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**Original Research Article**

# Peptide 17, an inhibitor of YAP/TEAD4 pathway, mitigates lung cancer malignancy

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## *Abstract*

***Purpose:*** *To investigate whether and how peptide 17 affects lung cancer cells.*
***Methods:*** *Human lung carcinoma cells, LLC and PC-9, were employed to study the therapeutic effect of peptide 17 on lung cancer. After exogenous expression of peptide 17, a co-immunoprecipitation experiment was used to examine the inhibitory effect of peptide 17. CCK8 assay was employed to assess the lung cancer cells' viability while clone formation assays were used to assess lung cancer cell proliferation. Colony number was also determined. The stimulatory effect of peptide 17 on lung cancer cell apoptosis was assessed by fluorescence-activated cell sorting (FACS).*
***Results:*** *Peptide 17 efficiently disrupted the interaction between YAP and TEAD4 ($p < 0.001$), and decreased the expression of CTGF and Cyr61. In addition, lung cancer cell viability and proliferation significantly decreased ($p < 0.001$) in a time- and concentration-dependent manner. On the other hand, the proportion of apoptotic cells was significantly elevated with rising concentration of peptide 17.*
***Conclusion:*** *Exogenous expression of peptide 17 activates Bcl2/Bax/caspase-9 signal and is responsible for its inhibitory effects on lung cancer cells. Thus, peptide 17 is a promising target drug in lung cancer treatment.*

***Keywords:*** *Lung cancer, Yes-associate protein, Transcriptional enhancer activation domain 4 (TEAD4), Peptide 17, Apoptosis*



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## INTRODUCTION

Lung cancer, a potentially fatal disease, was first identified in 1761 [1]. Until 1929, investigators believed that lung cancer initiation was closely associated with smoking [2]. Other risk factors, such as radon gas, asbestos, air pollution, and genetic mutations, are also associated with the evolution of lung cancer [3,4]. Similar to other malignant tumors, lung cancer is eventually caused by activation of oncogenes or inactivation of tumor suppressor genes. Kirsten rat sarcoma (KRAS) and epidermal growth factor receptor (EGFR) genes are the most commonly mutated genes in lung cancer [5,6]. On the basis of the molecular knowledge of lung cancer, specifically targeted treatments besides traditional surgery or radiotherapy, promote positive therapeutic outcomes [7]. For example, various small molecule drugs have been designed to tackle all possible situations, such as gefitinib and erlotinib [8-10].

Recently, several studies have reported that yes-associated protein (YAP) played a pivotal role in lung cancer progression. YAP, a transcriptional co-activator, is the downstream effector of the Hippo pathway that suppresses tumor growth. Mechanistically, when the Hippo pathway is inactivated, YAP interacts with transcriptional enhancer activation domain (TEAD) family members to promote cellular proliferation and inhibit apoptosis [11,12]. Given the critical role of YAP in lung cancer, peptide 17, a promising inhibitor of YAP/TEAD4 signaling, was supposed to ameliorate the malignancy of lung cancer [13,14].

## EXPERIMENTAL

### Cell culture

Human lung carcinoma cells, LLC and PC-9, were purchased from the Bena culture collection Co., Ltd (Jiangsu, China). Cells were cultured following the manufacturer's instructions. The cells were cultured with Dulbecco's modified Eagle's medium (DMEM), supplemented with 10 % FBS and 1 % penicillin/streptomycin (Gibco, USA). Cells were incubated in a humidified atmosphere containing 5 % $CO_2$.

### RNA extraction and reverse transcription polymerase chain reaction (RT-PCR) analysis

mirVana miRNA kit (Takara, China) was used to extract total RNA from the LLC and PC-9 cells following the manufacturer's instructions Of note, the internal control that we used was U6 small RNA. For detection of connective tissue growth factor (CTGF / CCN2) and cysteine-rich angiogenic inducer 61 (Cyr61 / CCN1) mRNA expression, a PrimeScript RT reagent kit (Takara, Dalian, China) was used to synthesize the first-strand cDNAs. The expressions of CTGF and Cyr61 were quantified by RT-PCR Mixture assays (Takara). GAPDH was used as the internal control. The primers used for RT-PCR are shown in Table 1.

### Cell viability assay

Lung cancer cells viability was assessed through a Cell Counting Kit-8 assay (CCK-8) according to the manufacturer's protocol (Dojindo; Tokyo, Japan). Cells ($2 \times 10^3$) were seeded into 96-well plates and incubated at 37 °C for 24 h, 48 h, or 72 h in a humidified chamber containing 5 % $CO_2$. Then, the CCK-8 solution (10 μL) was added to each well, and the plates were incubated for 1 h at 37 °C. The absorbance at 450 nm ($OD_{450}$) was measured in a microplate reader (Bio-Rad, USA).

### Western blot assays

Expression of proliferative proteins, such as Ki67, was determined by western blot. The LLC and PC-9 cells were lysed with RIPA buffer. Primary antibodies, such as rat anti Ki67 (Santa Cruz, 1 : 500), rat anti Bax (Sigma, 1 : 1000), and mouse anti Bcl-2 (Santa Cruz, 1 : 1000), were integrated with the targeted protein by incubation at room temperature for 1-2 h. Horseradish peroxidase (HRP) the labelled secondary antibodies were used to detect the expression of Ki67, Bax, and Bcl-2 through chemilumine-scence, huamn β-actin was used as a loading control.

### Colony formation assay

After transfection, 1 x $10^3$ cells were seeded into a 6-well plate and cultured for 24 h. Next, cells were cultured for 2 weeks in DMEM medium. Of note, DMEM should be supplemented with FBS at a final concentration of 10%. The colonies were then washed with PBS three times. Methanol and 0.1 % crystal violet were used to fixed and stain the colonies for 30 min. The number of colonies with > 50 cells were counted.

### Luciferase reporter assay

Human TEAD4 3'-UTR, which contains the peptide 17 binding site, was amplified by PCR and cloned into the pGL3-control vector (Ambion) at the NheI and XhoI sites. The resultant reporter plasmid was titled TEAD4-Wt-3'-UTR. For luciferase assays, LLC and PC-9 cells were cultured in 6-well plates and supplemented with peptide 17 (5, 10, 20 and 40 nM). The TEAD4-Wt-3'-UTR reporter plasmid (100 ng/well) and the pRL-TK luciferase reporters (25 ng/well) were transfected into the cells using lipofectamine 2000 (Invitrogen).

**Table 1:** Primers used for RT-PCR

| Genes | Forward primer | Reverse primer |
|---|---|---|
| CTGF | 5'-CTGCCTGGGAAATGCTGCGAGGAGT-3' | 5'-GTTGGGTCTTGGGCCAAATGT - 3'. |
| Cyr61 | 5'-ACCGCTCTGAAGGGGATCT-3' | 5'-ACTGATGTTTACAGTTGGGCTG - 3' |
| GAPDH | 5'-GGAGCGAGATCCCTCCAAAAT-3' | 5'-GGCTGTTGTCATACTTCTCATGG -3' |

Dual-Luciferase Reporter Assay kit (Promega, USA) was used to assay luciferase activity levels according to the manufacturer's instructions. Renilla-luciferase was used for normalization.

### Apoptosis assay

Apoptosis Detection Kits (BioVision, Mountain View, CA, USA), based on Annexin V/PI staining, were used to examine apoptosis of the LLC and PC-9 cells. 1× $10^6$ cells were harvested and washed with PBS. Then, the cells were resuspended by binding buffer (500 µL). Next, 5 µL of Annexin V/FITC and 1 µL of PI were introduced into the cells. Flow cytometry analysis was subsequently used to examine the apoptotic cells (BD, USA).

### Co-immunoprecipitation experiments

The LLC and PC-9 cells were harvested in immunoprecipitation (IP) lysis buffer supplemented with complete protease inhibitor cocktail (Sigma). The cell lysate was immunoprecipitated using anti-YAP or anti-TEAD4 antibody (Sigma, 1 : 1000), and the proteins were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) followed by immunoblotting.

### Data analysis

Data are presented as mean ± standard deviation. Statistical analyses between two groups were performed using Student's t-test via SPSS 16.0 (SPSS Inc, Team EQX), while statistical analyses between multiple groups were performed using one-way analysis of variance followed by the least significant difference post hoc test. Differences with values of $p < 0.05$ were regarded as statistically significant.

## RESULTS

### Peptide 17 efficiently inhibited the interaction of YAP and TEAD4

Given the important role of YAP signaling in lung cancer, we first examined the expression of YAP and TEAD4 in two lung cancer cell lines, LCC and PC-9. We found that the YAP/TEAD4 pathway was activated in both cancer cells. Next, the efficiency of peptide 17 in binding TEAD4 was tested. Peptide 17, at four different concentrations, was added to the LLC and PC-9 cells. Total protein was harvested, and the interaction of YAP and TEAD4 was verified. Co-immunoprecipitation results showed that peptide 17, a YAP analogue, could efficiently bind the protein TEAD4 in a concentration dependent manner. A luciferase reporter assay further demonstrated the efficiency of peptide 17 in binding TEAD4 (Figure 1 A). The CTGF and Cyr61 genes, which are responsible for cellular proliferation and apoptosis, were both targets of the YAP/TEAD signal. Therefore, after exogenous expression of peptide 17, the expression of Cyr61 and CTGF was subsequently examined. Results showed that supplementation of the cells with peptide 17 inhibited their expression (Figure 1 B-C). Consequently, peptide 17 could be a new method of targeting malignant proliferation of lung cancers cells.

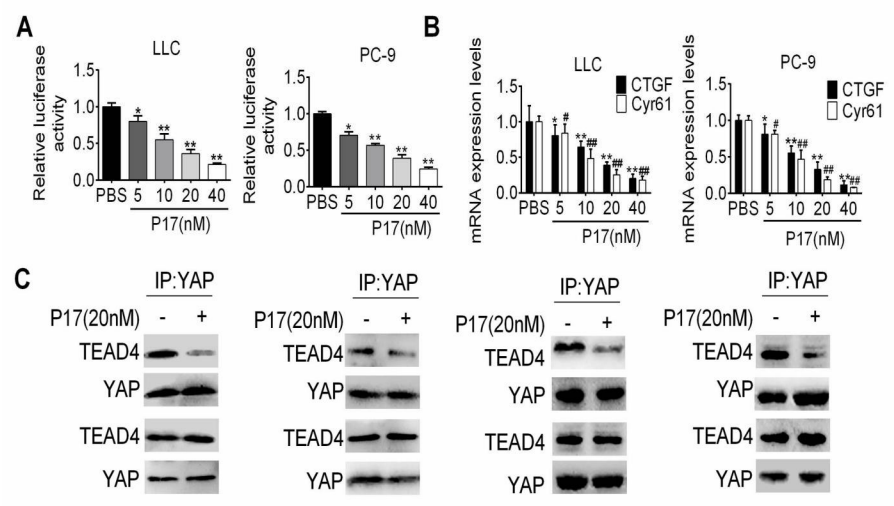


**Figure 1:** Peptide 17 efficiently disturbed the interaction of YAP and TEAD4 as well inhibited the expression of YAP downstream genes. (A) Luciferase reporter assay revealed that peptide 17 efficiently bound with TEAD4 in LLC and PC-9 cells. (B) RT-PCR results showed decreased expression of CTGF and Cyr61 in response to higher concentrations of peptide 17. (C) Co-immunoprecipitation assay directly demonstrated that peptide 17 efficiently disturbed the interaction of YAP and TEAD4; $^{***}p < 0.001$, vs. control

### Peptide 17 inhibits lung cancer cell proliferation

The CCK8 assay showed a lower viability with increasing peptide concentration for LLC and PC-9 cells (Figure 2). In addition, clone formation assay also revealed that peptide 17 at the concentration of 40 nM strongly inhibited LLC and PC-9 cells proliferation (Figure 3 A-B). Ki67, a proliferative marker of cells, was also down-regulated after supplementation with peptide 17 (Figure 4).

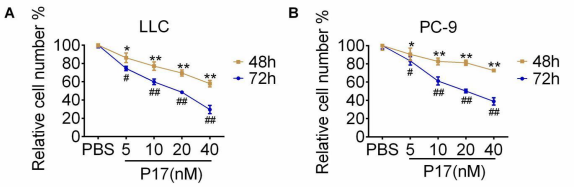


**Figure 2:** Peptide 17 efficiently restricted lung cancer cells viability. (A-B) CCK-8 assay revealed that LLC and PC-9 cells viability was decreased with raised in a time-and concentration-dependent manner

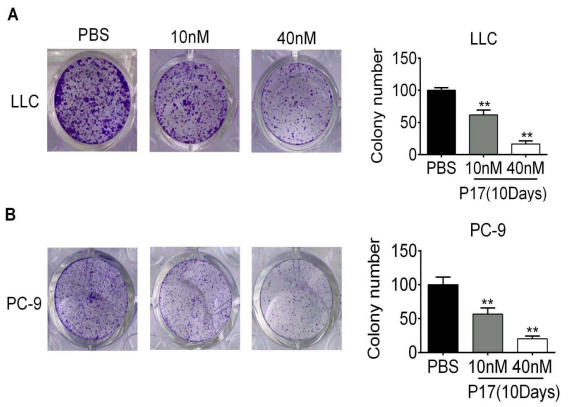


**Figure 3:** Peptide 17 efficiently inhibited lung cancer cells proliferation. (A) Clone formation assay revealed that a high concentration (40 nM) of peptide 17, compared to a lower concentration (10 nM), showed a strong inhibitory effect on LLC cell proliferation. (B) Clone formation assay also revealed that a high concentration (40 nM) of peptide 17 showed a strong inhibitory effect on PC-9 cell proliferation

### Peptide 17 promotes tumor cell apoptosis

To assess whether peptide 17 affected LLC and PC-9 cell apoptosis, cells supplemented with peptide 17 for 24 h were collected. The apoptosis assay indicated that a larger proportion of apoptotic cells was observed in response to an increase of peptide concentration (Figure 5).

Further, the effect of drug consumption time on cell apoptosis was also tested. The results showed that the proportion of apoptotic lung cancer cells was increased with prolonged treatment with peptide 17 (Figure 6). The concentration of apoptosis associated proteins, including BAX, was also increased and further promoted lung cancer cell apoptosis in a time- and concentration-dependent manner (Figure 7).

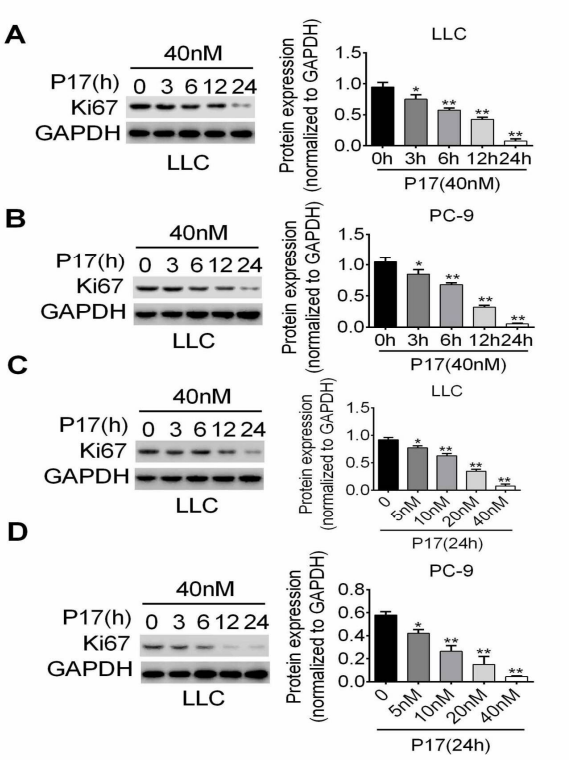


**Figure 4:** Effect of peptide 17 on expression of ki67 in lung cancer cells (A) Peptide 17, in a time-dependent manner, inhibited the expression of ki67 in LLC cells. (B) Peptide 17 inhibited the expression of ki67 in LLC cells in a time-dependent manner. (C) In LLC cells, peptide 17 efficiently inhibited ki67 expression in a dose-dependent manner. (D) Peptide 17, in a dose-dependent manner, efficiently inhibited ki67 expression in PC9 cells.

## DISCUSSION

Lung cancer, a devastating disease, was characterized by coughing, weight loss, weakness, fever and coughing up blood [15]. Chest radiograph, CT imaging and bronchoscopy were used to identify the type, extent, and histopathology of the disease [16]. For early stage lung cancer, surgery is the recommended treatment. About 70 % of patients that received surgery survived more than 5 years. Surprisingly, drugs targeted for early stage lung cancer therapy, such as adjuvant bevacizumab, adjuvant epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) and ALK inhibitor, showed no obvious benefit [17]. For advanced lung cancer therapy, two regimens are recommended based on genetic mutations [18]. For example, patients who are not candidates for an approved molecular drug usually receive

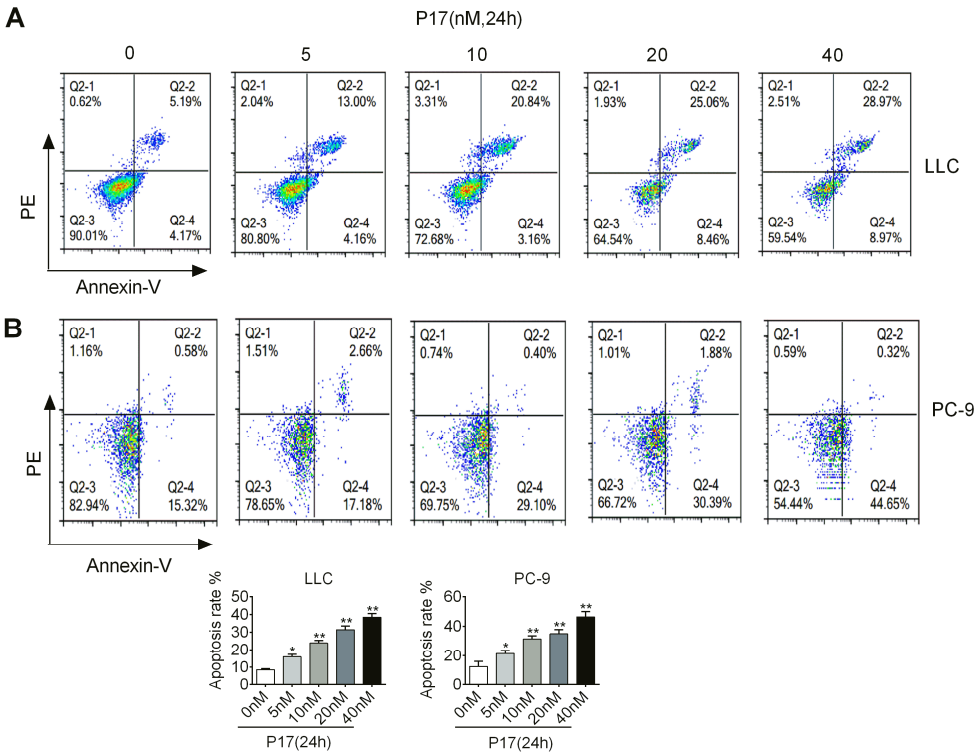


**Figure 5:** Peptide 17, in a concentration-dependent manner, facilitated lung cancer cell apoptosis. (A) In LLC cells, the proportion of apoptotic cells was elevated with rising concentrations of peptide 17. **(B)** In PC-9 cells, the proportion of apoptotic cells was also increased following rising concentrations of peptide 17. **(C)** Quantification of apoptotic cells after supplementation of peptide 17 in LLC and PC-9 cell cultures

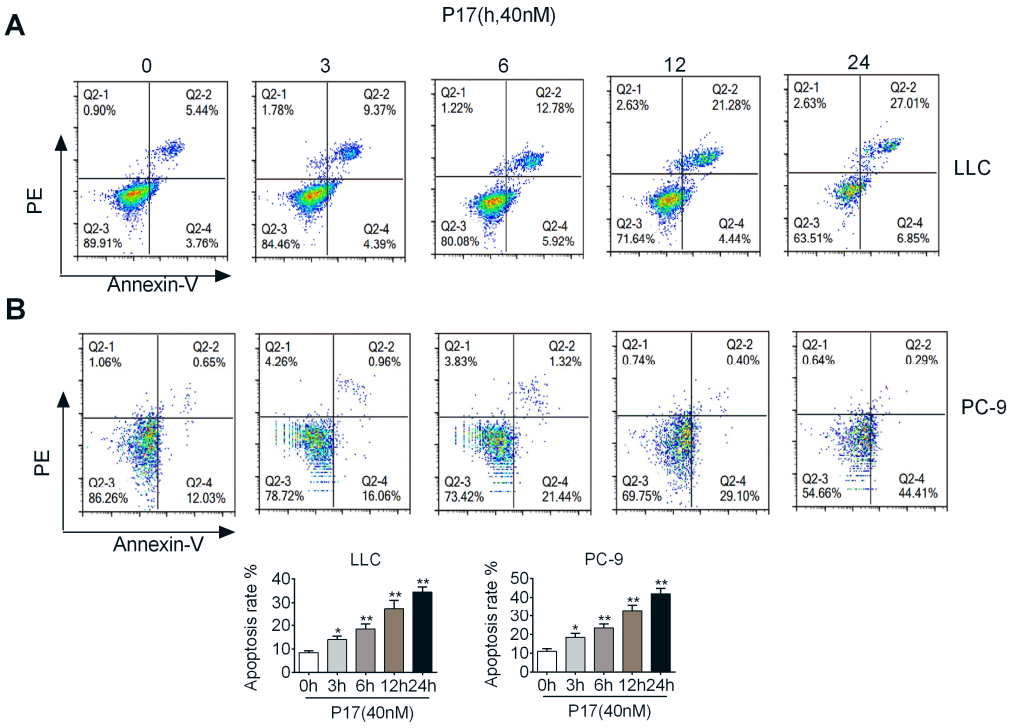


**Figure 6:** Following prolonged treatment with peptide 17, a larger population of lung cancer cells suffered from apoptosis. (A) In LLC cells, the proportion of apoptotic cells was elevated with prolonged treatment with peptide 17. (B) In PC-9 cells, the proportion of apoptotic cells was also increased in response to treatment with peptide 17. (C) Quantification of apoptotic cells after supplementation of peptide 17 in LLC and PC-9 cell cultures

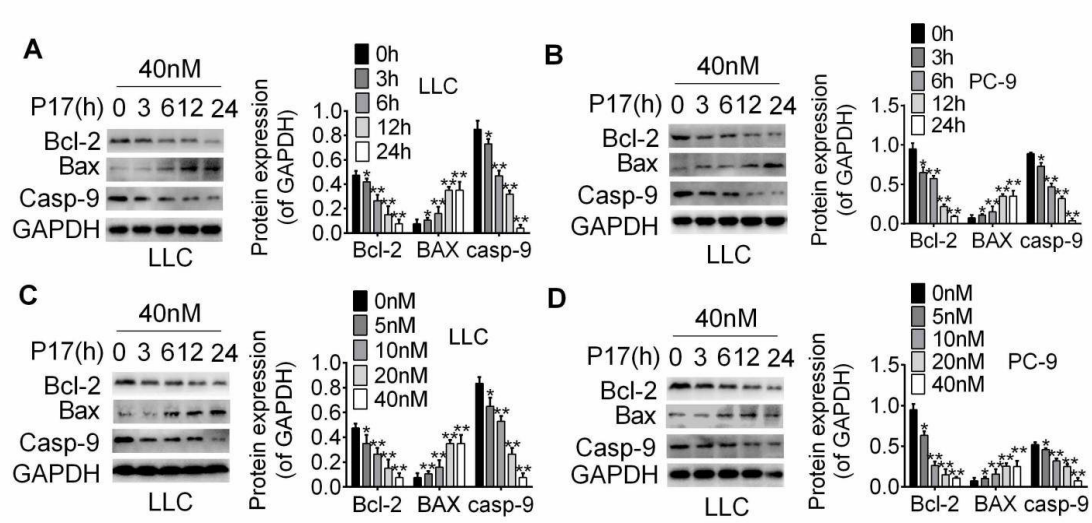


**Figure 7:** Bcl2/Bax/Caspase-9 signal mediated lung cancer cell apoptosis. (A-C) In LLC cells supplemented with peptide 17 (40 nM), western blot and RT-PCR results showed that Bcl2 / Bax / Caspase-9 signal was activated and that this effect was enhanced by increasing peptide concentration. (B-D) In PC-9 cells supplemented with peptide 17, western blot and RT-PCR results showed that Bcl2/Bax/Caspase-9 signal was also activated and that this effect was enhanced in a time dependent manner'

platinum-based therap. In contrast, patients with common gene abnormalities, such as EGFR, ALK, KRAS, and MET, are treated with the corresponding targeted inhibitors as an adjuvant therapy. The use of targeted drugs in advanced lung cancer has resulted in encouraging improvements in the overall survival rate. Unfortunately, there are still many patients with TKI resistance; therefore, other important molecular mechanisms urgently need to be investigated [19].

Recent studies showed that YAP is closely associated with lung cancers. There are at least three mechanisms of YAP function in lung cancers. First, YAP is essential to primary lung cancer cell proliferation. For example, Mao *et al* implied that YAP was critical to $KRAS^{G12D}$ – induced lung cancer [20]. YAP is expressed in the initial and later stages lung cancer. Deletion of YAP completely blocked $KRAS^{G12D}$, as well as P53 loss-driven adenocarcinoma initiation and progress. Next, YAP is responsible for lung cancer cell migration and metastasis [21]. Sun *et al*. reported that tenascin-C bound to the α9β1 receptor which is a type of intergrin and subsequently reduced the expression of YAP.. This signal cascade promoted lung cancer cells migration and invasion.

Finally**,** a high expression of YAP is closely associated with TKI resistance in lung cancer [22]. Given the important role of YAP in lung cancer cells, we subsequently examined the expression of YAP in LLC and PC-9 cells lines that originated from human lung cancer specimens. Results showed that YAP and its effector TEAD4 were highly expressed. Therefore, it is obvious that YAP signaling inhibitors would restore this effect. Several molecules have shown inhibitory effects on YAP. siRNAs have been designed to inhibit YAP activity [23], and YAP-like peptides without biological activity have been developed that show priority in combination with TEAD [14,24]. Other YAP inhibitors, for example statin, with restricted efficiency have also been applied to decrease lung cancer cell YAP expression [25].

Owing to the instability of nucleic acid drugs *in vivo*, peptide 17, a promising inhibitor that can efficiently disrupt the interaction between YAP and TEAD, was therefore investigated in lung cancer. Co-immunoprecipitation and luciferase reporter assay demonstrated the efficiency of peptide 17 in disturbing the YAP-TEAD4 interaction. In addition, peptide 17, at a concentration of 40nM, was the most efficient in binding TEAD4. Intriguingly, we found target genes of YAP signaling, such as CCN1 (Cyr61) and CCN2 (CTGF), were both down-regulated. CCN1 / 2 has been reported to be closely associated with tumor cell proliferation, apoptosis, and migration [26,27]. Results showed that peptide 17 efficiently inhibited LLC and PC-9 cell proliferation and induced a larger portion of cells to undergo apoptosis.

## CONCLUSION

Peptide 17 is a promising molecule for lung cancer treatment via inhibition of the interaction between YAP and TEAD. Furthermore, studies on the exact mechanism of YAP signaling in lung

cancer would provide a clear insight for translational research and clinical treatment.

## DECLARATIONS

### *Conflict of Interest*

No conflict of interest associated with this work.

### *Contribution of Authors*

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Jie Jiang designed all the experiments and revised the paper. Heng Du, Jing Zhuang and Qiuyue Xu performed the experiments, and Heng Du, Yaping Gui, Li Zhu and Le Gao wrote the paper.

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