22]. Studies have confirmed that when the dose of RES is not less than 30 mg/kg and the treatment lasts for 25–28 d, the tumor volume is significantly inhibited [23]. Importantly, preclinical studies have confirmed that this dose can inhibit tumor growth without causing obvious systemic toxicity, with good safety and efficacy [24]. Administration of very high doses of RES to humans, such as doses comparable to those used in some animal experiments, is not currently recommended due to concerns about potential side effects and interactions. Although RES has shown promising effects in preclinical studies, the limitations of translating these findings into human applications must be considered.

While our study provides evidence supporting the role of the RES-EPHB2 axis in LUAD progression, several limitations should be acknowledged. Firstly, the binding between RES and EPHB2, predicted by molecular docking and supported by CETSA, requires further direct validation through methods such as surface plasmon resonance (SPR) or isothermal titration calorimetry (ITC). Secondly, our *in vitro* experiments primarily utilized a single concentration of RES (100 μM) to demonstrate the phenotypic effects. Future studies incorporating a dose–response design would strengthen the conclusion and provide insights into the potency of RES. Thirdly, RES is known for its multi-target nature; although our study identified EPHB2 as a potential target, we cannot rule out the contribution of other off-target effects to the observed anti-tumor activities. Finally, and most importantly from a translational perspective, the concentrations of RES effective in our *in vitro* system (100 μM) and the dose used *in vivo* (40 mg/kg) are considerably higher than the peak plasma levels (typically in the low micromolar range) achievable through dietary intake or even high-dose supplementation in humans. This highlights a significant challenge in translating these findings directly into clinical practice. Future research should focus on developing innovative strategies to overcome this limitation. Plant biotechnology approaches, such as metabolic engineering for enhanced RES production or the synthesis of bioavailable derivatives, coupled with advanced drug delivery systems (e.g., nanoparticle encapsulation), hold promise for improving the pharmacokinetic profile and tumor-targeted delivery of RES or its analogues. Additionally, identifying more potent and specific EPHB2 inhibitors based on the RES pharmacophore represents another viable direction.

Taken together, our findings demonstrate that the anti-tumor effects of RES in LUAD are mediated, at least in part, through the

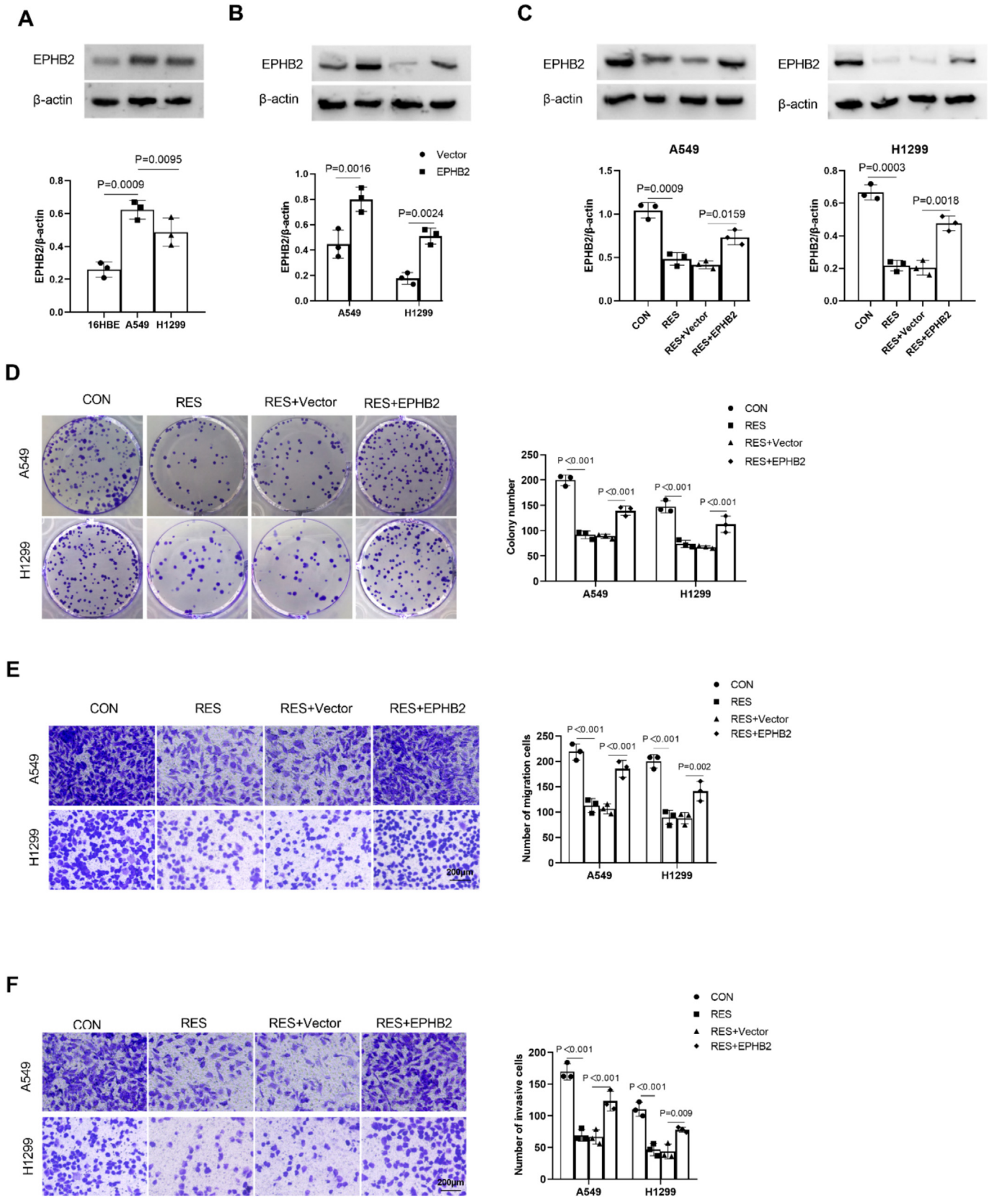

Fig. 4. Effect of RES and EPHB2 on LUAD cell proliferation and metastasis. (A) EPHB2 expression was examined by WB in LUAD cells and 16HBE cells (n = 3). (B) The transfection efficiency of EPHB2 overexpression vector was confirmed by WB (n = 3). (C–F) A549 and H1299 cells were transfected with vector/EPHB2 and treated with RES (100 μM) (n = 3). (C) EPHB2 protein expression was examined by WB. Cell proliferation, migration and invasion were determined using (D) colony formation assay and (E–F) transwell assay. A and C, one-way ANOVA with Tukey post-hoc test; B and D–F, two-way ANOVA with Tukey post-hoc test, with the tested factors: Cell line and Treatment.

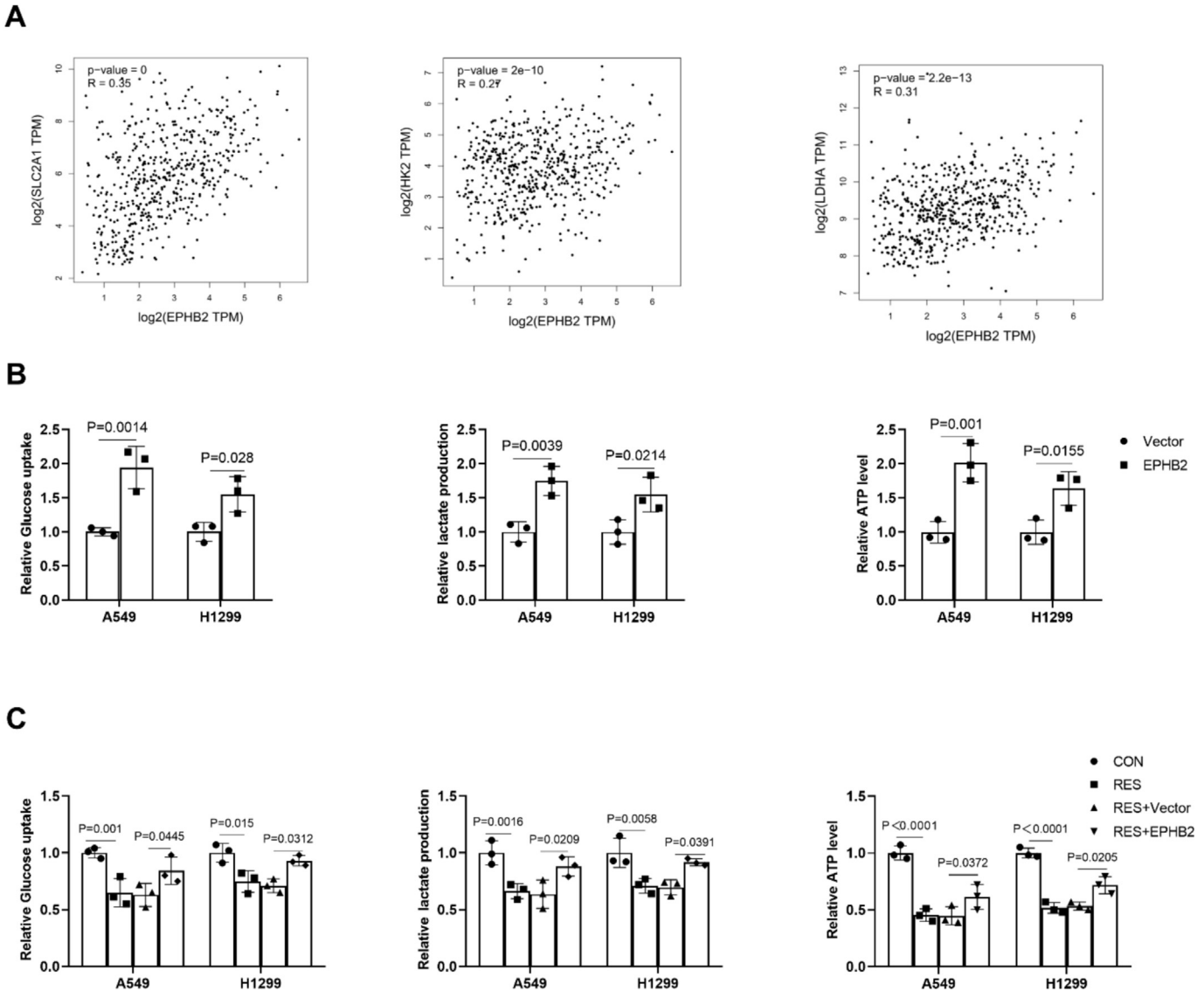

Fig. 5. Effect of RES and EPHB2 on LUAD cell glycolysis. (A) GEPIA database analyzed the correlation between EPHB2 and glycolysis-related proteins (SLC2A1, HK2 and LDHA). (B) Glucose uptake, lactate production and ATP levels were examined by corresponding kits in A549 and H1299 cells transfected with vector/EPHB2 (n = 3). (C) Corresponding kit was used to detect glucose uptake, lactate production and ATP levels in A549 and H1299 cells transfected with vector/EPHB2 and treated with RES (n = 3). B–C, two-way ANOVA with Tukey post-hoc test, with the tested factors: Cell line and Treatment.

direct targeting and downregulation of EPHB2. This work not only deciphers a novel molecular mechanism underlying RES's activity but also positions EPHB2 as a promising therapeutic vulnerability in LUAD. The RES/EPHB2 axis provides a rational foundation for future therapeutic development, suggesting that either natural compounds like RES with improved bioavailability, or more potent synthetic inhibitors targeting EPHB2, could represent viable strategies for LUAD management. Furthermore, combining EPHB2 modulation with conventional chemotherapy or targeted agents may open new avenues for overcoming drug resistance and improving patient outcomes.

CRediT authorship contribution statement

Nan Chen: Writing – original draft, Supervision, Resources, Project administration. **Yang Yang:** Data curation. **Zhuoyu Chen:** Software, Formal analysis. **Huanzhen Fan:** Software, Formal analysis. **Qing Lin:** Validation, Methodology. **Yanqiu Chen:** Writing – review & editing, Visualization, Investigation, Funding acquisition, Conceptualization.

Ethical approval (animals)

The study protocol was approved by the Animal Ethics Committee of ShunDe Hospital, GuangZhou University of Chinese Medicine (ShunDe District Hospital of Chinese Medicine of Foshan City).

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Declaration of competing interest

The authors declare that they have no conflict of interest.

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Supplementary material

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Data availability

The data are available from the corresponding author on reasonable request.

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