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Ticagrelor inhibits the growth of lung adenocarcinoma by downregulating SYK expression and modulating the PI3K/AKT pathway

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Lung cancer is one of the malignant tumors with the highest morbidity and mortality in China. Despite the use of some targeted therapies in lung cancer treatment, the prognosis remains suboptimal, highlighting the urgent need for new, effective drugs to enhance outcomes. Ticagrelor, a marketed anti-platelet drug, has been reported to have anti-tumor effects. This study primarily investigates the inhibitory effect of Ticagrelor on lung adenocarcinoma in both in vivo and in vitro models, as well as its molecular mechanisms. Firstly, the effects of ticagrelor on the proliferation (CCK-8 and Edu staining), migration (scratch test), and invasion (Transwell chamber) of lung adenocarcinoma cells were evaluated using a variety of lung adenocarcinoma cell models. Secondly, the efficacy of ticagrelor on lung adenocarcinoma in vivo was evaluated by A549, H1975 tumor-bearing mouse models. Finally, transcriptomic sequencing (RNA-Seq) and immunohistochemistry were used to explore the molecular mechanism of the intervention effect of ticagrelor on lung cancer. Ticagrelor significantly inhibits the proliferation, migration and invasion of various lung cancer cells in vitro, and markedly suppressed tumor growth in A549 and NCI-H1975 CDX model in vivo. The pathological results showed that the number of tumor cells in the intervention group was significantly reduced, with large area necrosis, and the expression of Ki-67 in the intervention group was significantly decreased by immunohistochemistry. RNA-seq sequencing results from NCI-H1975 xenograft showed that several integrin-related pathways were down-regulated in the Ticagrelor treatment group, along with a significant reduction in spleen tyrosine kinase (SYK), a pivotal protein related to integrin signaling. Furthermore, we demonstrated that ticagrelor inhibits lung adenocarcinoma by down-regulating SYK and regulating PI3K/AKT pathway using WB. Ticagrelor has obvious inhibitory effect on a variety of lung adenocarcinoma cell lines and cell line transplanted tumors, and its antitumor effect may be related to the inhibition of SYK signaling pathway and PI3K/AKT pathway.

Keywords Ticagrelor, Lung cancer, SYK

Lung cancer is one of the most common cancers in the world[1,2]. Lung cancer can be divided into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) according to histological types, of which non-small cell lung cancer accounts for 85% of all lung cancers and mainly includes lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC)[1,3]. Early-stage lung cancer is primarily treated with surgical resection[4], and for some patients with advanced lung cancer and metastatic lung cancer, chemotherapy and radiotherapy are the main treatment methods[4,5]. At present, some targeted drugs such as gefitinib and erlotinib are used to treat non-small cell lung cancer[6,7]. However, the treatment of lung cancer needs to be improved. The search for new, effective, and low-toxicity anti-lung cancer drugs has been a key issue in current research.

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Ticagrelor is one of the most recent antiplatelet agents, which used to inhibit platelet aggregation via blocking the ADP receptors of the subtype P_2Y_{12}[8,9]. Current studies have shown that ticagrelor has anti-tumor effects[10]. Ticagrelor decreased the viability and proliferation of GBM cells, suppressed colony formation and migration potential, altered the expression of metalloproteinases, and induced autophagy in GBM cells[10]. Additionally, it was found that Ticagrelor can enhance the phagocytic effect of macrophages on tumor cells through the inhibition of P2Y12, thereby playing an anti-tumor role in hepatoblastoma[11]. In addition, Ticagrelor inhibits rosuvastatin transport mediated by breast cancer resistance protein (BCRP) and organic anion transport polypeptides (OATP) 1B1, 1B3, and 2B1 in vitro[12]. However, the effect and mechanism of Ticagrelor on lung cancer are still unclear.

Spleen tyrosine kinase (SYK) is an important intracellular signaling molecule that is widely involved in a variety of biological processes as well as the occurrence and development of numerous diseases[13]. SYK was initially thought to mainly play a role in the signal transduction of adaptive immune receptors[13]. However, studies in recent years have uncovered its critical functions in other areas, including cell adhesion, innate immune recognition, osteoclast maturation, platelet activation and vascular development[13–15]. SYK activates downstream signaling by phosphorylating the cytoplasmic domains of immunoreceptor tyrosine-based activation motifs (ITAMs), thereby regulating multiple cellular responses, such as proliferation, differentiation and phagocytosis[16]. The mechanism by which SYK functions in various types of cancer is complex and varied. In hematologic malignancies, SYK promotes cell proliferation, differentiation, and survival by activating downstream signaling pathways such as PI3K/AKT, ERK, and BTK/PLCγ2[17]. In solid tumors, SYK regulates the mTOR/S6 signaling pathway to affect tumor growth, and its inhibition can significantly inhibit tumor cell proliferation and migration[18]. However, the role of SYK in lung adenocarcinoma is not yet clear.

In this study, we focused on exploring the inhibitory effect of ticagrelor on lung adenocarcinoma and its mechanism, so as to provide a novel treatment strategy for lung adenocarcinoma. Ticagrelor is a listed antithrombotic drug with established safety, and the discovery of its new effect has great clinical translational value.

Methods and materials

Animals

The NOD-SCID mice were procured from Cyagen Biosciences and housed in a specific pathogen-free (SPF) animal facility maintained at a temperature of 20–26 °C and a relative humidity of 50 ± 10%. Upon completion of the experiment, all animals were humanely euthanized using CO2 anesthesia. The experimental protocol, including any modifications, has been duly approved by the Institutional Animal Care and Use Committee (IACUC) of Nanchang Royo Biotech Co., Ltd (RYE2022011201). Confirmation that all experimental protocols have been approved by the designated authority and/or licensing board. Confirm that all methods were performed in accordance with relevant guidelines and regulations. Confirmation that all methods are reported in accordance with the ARRIVE guidelines (https://arriveguidelines.org).

Cell lines

A549, NCI-H1975, NCI-H358 cell lines were obtained from Fuheng Biology, and all cells were identified by STR. All culture media were supplemented 10% fetal bovine serum (Gibco, C11995500BT).

CCK-8

Cells were seeded at 2000 cells per well in a 96-well plate. And after 2 h, cells were treated with Ticagrelor for 48 h. The media were replaced with 10% CCK-8 medium (Pointbio, ECCK0100) and incubated for 4 h. The optical density (OD) was measured on a Thermo LabSystems microplate reader (MK3, USA) at 450 nm. The half-maximal inhibitory concentration (IC50, μM) of Ticagrelor was calculated using GraphPad Prism 8.0 software.

Edu staining

5-Ethynyl-2′-deoxyuridine (EdU) (Beyotime, C0075S) was diluted to 20 μM with complete culture medium, and 100 μl of diluted EdU working liquid was added to each well of the 96-well plate to make its final concentration 10 μM, followed by incubation at 37 ℃ for 2 h. The cells were then fixed with 4% PFA for 0.5 h. The reaction solution was prepared according to the kit instructions, and the reaction solution was then added for staining. Subsequently, the cells were stained with Hoechst 33342 at room temperature for 10 min away from light. Finally, images were taken with a fluorescence microscope.

Wound-healing assay

Cells were seeded at a density of 400,000 per well in a 6-well plate. On the second day, straight lines were drawn using a 200-μl pipette tip, and then the cells were washed three times with PBS to remove cell debris. A microscope was used to photograph the wound area at 0 h and 24 h. Wound healing was measured on the images. Subsequently, 100 μl permeabilization solution (0.5% Triton X-100 in PBS) was added and incubated at room temperature for 15 min.

Cell migration assay

Transwell chamber was used to evaluate cell migration. The upper compartment surface of the bottom membrane of the Transwell chamber was coated with Matrigel (6 mg/mL, 80 μl) (Corning, 356234) and left for 4 h in a 37° constant temperature incubator to form glue. An appropriate volume of cell suspension (100 μL to 200 μL) was added to the upper compartment of the Transwell chamber. The lower chamber was typically filled with culture medium. The cells were cultured for 24 h.

Efficacy evaluation in vivo by lung cancer xenograft model

The lung cancer cell lines A549, NCI-H1975, and were injected subcutaneously into NOD-SCID or C57BL/6 mice at a concentration of 1×10^6 cells in 200 µL of Matrigel. The Ticagrelor group received ticagrelor at a dose of 100 mg/kg once daily. Once the tumor volume exceeded 1000mm^3, the tumor tissue was uniformly dissected into small pieces and subsequently transplanted into the lungs of NOD-SCID or C57BL/6 mice. Upon reaching a tumor volume of 50-100mm^3, the mice were divided into groups consisting of 5 to 8 individuals each. Saline and ticagrelor were administered separately to each group, while regularly monitoring the tumor volume and body weight of the mice. The formula used to calculate tumor volume in mice is (length * width^2)/2.

RNA sequencing

Total RNA was isolated from tumors of NCI-H1975 xenograft model using the RNeasy Mini kit (Qiagen). Differentially expressed genes, GO annotation, functional annotations for biological processes, and protein–protein interaction (PPI) networks network were evaluated[19–22].

Cell adhesion assay

50–100 µL of the gel solution was added to each well, and then placed in an incubator at 37 °C for 2 h. After that, the residual liquid was aspirated and the wells washed it twice with the basal medium. Subsequently, the plates returned it to the 37 °C incubator and dried it for 15–30 min. Next, the cells were digested and cell suspensions were prepared cell suspensions in different Ticagrelor—containing media at a cell density of around 10×10^4/mL. 100 µL of the cell suspension was added to each well. Cell adhesion was observed within 0–30 min and took pictures.

Data statistics

Statistical analysis was performed using GraphPad Prism 9.00 (GraphPad software, Inc.). Comparisons between groups were made using unpaired student t-tests, Dunnett's multiple comparisons tests and two-way ANOVA for repeated measures. The GO pathway enrichment figures were drawn using online platform of SR plot[23].

Result

Ticagrelor significantly inhibited the proliferation of lung cancer cells

It has been reported that ticagrelor has an inhibitory effect on a variety of tumors such as pancreatic cancer and breast cancer[24,25]. To investigate the potential inhibitory effect of Ticagrelor on lung cancer cell, we assessed its impact on the proliferation of A549, NCI-H1975, NCI-H358 lung adenocarcinoma cell lines using CCK-8 assay and EdU staining. The results showed that Ticagrelor could effectively inhibit the proliferation of lung cancer cell lines with IC50 values of 37.72 µM, 40.31 µM, 49.67 µM, and 39.13 µM for A549, NCI-H1975, NCI-H35 cell lines, respectively (Fig. 1A). Edu staining showed that cell proliferation was significantly reduced in NCI-H1975 cell line after Ticagrelor treatment (Fig. 1B,C).

Ticagrelor inhibited the migration and invasion of lung cancer cells.

Next, in order to explore the effects of ticagrelor on migration and invasion of lung cancer cells, we used cell Wound-Healing assay and Transwell assay. The results showed that Ticagrelor (30 µM) significantly impaired the migratory and invasive abilities of NCI-H1975 cells (Fig. 2).

Ticagrelor inhibited the growth of lung cancer xenograft.

To further investigate the in vivo efficacy of Ticagrelor, we established A549, NCI-H1975 xenograft models and administered oral Ticagrelor at a dose of 100 mg/kg once daily. The results demonstrated that Ticagrelor significantly suppressed the growth of A549 and NCI-H1975 lung cancer xenograft tumors (Fig. 3A–D). Histological examination revealed extensive necrosis within the tumor cells, accompanied by a reduction in malignant cell count, fragmentation of cell nuclei, vacuolar necrosis within the tumor cells, and the presence of loose edema and fibrosis within the tumor tissues of NCI-H1975 xenograft tumors following administration of Ticagrelor (Fig. 3E).

Ticagrelor inhibited lung cancer by down-regulating SYK gene and modulating the PI3K/AKT pathway

To investigate the mechanism of action of ticagrelor in inhibiting lung cancer, we examined the gene expression of NCI-H1975 xenograft tumors in mice treated with oral Ticagrelor, compared to a control group. The results showed that 100 genes were up-regulated and 113 genes were down-regulated after drug administration (Fig. 4A,B). Through GO and KEGG analysis, Ticagrelor was found to be associated with the integrin-mediated signaling pathway, integrin complex, integrin binding, platelet activation and so on in lung cancer (Fig. 4C–E). We found that SYK gene expression was high in NCI-H1975 transplanted tumors, but decreased after Ticagrelor treatment (Fig. 5A), as shown by differential analysis in RNA-seq.

To further verify the mechanism by which Ticagrelor affects lung adenocarcinoma, we used a cell adhesion assay to find that the number of adherent cells was significantly reduced after treatment with Ticagrelor (40 µM) for 30 min (Fig. 5B,C).

Next, we performed Western blot (WB) to verify the expression of SYK, PI3K and AKT proteins in NCI-H1975 non-small cell lung adenocarcinoma after the administration of Ticagrelor. The results showed that Ticagrelor significantly inhibited the expression of SYK and affected the PI3K/AKT pathway, thereby influencing the growth of non-small lung cancer cells (Fig. 5D–I).

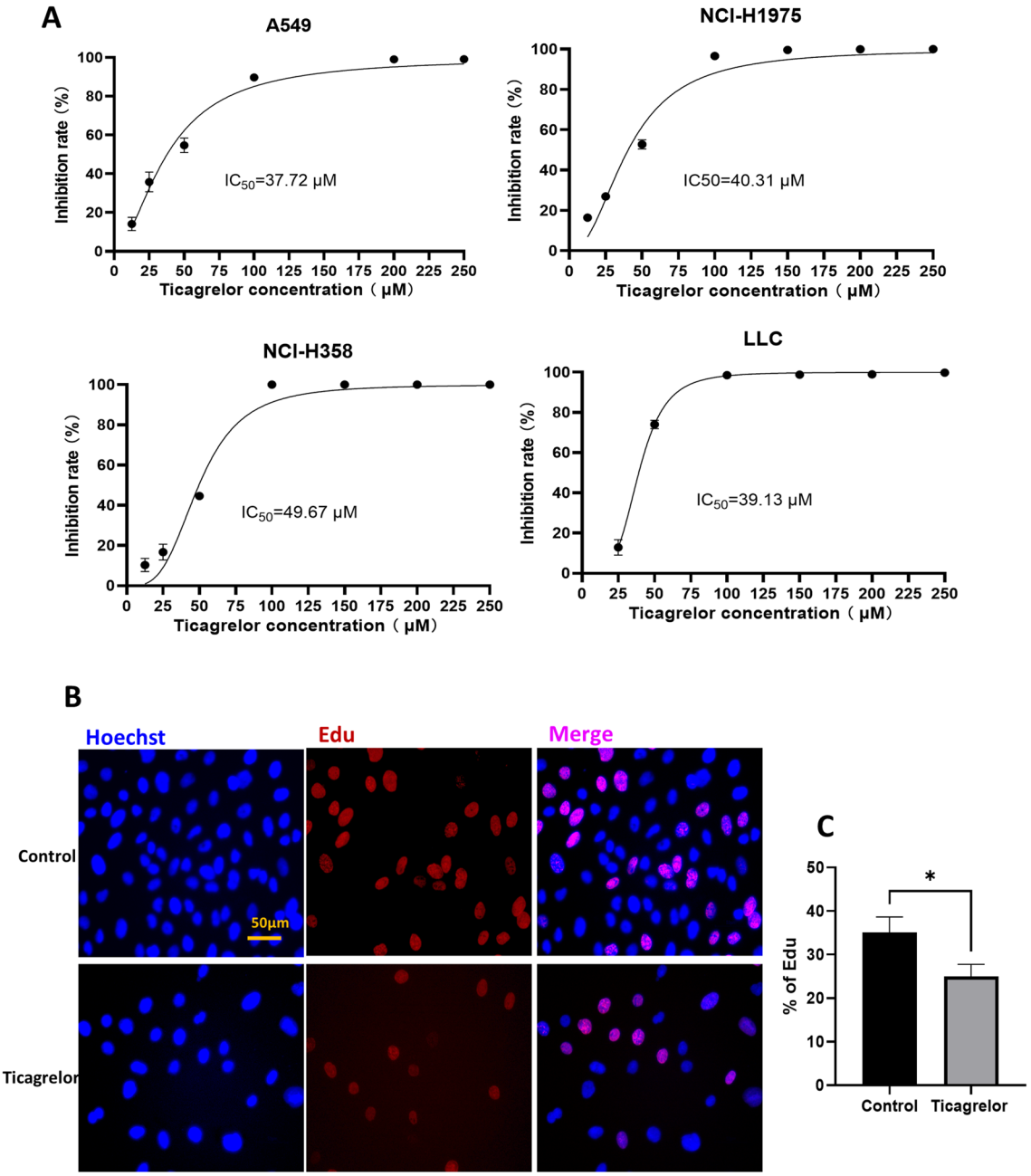

Fig. 1. Ticagrelor can inhibit the proliferation of lung cancer cell lines. (**A**) The dose–effect curve of Ticagrelor on A549, NCI-H1975, NCI-H358cells was detected by CCK-8. (**B**,**C**) Ticagrelor inhibits HCl-H1975 cell proliferation, as assessed by Edu staining (*p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001, ns: no significance).

Discussion

Our findings suggest that ticagrelor exhibits a strong anti-lung cancer effect. Ticagrelor is a clinically approved drug used to treat platelet aggregation, and its safety has been recognized. It reported that Thrombocytosis in cancer patients is associated with poor survival outcomes[26]. Platelets can promote tumor migration, and tumors can promote platelet activation[26,27]. Thromboembolism and thrombocytosis have been found to be important prognostic factors in tumor patients[26]. Based on our findings, it can be inferred that Ticagrelor not only inhibits tumor growth, but also alleviates thromboembolism in tumor patients, which is well benefit for the cancer treatment. Ticagrelor holds substantial potential for clinical application in anti-tumor therapy. The intracellular structural domain of the integrin β chain binds directly to the N-terminal SH2 structural domain of SYK without the need for phosphorylation of the immunoreceptor tyrosine activation motif (ITAM). This binding is dependent on specific non-phosphorylated tyrosine residues of the integrin β chain, which directly triggers autophosphorylation and activation of SYK. When SYK is activated by platelet integrin αIIbβ3, even if the ITAM binding site of SYK is disrupted, SYK can still be directly activated via the β3 intracellular domain,

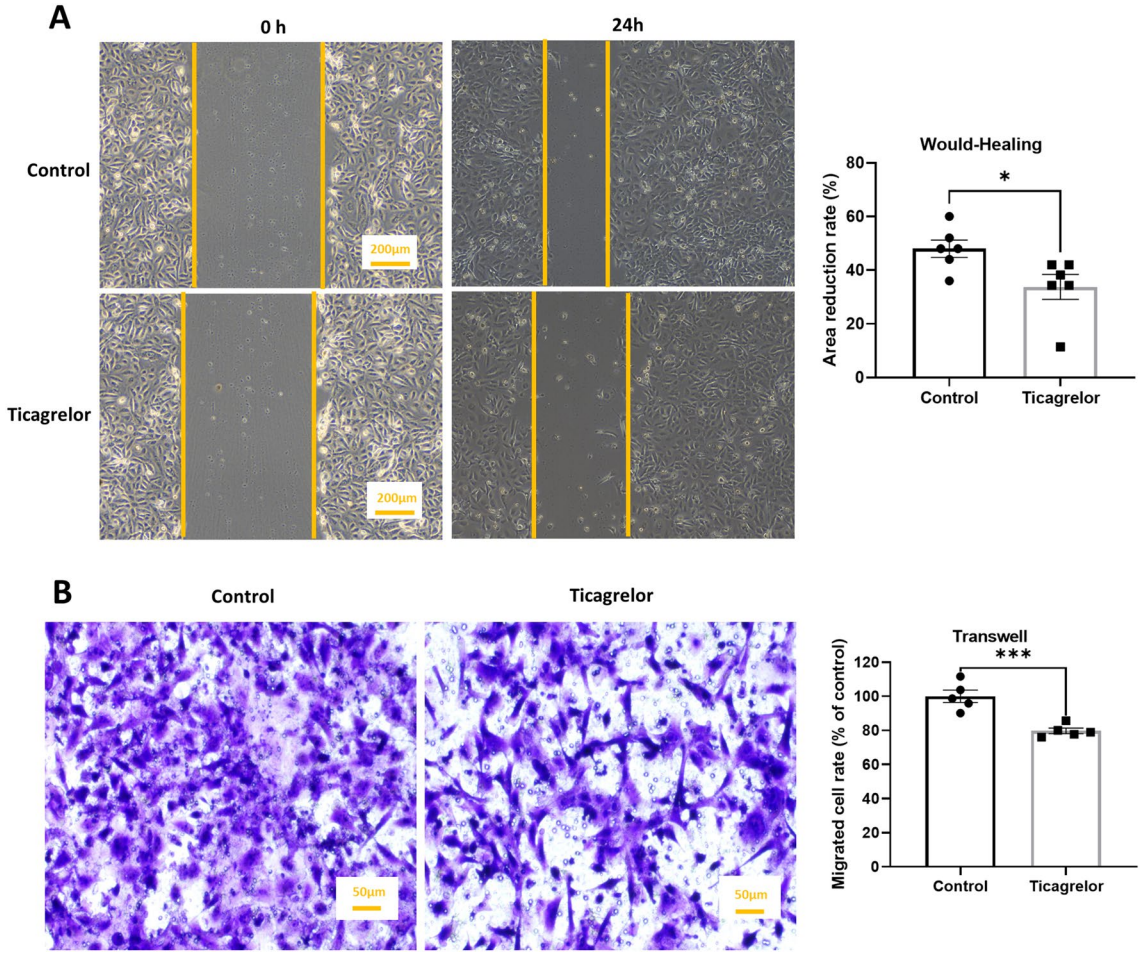

Fig. 2. Ticagrelor inhibited the migration and invasion of NCI-H1975 cell. (**A**) Ticagrelor inhibited the migration of NCI-H1975 in Would-Healing test. (**B**) Ticagrelor inhibited the migration and invasion of NCI-H1975 cell in Transwell test (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$, ns: no significance).

which demonstrates that there is an ITAM-independent pathway that directly regulates SYK through integrins and platelet integrins. Moreover, in immune cells, after binding to ligands, integrins phosphorylate the ITAM motifs on transmembrane adaptor proteins (e.g., DAP12, FcRγ) via SRC family kinases (e.g., Lyn, Fyn), which in turn recruits the tandem SH2 structural domains of SYK to activate downstream signaling, also suggesting that there is a model of regulation of SYK mediated by ITAM[27,28]. This led us to hypothesize that SYK may serve as a potential mediator of Ticagrelor's anti-tumor effects. SYK played dual role as both a tumor promoter and tumor suppressor in cancer[28]. In many tissues including the brain, colon, kidneys, and ovaries, the levels of SYK mRNA are often higher in cancerous tissues than in normal tissues[29]. Most SCLC cell lines demonstrate SYK mRNA overexpression[30]. Analysis of co-expressed genes in SCLC suggests that SYK is a potential oncogenic driver. Our study show that Ticagrelor can decrease the expression of SYK in NCI-H1975 (NSCLC) cells. This suggests that SYK may serve as a novel target for ticagrelor acting on SCLC and NSCLC. SYK is also expressed in platelets, where it plays a key role with thrombosis[31]. Studies have shown that the role of SYK in tumor adhesion is mainly reflected in its regulation of cell–cell adhesion and epithelial polarity. For example, in breast cancer cells, SYK promotes the phosphorylation of E-Cadherin and α-Catenin, thereby enhancing the adhesive force between cells[32]. In NSCLC, SYK simultaneously inhibits the invasion and migration of NSCLC cells while promoting cell adhesion[33]. These findings are consistent with our experimental results.

Our RNA-seq result showed that Ticagrelor affected the platelet activation and integrin signaling. It has been reported that Phosphatidylinositol 3-Kinases (PI3Ks) have emerged as crucial players in platelet activation, and they are directly implicated in the regulation of integrin function[34]. The PI3K/AKT pathway plays an important role in tumor development, proliferation, drug resistance and apoptosis[35,36]. And we found that Ticagrelor was also affected the PI3K/ AKT pathway in NCI-H1975 cell line, which was also consistent with previous reported.

Ticagrelor is an inhibitor of P2Y12 receptor[37]. It has been reported that Ticagrelor inhibits platelet activation through the P2Y12 receptor on platelets, thereby inhibiting breast cancer migration[38]. Consistent with the results of our cell migration experiments, studies have shown that the reduction of P2Y12 receptor can promote the migration of lung cancer[39]. Our RNA-seq analysis show that the expression of P2Y12 receptor did not

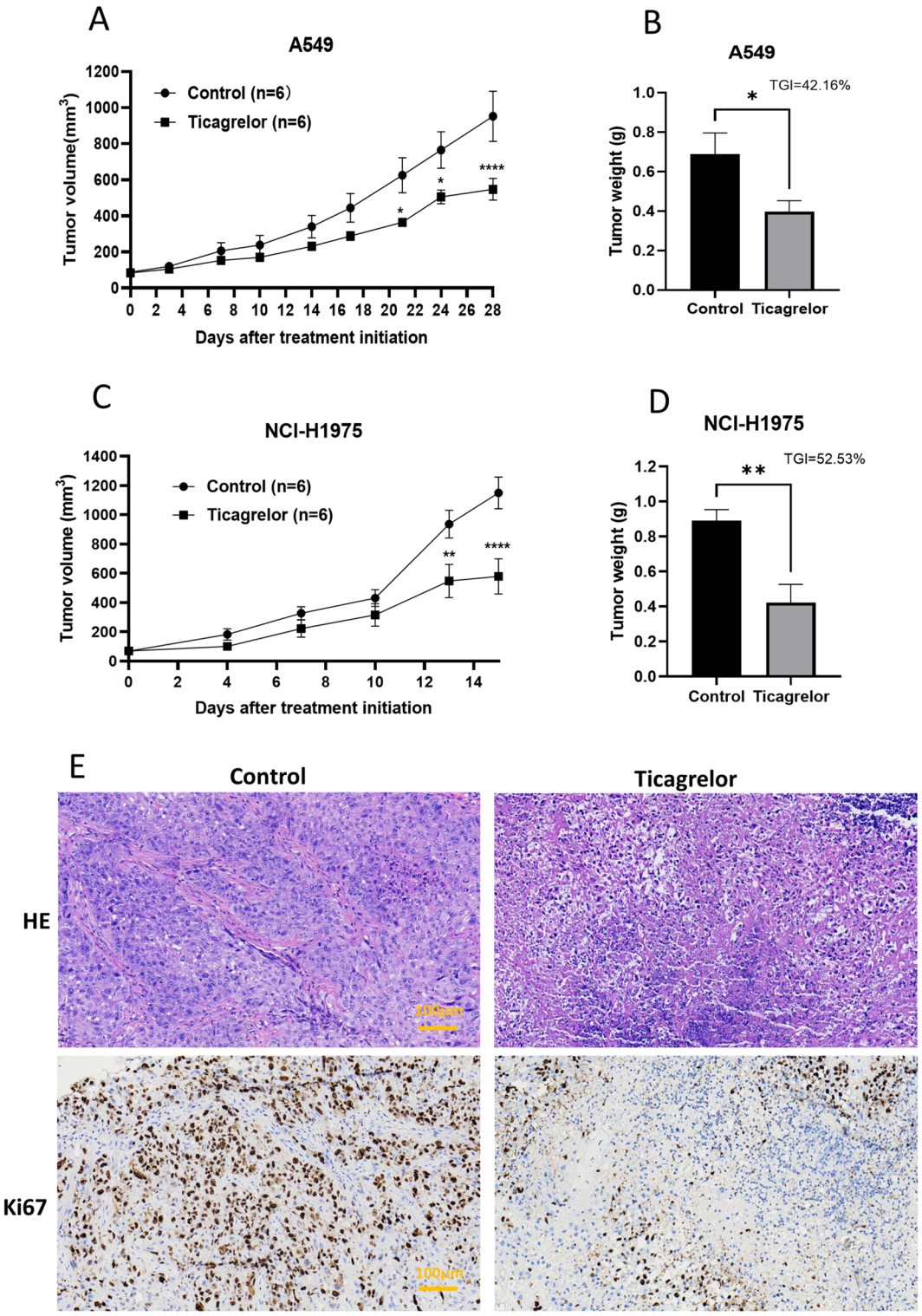

Fig. 3. Ticagrelor inhibited the growth of A549 and NCI-H1975 cell-derived xenograft. (**A**,**B**) Ticagrelor inhibited the tumor volume and weight of A549-cell derived xenograft. (**C**,**D**) Ticagrelor inhibited the tumor volume and weight of NCI-H1975 cell-derived xenograft. (**E**) The difference of the pathological morphology and Ki67 expression in NCI-H1975 cell transplanted tumors treated by Ticagrelor (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$,ns: no significance).

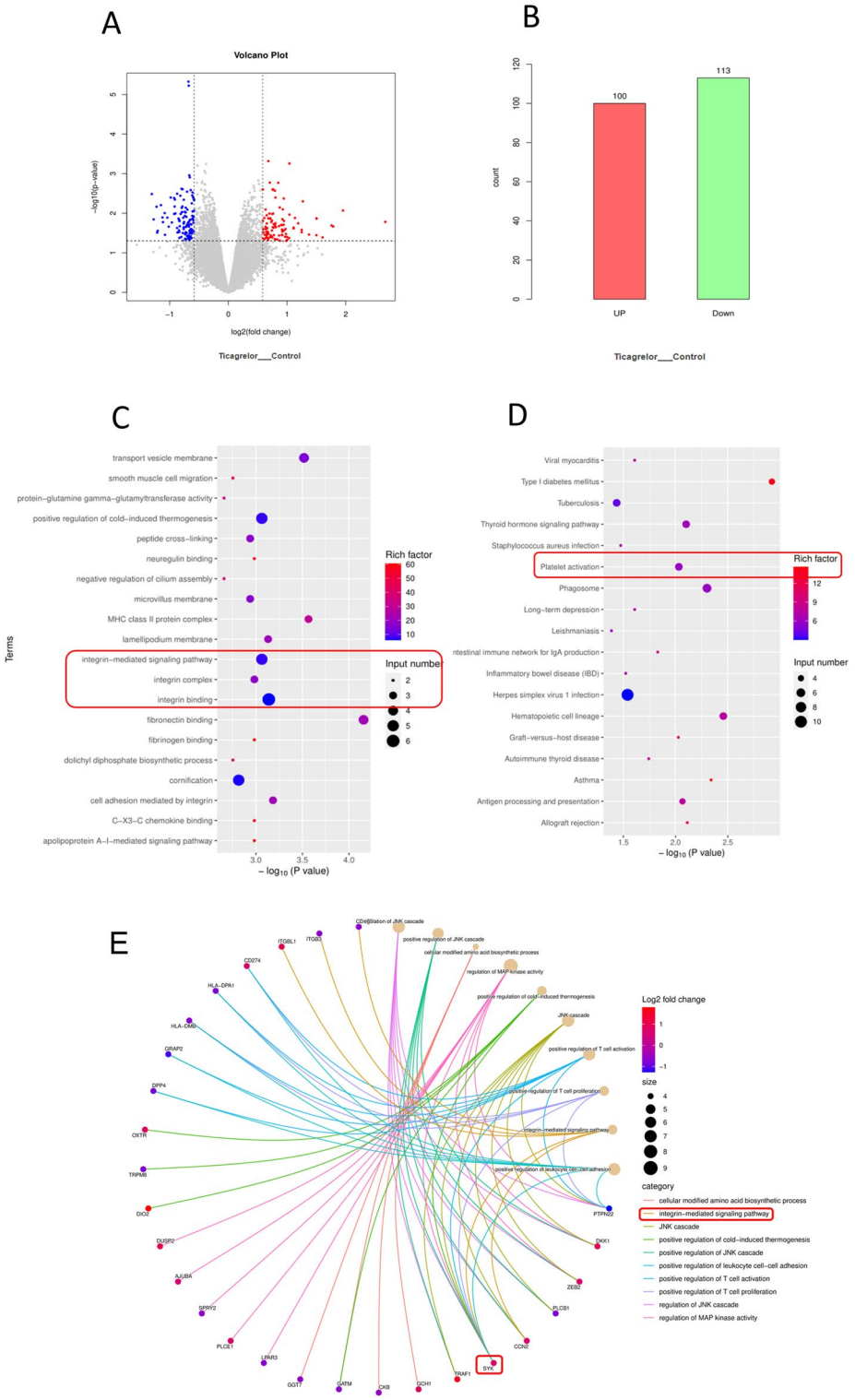

Fig. 4. RNA-Seq analysis reveals genes and pathways targeted. (**A**) Volcano plot of gene expression in Ticagrelor treatment group. Up-regulated DEGs (differentially expressed genes) are labeled as red dots, whereas down-regulated DEGs are labeled in blue. (**B**) Statistical map of up-regulated and down-regulated genes. (**C**) GO enrichment. (**D**) KEGG pathway. (**E**) GO enrichment.

significantly increase after ticagrelor treatment in NCI-H1975 xenograft model. We hypothesize that Ticagrelor acts on lung cancer through multiple targets, affecting the migration and growth of lung cancer respectively.

Our experimental results provide a new potential drug for the treatment of lung cancer, but there are still many unanswered questions that need to be further explored. However, the antitumor activity of ticagrelor in lung

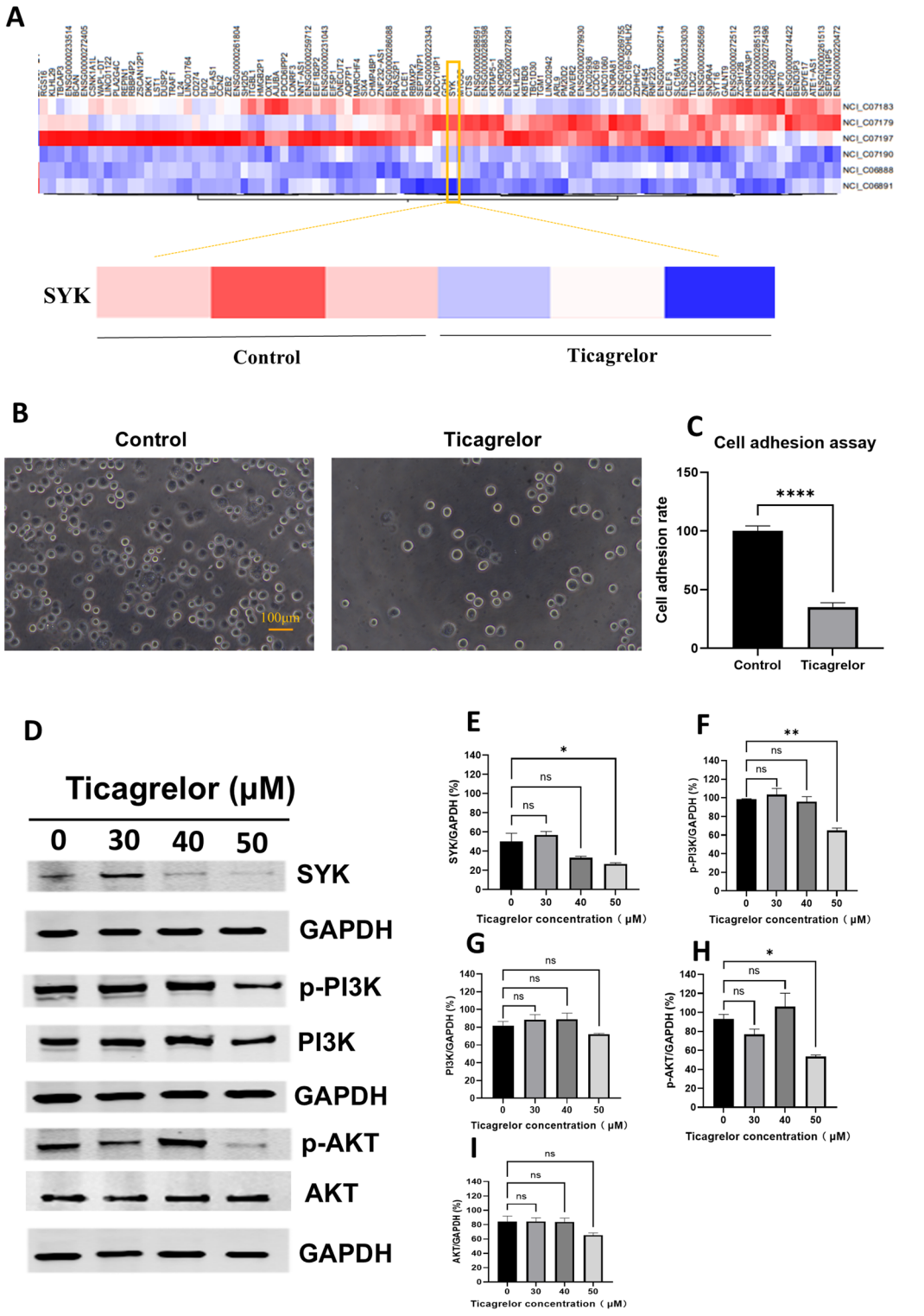

Fig. 5. Ticagrelor inhibited NCI-H1975 cell line by downregulating SYK expression and modulating the PI3K/AKT pathway. (**A**) Heatmap of genes in ticagrelor treatment. (**B**) Ticagrelor (40 μM, 30 min) reduced cell adhesion in NCI-H1975 cells. (**C**) Cell adhesion rate assay. (**D**–**I**) The expression of the SYK, p-PI3K, PI3K, p-AKT and AKT was reduced in the ticagrelor group by WB. (*p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001, ns: no significance).

adenocarcinoma has some limitations, among them the lack of clinical or patient validation, and our future work will validate the findings using patient-derived samples, organ tissues, or PDX models to improve translational relevance. Further planned studies will evaluate its modulatory effects on platelet-driven immunosuppression, angiogenesis and T cell activation on the tumor microenvironment. Next studies will use resistance models to test the potential of Ticagrelor to overcome or synergize with existing therapies. These strategies aim to integrate mechanistic understanding, therapeutic optimization, and clinical application in order to enhance the potential of ticagrelor as a promising therapeutic candidate for lung adenocarcinoma (Supplementary Information).

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions
Yuanhong Song and Ling Huang designed the experiments. Yuanhong Song, Lanhui Zeng, Suwei He and Yuanqiao He performed experiments and analyzed date. Ling Huang wrote the manuscript. These authors contributed equally: Yuanhong Song and Suwei He All the authors reviewed the manuscript.

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Declarations

Ethics approval
All experimental animals were housed and maintained in standard laboratory conditions according to the Guidelines for Animal Welfare in Experimental Animals (Issued by the Ministry of Science and Technology of the People's Republic of China in 2006) and the agreement of the Institutional Animal Care and Use Committee of Jinggangshan University (2016).

Competing interests
The authors declare no competing interests.

Additional information
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