doi:10.4149/neo_2021_210904N1271

# HABP1 promotes proliferation and invasion of lung adenocarcinoma cells through NFκB pathway

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**Received September 4, 2021 / Accepted November 8, 2021**

The aim of this research was to investigate the role of hyaluronan-binding protein 1 (HABP1) in lung adenocarcinoma. It was demonstrated by bioinformatics analysis that HABP1 was one of the differentially expressed genes in lung adenocarcinoma. Then, it was confirmed by qPCR, western blot, and immunohistochemistry analysis that HABP1 was upregulated in human tissue specimens we collected. Survival analysis showed that HABP1 was promised to serve as a new biomarker to predict the progress and prognosis of lung adenocarcinoma patients. In addition, we further studied the effects of regulating the expression of HABP1 on lung adenocarcinoma cells, indicating that altered expression of HABP1 could adjust cell proliferation and invasion through the NFκB signaling pathway.

*Key words: lung adenocarcinoma, HABP1, NFκB, proliferation, invasion*

Lung cancer is one of the most common malignant tumors in the world [1]. In China, there are about 300,000 new lung cancer patients per year, and more than 250,000 people die of this disease every year [2]. Lung adenocarcinoma, one of the most common types of lung cancer, accounts for 30–35% of primary pulmonary tumors [3]. However, the pathogenesis of lung adenocarcinoma has not been completely interpreted [4]. Many scholars are committed to the research of key targets and driving genes, which have always been exploration hotspots [5]. Fortunately, great progress has been made and many target genes have been found, providing a solid basis and research direction for drug developments [6]. Even so, there are still lots of blanks and unsolved mysteries in key targets and driving genes of lung adenocarcinoma [7].

Hyaluronan-binding protein 1 (HABP1), whose gene was mapped at chromosome 17p12-p13, was an important hyaladherin, firstly identified in 1985 as a glycoprotein rich in glycine and glutamate, containing sialic acid [8]. HABP1 identical to the splicing factor associated protein (p32) and the receptor of the globular head of the complement component (gC1qR), has been extensively researched in immunological response, splicing mechanism, sperm-oocyte interactions, and cell cycle regulation to cancer, and this protein was also referred as HABP1/p32/gC1qR in other studies [9, 10]. Besides, knockdown of HABP1 induced lamellipodia disruption of tumor cells, thus preventing tumor migration and formation [11]. In breast cancer, increased expression of HABP1 leads to cells metastasis, connected to patients' poor survival, and its antibody therapy inhibited tumor growth in an orthotopic murine xenotransplant model of triple-negative breast carcinoma [12, 13]. Elevated HABP1 expression, concerned with clinicopathological characteristics, leads to an unfavorable prognosis in endometrial cancer [14]. It was also evidenced that HABP1 was a biomarker for gastric cancer tumorigenesis, possibly becoming a potentially useful treatment target [15]. Nevertheless, the molecular mechanism of HABP1 in the occurrence and development of lung adenocarcinoma is not clear [16].

In this research, we investigated HABP1 expression in lung adenocarcinoma through bioinformatics analysis and experiments on human tissue specimens and analyzed its expression effects on patients' survival. In addition, a series of cell experiments were conducted to further illustrate the influence of HABP1 expression on lung adenocarcinoma cell proliferation and invasion.

## Patients and methods

**Bioinformatics analysis.** This study screened three gene chips from the GEO database, GSE10072, GSE32867, and

GSE43458, including 196 lung adenocarcinoma samples and 137 normal lung tissue samples. Differential expression analysis was performed through the online analysis tool GEO2R (https://www.ncbi.nlm.nih.gov/geo/geo2r/) on the microarray and overlap statistical analysis was conducted using Venn online tools (http://bioinformatics.psb.ugent.be/webtools)/venn/). The expression of HABP1 in lung adenocarcinoma was evaluated by TCGA (The Cancer Genome Atlas) database (https://portal. gdc. cancer. gov/).

**Patients and tissue samples.** Approved by Human Research Ethics Committee, the lung adenocarcinoma specimens were obtained from patients in Jiangyin People's Hospital from 2014–2015, who were all newly diagnosed without treatments of radiotherapy or chemotherapy before operation. All the tissues obtained from operations were immediately frozen at –80 °C.

**Antibodies.** Anti-HABP1 antibody (western blot, immunohistochemistry, and immunofluorescence, ab24733; Abcam), anti-Ki-67 antibody (immunohistochemistry, MIB-1; Dako), anti-glyceraldehyde-3-phosphate dehydrogenase (GAPDH) antibody (western blot, ab9485; Abcam), anti-P65 antibody (western blot and immunofluorescence, CST6956; Cell Signaling Technology), anti-P84 antibody (western blot, ab487; Abcam), anti-p-IκBα antibody (western blot, CST2859; Cell Signaling Technology), anti-IκBα antibody (western blot, CST4814; Cell Signaling Technology).

**Cell culture.** Lung adenocarcinoma cell lines A427, SPCA1, A549, PC9, and H1299 were purchased from the cell library of the Chinese Academy of Sciences and were grown in Dulbecco's Modified Eagle Medium (DMEM) with 10% fetal bovine serum (FBS) at 37 °C with 5% $CO_2$.

**qPCR.** We used FastStart Universal SYBR Green Master (Roche, Mannheim, Germany) and the ABI 7500 Fast Real-time PCR Detection System (Applied Biosystems, Foster City, CA, USA) to conduct this experiment. The TaqMan probe labeled with fluorescein was mixed with the template DNA to complete the thermal cycle of high temperature denaturation, low temperature renaturation and suitable temperature extension. The sequences of the primers used were as follows: HABP1-1: 5'-GGACTGAAAGCTAACTTCCCTGAT-3'; HABP1-2: 5'-CCCAATTTCGTGGTTGAAGTTATA-3'.

**Western blot analysis.** The proteins were treated as loading samples, which were electrophoresed by 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and then transferred to polyvinylidene fluoride (PVDF) films. Then, the proteins were separated on the PVDF films, incubated with the first and second antibodies successively. The antibodies were combined with the corresponding proteins on the PVDF films, which were detected by the enhanced chemiluminescence (ECL) detection system.

**Plasmid and transient transfection.** Overexpression plasmid of HABP1 was constructed by cloning the PCR-amplified full-length human HABP1 cDNA into the pMSCV retrovirus. Short hairpin RNAs (shRNA) of HABP1 oligonucleotides sequences were synthesized by Invitrogen (Shanghai, China). Scramble shRNA plasmid was used as a negative control. Cells were infected with lentivirus particles containing the shRNAs with Lipofectamine 2000.

**Immunohistochemistry.** We used the horseradish peroxidase (HRP) two-step method. In short, after baking for 6 hours to retrieve the antigen, the sections were incubated with primary and secondary antibodies. No immune serum was used as a negative control, while Ki-67 was used as a positive control. At last, they were stained with 3,3-diaminobenzidine (DAB) and hematoxylin.

Two pathologists were invited to evaluate the immunostaining independently without any previous information about the specimens. Intensity was estimated as follows: 0 (negative staining); 1 (weak staining); 2 (moderate staining); 3 (strong staining). Percentage of tumor cells stained positive was scored as follows: 0 (<10%); 1 (11–25%); 2 (26–50%); 3 (51–75%); 4 (>75%). Then the two scores were added, and 0–3 were counted as a low expression, while 4–7 were counted as a high expression.

**Immunofluorescence.** Firstly, cells were seeded on coverslips in a 24-well plate overnight. Then, after fixing with 4% paraformaldehyde and blocking in 5% bovine serum album (BSA), they were incubated with the primary antibodies, and then secondary antibodies with fluorophores. For DNA staining, cells were incubated with Hoechst 33342 dye. At last, coverslips were put face down on the slides to be detected by a Leica fluorescence microscope.

**Cell proliferation and invasion assay.** A commercial Cell Counting Kit (CCK)-8 (Dojindo, Kumamoto, Japan) was used for cell proliferation assay. We followed the manufacturer's instructions and measured the absorbance at the wavelength of 490 nm by ImmunoMini NJ-2300.

A Transwell chamber (Corning, 8 μm pore size) was used to perform the cell invasion experiment. Cells were cultured in DMEM without FBS in the upper chamber, and DMEM with 10% FBS was put in the lower chamber. After some time, top (non-migrated) cells were removed and bottom (migrated) cells were fixed, and then the bottom cells were stained with crystal violet and counted immediately.

**Statistical analysis.** All statistical analyses were performed using SPSS 13.0 software. The expression between HABP1 and Ki-67 in immunohistochemistry was evaluated by Spearman rank correlation analysis. Kaplan-Meier (K-M) curves and log-rank test were used for univariate survival analysis, while Cox's proportional hazards regression model was used for multivariate survival analysis. We applied the Chi-square ($\chi^2$) test for the analysis of the relationship between HABP1 expression and the clinicopathological features. The significance of differences in two groups was analyzed by Student's t-test, while multiple groups by one-way ANOVA. Data were presented as mean ± standard deviations (SD). All the experiments were carried out at least three times independently. p-values <0.05 were considered to be statistically significant.

## Results

**HABP1 expression in lung adenocarcinoma was increased compared with normal samples.** We used online analysis tools to find differentially expressed genes in three lung adenocarcinoma microarrays of the GEO database. Three gene chips, GSE10072, GSE32867, and GSE43458, contained 107, 116, and 110 samples separately. Figure 1A is part of the heatmap and histogram of significantly different genes, from which we made out that the expression of HABP1 is upregulated in GSE43458 and downregulated in GSE10072. Next, we focused on the differentially expressed gene HABP1 and analyzed its expression in TCGA database. Figure 1B shows that HABP1 was upregulated in lung adenocarcinoma compared to normal subjects ($p<0.05$). It was further authenticated by qPCR that HABP1 mRNA was higher in lung adenocarcinoma than normal in fresh human specimens ($p<0.05$, Figure 1C). We performed western blot analysis and immunohistochemistry on the 80 lung adenocarcinoma tissues we collected, which showed that HABP1 protein expression ascended when WHO grade raised, positively correlated with Ki67, which is widely used as a proliferation index in lung adenocarcinoma [17] ($r=0.658$, $p<0.05$, Figures 1D, 2A, 2B).

**Increased HABP1 expression was associated with a poor prognosis in lung adenocarcinoma.** The clinicopatho-

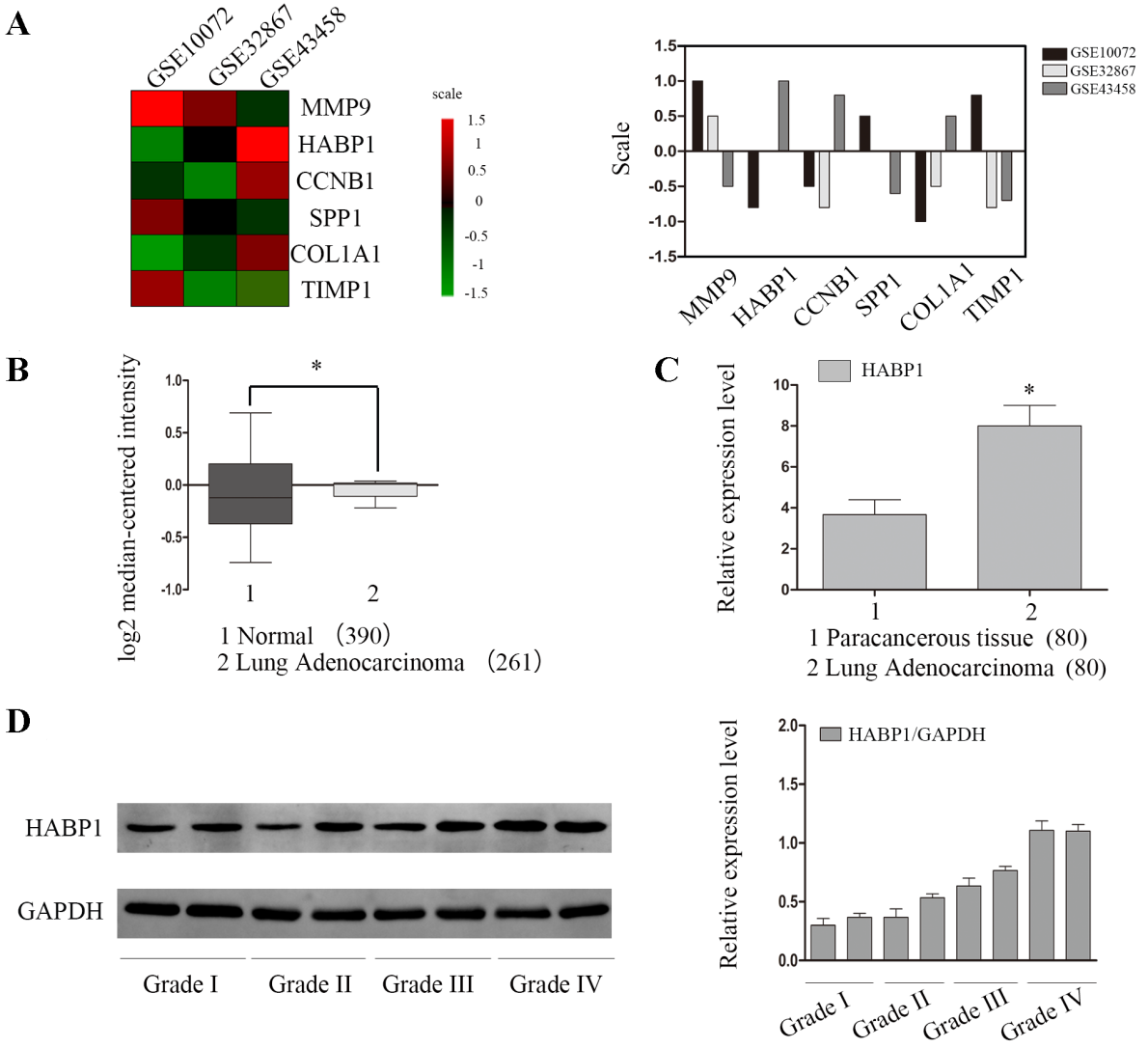


**Figure 1. HABP1 expression in lung adenocarcinoma. A) Through differential analysis of three gene chips GSE10072, GSE32867, and GSE43458, and further screening by statistical means, we finally obtained six differentially expressed genes. Red indicates the upregulation and green indicates the downregulation. B) The analysis of TCGA database showed that the expression of HABP1 in lung adenocarcinoma was higher than that in normal subjects. *p<0.05 C) qPCR analysis results of HABP1 in 80 lung adenocarcinoma tissue samples and 80 paracancerous tissue samples we collected. *p<0.05 D) Western blot results of HABP1 in eight fresh lung adenocarcinoma tissues. Bar charts were HABP1 compared to GAPDH.**

logical parameters of the 80 samples are presented in Table 1, including 10 Grade I cases, 12 Grade II cases, 36 Grade III cases, and 22 Grade IV cases. According to the scoring criteria shown in the method of immunohistochemistry, less than or equal to 3 points was determined as a low expression, while a score greater than 3 points was determined as a high expression. Among the 80 specimens, 33 cases were rated as HABP1 low expression and 47 cases as HABP1 high expression. It was analyzed by $\chi^2$ test that HABP1 expression differed between different grades of lung adenocarcinomas ($\chi^2$=7.898, p<0.01). K-M survival curves and log-rank test results indicated that higher HABP1 expression was related to a poorer prognosis of lung adenocarcinoma patients (p<0.05, Figure 2C). From the results of multivariate survival analysis in Table 2, we found that similar to WHO Grade, HABP1 was an independent prognostic factor of lung adenocarcinoma (p<0.01).

**Table 1. HABP1 expression and clinical pathology characteristics in 80 cases of lung adenocarcinoma specimens.**

| Variable | Total | HABP1 expression | | $\chi^2$ value | p-value |
|---|---|---|---|---|---|
| | | Low | High | | |
| Age (years) | | | | | |
| <50 | 21 | 8 | 13 | 0.117 | 0.732 |
| ≥50 | 59 | 25 | 34 | | |
| Gender | | | | | |
| Female | 44 | 17 | 27 | 0.276 | 0.600 |
| Male | 36 | 16 | 20 | | |
| Tumor location | | | | | |
| Left upper lobe | 18 | 7 | 11 | 0.145 | 0.703 |
| Left lower lobe | 17 | 7 | 10 | | |
| Right upper lobe | 20 | 8 | 12 | | |
| Right middle lobe | 10 | 4 | 6 | | |
| Right lower lobe | 15 | 7 | 8 | | |
| Tumor size (cm) | | | | | |
| <3 | 33 | 15 | 18 | 0.410 | 0.522 |
| ≥3 | 47 | 18 | 29 | | |
| WHO Grade | | | | | |
| I | 10 | 7 | 3 | | |
| II | 12 | 8 | 4 | 7.898 | 0.005* |
| III | 36 | 12 | 24 | | |
| IV | 22 | 6 | 16 | | |
| Extent of resection | | | | | |
| Wedge resection | 16 | 6 | 10 | 0.116 | 0.944 |
| Segmentectomy | 45 | 19 | 26 | | |
| Lobectomy | 19 | 8 | 11 | | |

Notes: We analyzed the expression of immunohistochemistry in different groups, and 0–3 were counted as low expression, while 4–7 were counted as high expression. Pearson $c^2$ test for statistical analysis. *p<0.01

**Table 2. Contribution of various potential prognostic factors to survival by Cox regression analysis on 80 lung adenocarcinoma specimens.**

| Characteristic | Hazard ratio | 95% CI | p-value |
|---|---|---|---|
| Age | 1.413 | 0.725–2.103 | 0.413 |
| Gender | 1.357 | 0.694–2.057 | 0.238 |
| Tumor location | 0.824 | 0.678–1.301 | 0.737 |
| Tumor size | 1.359 | 0.724–2.540 | 0.346 |
| WHO Grade | 4.810 | 2.878–7.804 | 0.000* |
| Extent of resection | 0.975 | 0.736–1.314 | 0.932 |
| HABP1 expression | 2.843 | 1.596–5.116 | 0.001* |

Notes: *p<0.01; Abbreviations: CI-confidence interval

**HABP1 expression and location in lung adenocarcinoma cells.** Western blot was used to detect the expression of HABP1 in five kinds of lung adenocarcinoma cells (A427, SPCA1, A549, PC9, H1299), with the highest expression in A549 cells and the lowest expression in A427 cells (Figure 3A). Immunofluorescence experiments, applied to localize some protein, showed that HABP1 was mainly expressed in the cytoplasm (Figure 3B).

**Effects of silencing HABP1 on lung adenocarcinoma cells.** Control shRNA and shRNAs of HABP1 were transfected into A549 cells, which have a higher expression of HABP1 compared to others, and knockdown efficiency was revealed in Figure 4A. Next, when HABP1 was knocked down, we examined the protein expression of P65 (nucleus) and p-IκBα whose expression level reflected the activation status of the NFκB signaling pathway. Compared to sh-NC, P65 (nucleus) and p-IκBα expressions were reduced in the group of shHABP1-1 (p<0.05, Figure 4B). It was further tested by CCK-8 and Transwell analysis to investigate the effects of downregulation of HABP1 on proliferation and invasion of lung adenocarcinoma cells. From the results in Figures 4C and 4D, it's apparent that silenced expression of HABP1 inhibited cell proliferation and invasion (p<0.05).

**Increased HABP1 expression promoted proliferation and invasion of lung adenocarcinoma cells through the NFκB pathway.** HABP1 overexpression plasmid and NFκB antagonist pyrrolidine dithiocarbamate (PDTC) were used to conduct these experiments. It's displayed by western blot that expressions of P65 (nucleus) and p-IκBα were elevated when H1299 cells were transfected with HABP1 overexpression plasmid (p<0.05), and PDTC could make a turn for the result (p<0.05) (Figure 5A). We then used immunofluorescence to show the translocation of P65. As shown in Figure 5B, the upregulation of HABP1 significantly increased P65 entry into the nucleus, which was reversed by PDTC. At last, CCK-8 and Transwell tests were carried out, indicating that increased HABP1 expression promoted cell proliferation and invasion (p<0.05), which could be abated by NFκB agonist PDTC (p<0.05, Figures 5C, 5D).

## Discussion

This paper explored the possible character of HABP1 in the occurrence and development of lung adenocarcinoma from three aspects: bioinformatic analysis, clinical specimens, and cell experiments, which confirmed that HABP1 precipitated cell proliferation and invasion through the NFκB signaling pathway and performed as an indicator for the prognosis for lung adenocarcinoma.

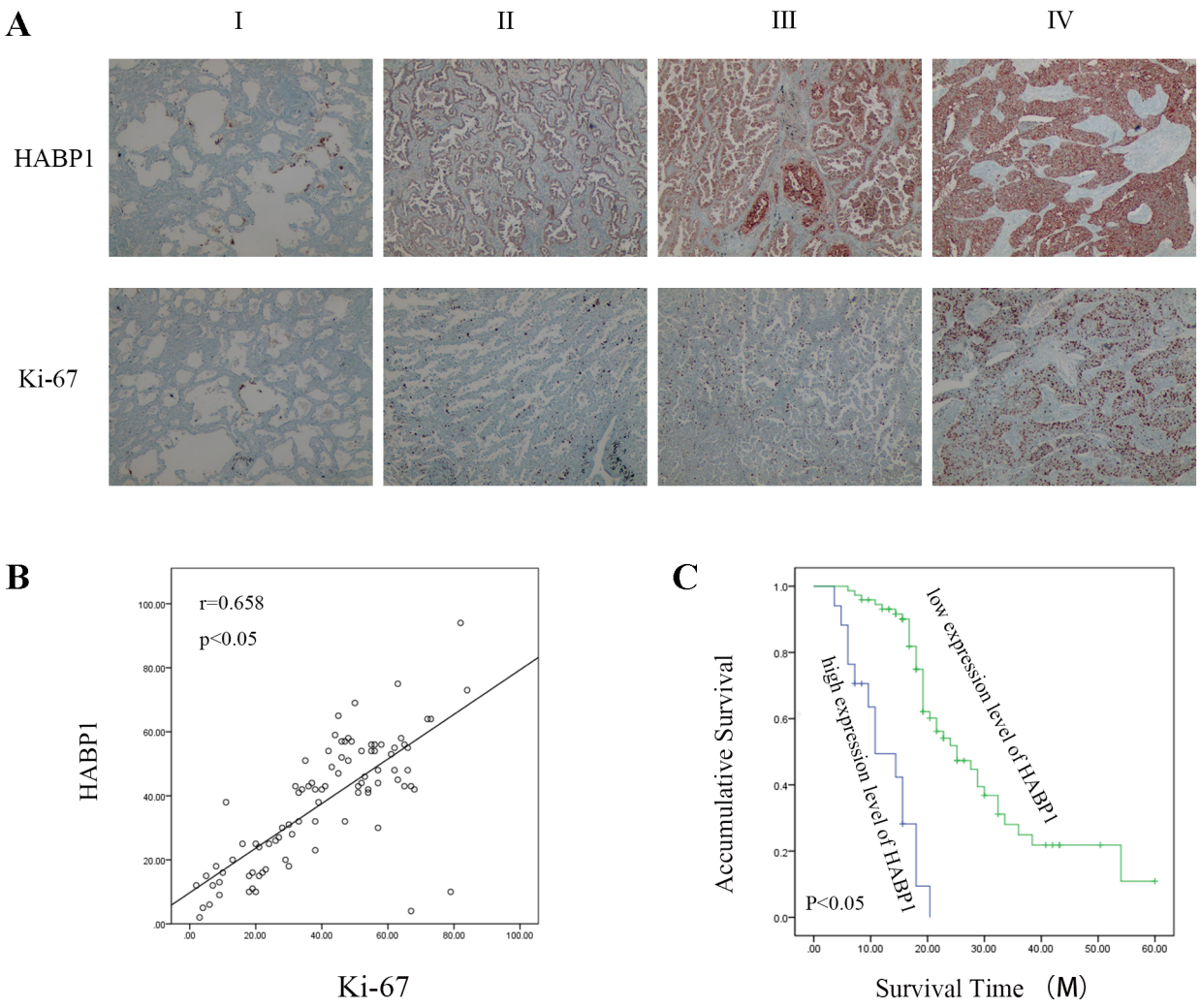


**Figure 2. Higher expression of HABP1 was connected with a poorer prognosis of lung adenocarcinoma. A) Immunohistochemistry results of HABP1 in lung adenocarcinoma. B) Scatter pots indicated HABP1 and Ki-67 expression in immunohistochemistry. C) K–M survival curve and survival analysis results for high and low HABP1 expression in 80 lung adenocarcinoma patients.**

It has been reported that HABP1 regulated a variety of biological processes through cellular signaling pathways. In human liver cancer cell line HepG2, HABP1 regulates cyclin D1 through the Akt-dependent pathway, resulting in increased hyaluronic acid synthesis and cell proliferation [18]. *In vitro* studies by Majumdar et al. using normal rat fibroblasts (F111) and transformed (Hela) cells showed that HABP1 was the substrate of ERK and a component of a MAP kinase cascade, which translocated to the nucleus upon mitogenic stimulation [8]. In triple-negative breast cancer, a decrease of HABP1 inhibited the activation of the PKC-NFκB signaling pathway, resulting in suppressed expression of VCAM-1 by reducing the number of P65 in the nucleus [19].

NFκB is a large family, including Rel-A (p65), c-Rel, Rel-B, NFκB1 (P50/P105), and NFκB2 (p52/P100), with Rel-A (p65) the most deeply studied. Under resting state, P65 binds to IκBα in the cytoplasm and P65 does not play the role of the signal molecule and transcriptional factor [20]. When there is external stimulation, IκBα is phosphorylated by IκB kinase (IKK), that dissociates P65 from IκBα, and then P65 is dragged to the cell nucleus by P50 [21]. Once P65 enters the karyon, P65 binds to mRNA, activated to play a messenger role at this time [22]. In conclusion, the nuclear localization of P65 and the phosphorylation of IκBα reflect the activation state of the NFκB signal pathway [23]. NFκB antagonist PDTC, a metal chelator and antioxidant, specifically suppresses the release of the inhibitory subunit IκB, which gets P65 deprived of freedom, thus depressing the activation of the NFκB signaling pathway [24].

In this paper, experiments on lung adenocarcinoma cells proved that depressed expression of HABP1 inhibited expres-

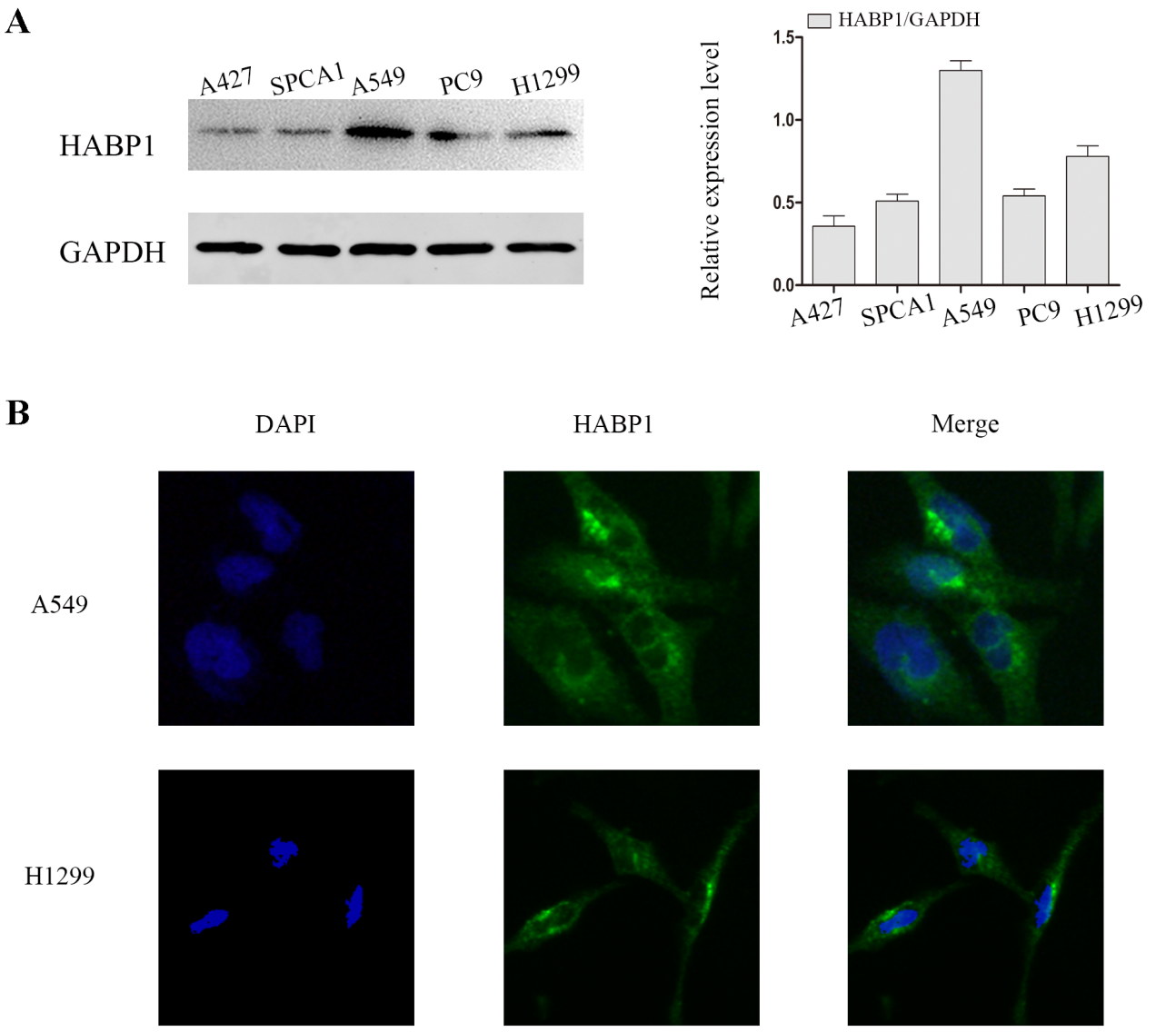


**Figure 3. Expression and localization of HABP1 in lung adenocarcinoma cells. A) Western blot results of HABP1 in different kinds of lung adenocarcinoma cells. B) Immunofluorescence results displayed the localization of HABP1 in lung adenocarcinoma cells.**

sion of P65 (nucleus) and p-IκBα (Figure 4B). When HABP1 was overexpressed, the expression of P65 (nucleus) and p-IκBα increased (Figure 5A), and P65 entry into the nucleus was enhanced (Figure 5B). When the HABP1 overexpression plasmid was combined with PDTC, changes of P65 and p-IκBα were weakened (Figures 5A, 5B). All the above experimental results authenticated that HABP1 can regulate the NFκB signaling pathway through NFκB subunit p65. According to previous studies, HABP1 has been observed to interact with integrin $\alpha_v\beta_3$, leading to phosphorylation of nuclear inducing kinase (NIK) and IκBα, followed by downstream translocation of NFκB subunit P65 [25]. Activation of the NFκB signaling pathway drives upregulation of transcriptional factor membrane type 1 matrix metalloprotease (MT1-MMP) expression, resulting in activation of the well-known cell migration molecule Matrix Metallopeptidase 2 (MMP-2) in *in vitro* and *in vivo* studies [26]. Our experimental results are consistent with them, and we also verified by CCK-8 and Transwell tests that HABP1 regulated cell proliferation and invasion via the NFκB signaling pathway (Figures 5C, 5D).

At last, there are still lots of areas needed to be further completed and improved in our studies. For example, the number of fresh human tissue specimens needs to be broadened and more lung adenocarcinoma patients should be followed up in the future to get more accurate analysis data about prognosis. Besides, we only explained the relationship

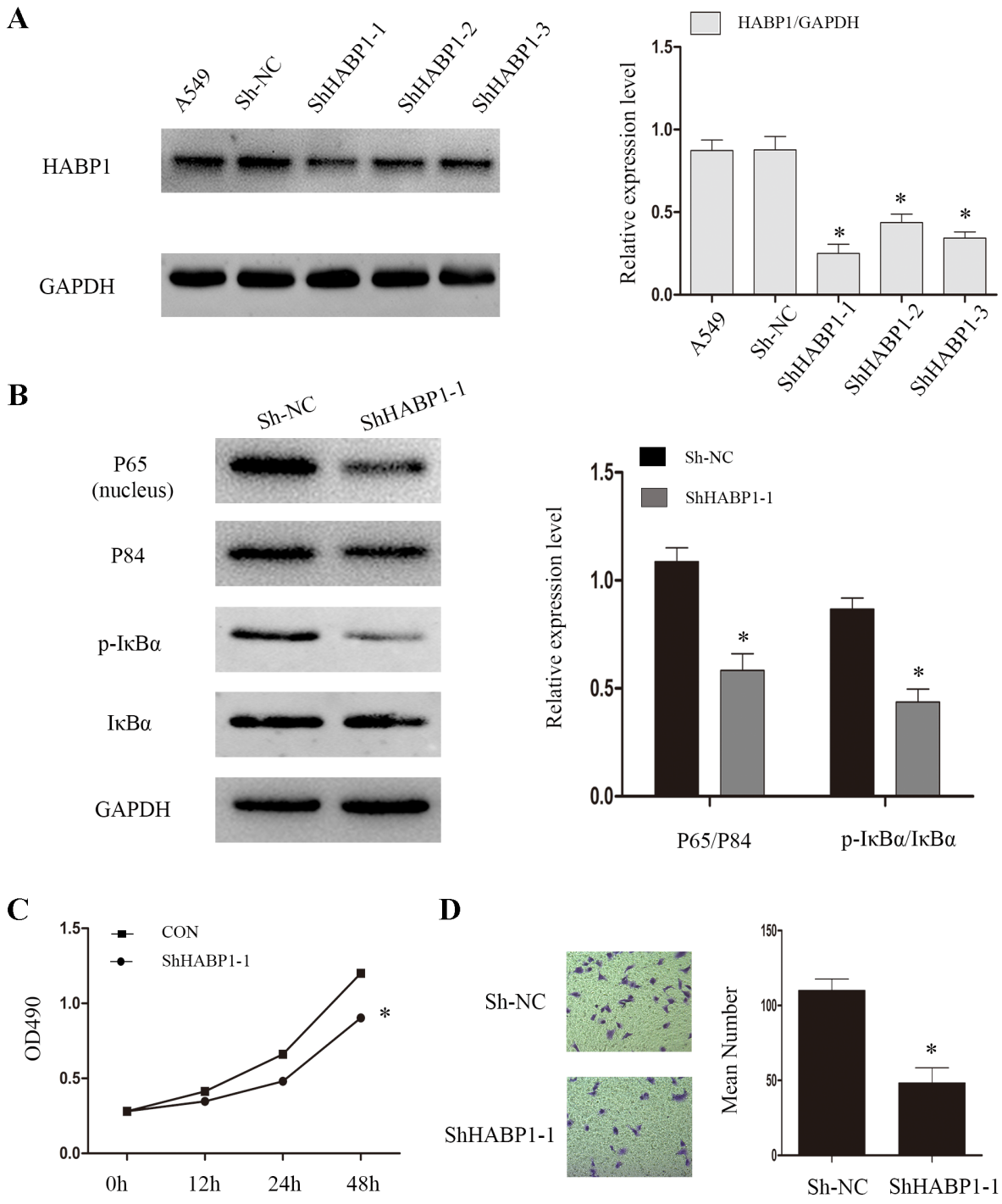


**Figure 4. Effects of silencing HABP1 on lung adenocarcinoma cells. A) Gene silencing effects of different sh-RNAs of HABP1. *p<0.05 B) Western blot showed the effects of silencing HABP1 on p65 and p-IκBα expression. *p<0.05 C) CCK-8 analysis indicated the effects of HABP1 downregulation on cell proliferation. *p<0.05 D) Transwell test showed the effects of HABP1 downregulation on cell invasion. *p<0.05**

between HABP1 and the NFκB pathway in lung adenocarcinoma. How does HABP1 adjust other signaling pathways in lung adenocarcinoma? It could be speculated that HABP1 accumulates in a subcellular compartment from those bright green clusters in Figure 3B. Where does HABP1 locate subcellular and how does HABP1 function through protein-

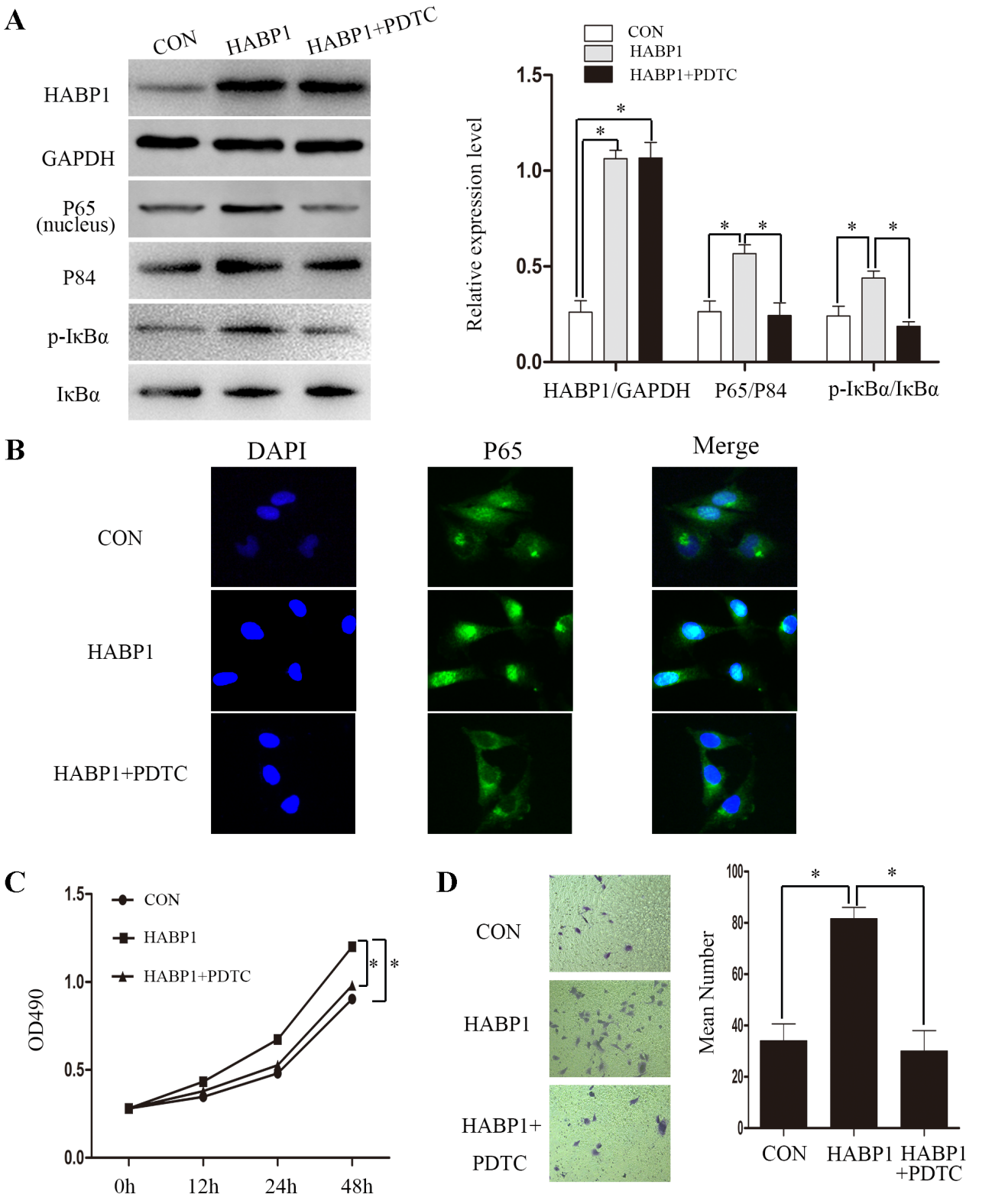


**Figure 5. Effects of HABP1 overexpression and NFκB antagonist PDTC on lung adenocarcinoma cells. A) Western blot results of expression changes of HABP1, P65, and p-IκBα of H1299 cells overexpressed with HABP1 and mantled with PDTC. *p<0.05 B) Immunofluorescence showed the nuclear translocation of p65 in H1299 cells overexpressed with HABP1 and mantled with PDTC. C) CCK-8 analysis indicated the changes of cell proliferation with different processions. *p<0.05 D) Transwell test showed the effects of different processions on cell invasion ability. *p<0.05**

protein interaction? In addition, our results are based on cell experiments *in vitro*. Under tumor microenvironment *in vivo*, many unknown changes may take place in tumorigenic effect, which needs many more verifications and examinations [27, 28].

In conclusion, this study illustrated that HABP1 made contributions to tumorigenesis of lung adenocarcinoma through biological information, clinical specimens, and cell experiments and affected cell proliferation and invasion by the NFκB signaling pathway. All the results highlighted the potential role of HABP1 as a therapeutic molecular target of lung adenocarcinoma.

Acknowledgments: This study was supported by grants from the scientific research fund project of Jiangyin, China (G202001).

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