

## Original Article

# KIAA0101 up-regulates SERPINE-1 expression in p53 signalling pathway in gastric cancer

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**Abstract:** Background: Gastric cancer has poor prognosis and high postoperative recurrence in advanced stages due to the lack of reliable early diagnostic biomarkers. The mechanism of the p53 pathway regulation by KIAA0101 in the development of gastric cancer remains to be elucidated. This study aimed to investigate the regulatory mechanism of KIAA0101 effects on the p53 pathway. Methods: Human gastric cancer tissues matched with adjacent non-cancerous gastric tissues were collected from 80 patients diagnosed by pathology, in which 3 were randomly selected for microarray analysis. The gene changes and downstream pathways were identified by microarray and bioinformatics analyses. The KIAA0101 and SERPINE-1 mRNA expression levels between gastric cancer tissues and matched adjacent non-cancerous gastric tissues were compared using student t-test. Western blot was used to validate the expression of SERPINE-1 between gastric cancer tissues and matched adjacent non-cancerous gastric tissues. The Spearman correlation analysis was used to assess the expressional correlation between KIAA0101 and SERPINE-1. Results: KIAA0101 expression influences the changes in SERPINE-1 expression. Bioinformatics analysis suggested a role of SERPINE-1 in the p53 signalling pathway. Relative KIAA0101 mRNA and SERPINE-1 mRNA expression levels in gastric cancer were significantly higher than the values in matched adjacent non-cancerous tissues. SERPINE-1 protein had a significantly higher level in gastric cancer tissues compared to the matched adjacent non-cancerous tissues. Expression of SERPINE-1 mRNA was significantly correlated with KIAA0101 expression ( $P = 0.005$ ). Conclusion: KIAA0101 correlation with SERPINE-1 gene expression in the p53 signalling pathway could be an unknown mechanism related to proliferation, invasion, lymphatic metastasis and poor prognosis for gastric cancer.

**Keywords:** KIAA0101, SERPINE-1, p53, regulation, biomarker, gastric cancer

## Introduction

Gastric cancer is one of the most-common malignant tumours, and yet, it has poor prognosis and high postoperative recurrence in advanced stages [1, 2]. The diagnosis and treatment of gastric cancer need to be addressed by finding the corresponding biomarkers [4].

A growing body of clinical studies has demonstrated the prognostic value of KIAA0101 expression in malignancies [3-5]. Previous studies showed that the expression of the KIAA0101 gene may play a role in the progression and metastasis of gastric cancer, eventually resulting in recurrence and mortality [6]. However, its action mechanism and impact on downstream pathways that lead to poor prognosis are still unclear. KIAA0101 overexpression in cancer is

closely correlated with p53 mutations. A loss of p53 function, either directly through mutations or indirectly through other pathways, plays a significant role in the development of hepatocellular cancer [7]. cDNA microarray analysis for p53-regulated genes in pancreatic cancer also found the possibility that KIAA0101 expression was down-regulated by adenovirus-mediated introduction of p53 [8]. The expression levels of several genes, such as PCNA, FEN1, POLD1 and serpine-1(PAI-1) were regulated by the p53 pathway [9-12]. However, the mechanism of the p53 pathway regulation by KIAA0101 in the development of gastric cancer remains to be elucidated.

In this study, we compared the KIAA0101mRNA expression in gastric cancer tissues with matched adjacent non-cancerous gastric tissues.

**Table 1.** Clinicopathological characteristics of the patients

Variables	No. cases	(%)
Gender		
Male	53	66.3
Female	37	33.7
Age (years)		
<60	59	73.8
≥60	21	26.2
pTNM stage		
I–II	37	47.3
III–IV	43	52.7
Tumor invasion		
T1-T2	27	33.8
T3-T4	53	66.2
Lymph node		
Negative	31	38.8
Positive	49	61.2

KIAA0101-related gene changes and downstream pathways were identified by microarray and bioinformatics analyses. The results showed that overexpression of KIAA0101 correlates with SERPINE-1 gene expression, which demonstrated, for the first time, a mechanism of KIAA0101 action on the p53 pathway. Based on this mechanism, we further explained how KIAA0101 is involved in the carcinogenesis of gastric cancer. Patients may benefit from elucidation of this mechanism for selection of therapeutic targets.

## Materials and methods

### Tissue preparation

Human gastric adenocarcinoma tissues matched with adjacent non-cancerous gastric tissues (3 cm to 5 cm from cancer tissue) were collected from 80 patients diagnosed by pathology. 3 matched samples were randomly selected for microarray analysis and western blot. All 80 patients were selected for RT-PCR validation. Patients underwent surgery in the Oncology Surgery Department of the First Affiliated Hospital of Xi'an Jiaotong University from January 2017 to July 2018. Patients with histopathologically confirmed gastric cancer were enrolled, and there were no sex and age restrictions. The exclusion criteria included previous cancer and previous chemotherapy or radiotherapy. The histopathological diagnoses were performed according to the World Health Organization criteria. The clinicopathological characteristics of the patients are shown in Table 1.

All fresh specimens were snap-frozen at the time of surgery and stored at -80°C for future experiments. This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University and all patients gave their informed consents.

### RNA extraction and RT-PCR

Total RNA was extracted from 80 replicates of gastric cancer tissues and matched adjacent non-cancerous gastric tissues using the Trizol procedure (Invitrogen, Carlsbad, CA, USA). Reverse transcription used a First-strand cDNA Synthesis Kit (Fermentas, Burlington, ON, Canada). Q-PCR analysis used SYBR Premix Ex Taq (TaKaRa, Ohtsu, Shiga, Japan) according to the manufacturer's instructions. All PCR reactions were performed in a final volume of 20 µL containing 1 µL of cDNA template in an iQ5 system (BioRad, Hercules, CA, USA). Each sample was analysed in triplicate. The mRNA level of GAPDH was amplified simultaneously as an internal control in each PCR.

### Microarray analysis

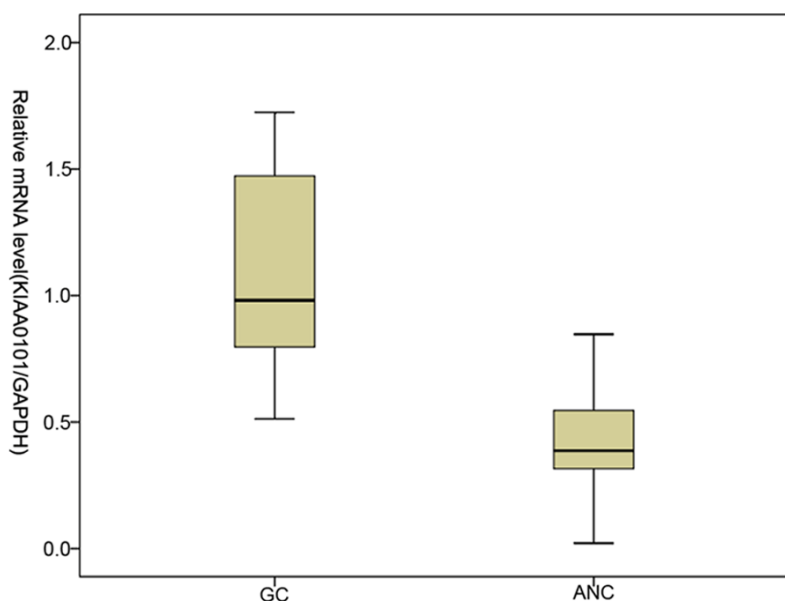
Gene Chip Prime View Human (Affymetrix, Shanghai, China) was used for gene expression microarrays. Gene chips were washed in Gene Chip Hybridization Oven 645 system and stained in Gene Chip Fluidics Station 450. For validation, the Gene chips were scanned three times per sample using the Gene Chip Scanner 3000. Significant difference in fold-change was defined as a difference greater than 1.2 ( $P < 0.05$ ). The list of differential expressed genes was imported into the DAVID database for pathway enrichment and cluster analyses.

### Bioinformatics analysis

The cBioPortal database (<http://www.cbioportal.org/>) in the TCGA was used to identify the expression of the KIAA0101 gene in gastric cancer. According to the data returned by the database, for further correlation analysis the percentage of total clinical samples was calculated by up-regulating mRNA levels. The KEGG website was used to draw the access map. The relevant genes in the input list were marked.

### Western blot

Treated tissues were lysed in buffer (50 mM Tris-HCl, pH 8.0, 150 mM NaCl, 100 µg/mL



**Figure 1.** KIAA0101 mRNA expression levels in gastric cancer tissues and matched adjacent non-cancerous tissues. The relative KIAA0101 mRNA expression levels in gastric cancer tissues were  $1.104 \pm 0.379$ , significantly higher than the values in three matched adjacent non-cancerous tissues ( $0.421 \pm 0.172$ ;  $P < 0.05$ ). GC: gastric cancer tissue; ANC: adjacent non-cancerous tissue.

PMSF, 1% Triton X-100). The membranes were incubated with primary antibodies specific for KIAA0101 (Abnova, Taiwan), SERPINE-1 (Santa Cruz Biotechnology, Santa Cruz, CA, USA) and GAPDH (1:1000; Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA) at 4°C overnight, then incubated with secondary antibodies for an hour, after which they were incubated with an HRP-conjugated secondary antibody (Goat Anti-Mouse/Rabbit IgG; 1:2000 dilution; Pierce Biotechnology, Inc.) for another hour. The SERPINE-1 expression level was determined by normalizing the signal intensity of SERPINE-1 to that of GAPDH using the Gel-Pro Analyser Software (Media Cybernetics, Washington, DC, USA). Each sample was analysed at least three more times to establish high reliability. Images were analysed using ImageJ 1.44p software (developed by Wayne Rasband, National Institutes of Health [NIH], Bethesda, MD, USA) and the G: BOX Bio Imaging System (Sygene, Cambridge, UK).

#### Statistical analysis

The data analyses were performed using SPSS 19.0 Software (SPSS, Chicago, IL, USA). Consecutive data were presented as the mean  $\pm$  standard deviation (SD). The Student's t-test

was used to assess the statistical significance of differences between groups. The Spearman correlation analysis was used to assess the expressional correlation between KIAA0101 and SERPINE-1.  $P < 0.05$  was considered statistically significant [6].

#### Results

##### *Expression of KIAA0101 is up-regulated in gastric cancer*

To assess KIAA0101 levels in prepared gastric cancer tissues, we first performed quantitative real-time RT-PCR from 80 gastric cancer patients with 80 matched adjacent non-cancerous gastric tissues. As shown in **Figure 1**, the expression of KIAA0101 in gastric cancer is up-regulated, compared

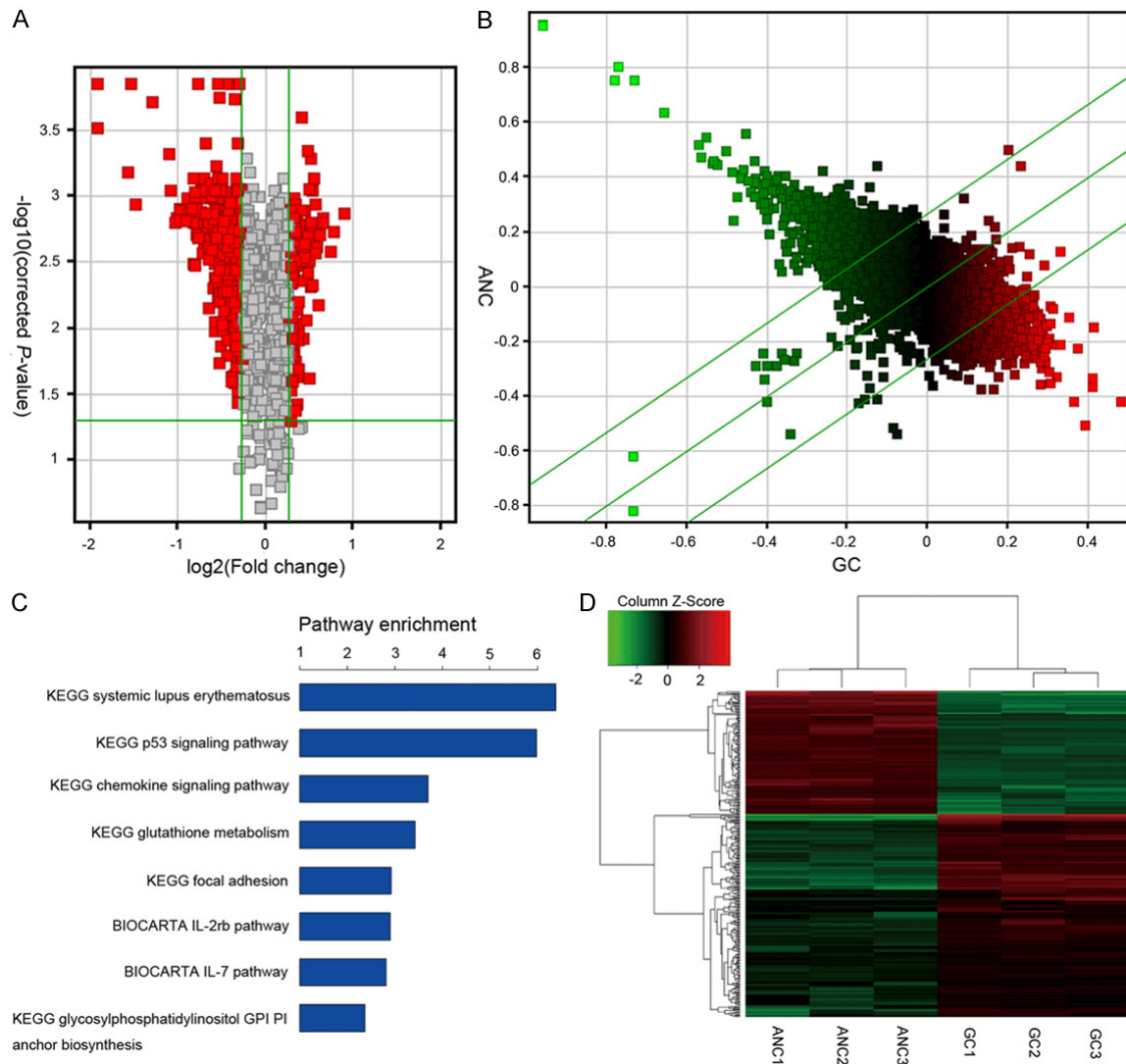
to the matched adjacent non-cancerous gastric tissues ( $1.104 \pm 0.379$  vs  $0.421 \pm 0.172$ ;  $P < 0.05$ ).

##### *Differential genes expression in microarray tests*

Using human gene expression microarray tests, we screened up-regulated RNAs in three KIAA0101-overexpressing gastric cancers and three matched adjacent non-cancerous tissues. The sets of genes that were consistently and significantly different (by fold-change  $> 1.2$ ) in each sample were selected. The results showed that, compared to the control group, when KIAA0101 expression was increased, the number of significantly up-regulated genes was 144, while the number of significantly down-regulated genes was 206 (**Figure 2A**).

In the following scatter plots, results showed that different levels of KIAA0101 expression were associated with a significant number of gene changes (**Figure 2B**).

The changes in KIAA0101 expression mainly affected gastric cancer-related pathways and processes: the p53 pathway, chemokine signalling pathway, and glutathione metabolism (**Figure 2C**). The heat map of differentially expressed



**Figure 2.** Microarray analysis and enrichment analysis. A. Volcano plots of differential expression genes. The red squares represent differential expression of genes, while grey squares represent genes with no differential expression. B. Scatter plot of differential expression genes. Green dots: genes with normal expression; red dots: up-regulated genes. C. Enrichment analysis of top eight pathways for differential expressed genes. D. Heat map of differentially expressed genes showed good consistency with enrichment analysis. GC 1-3 represent gastric cancer tissues. ANC 1-3 represent adjacent non-cancerous tissues [11].

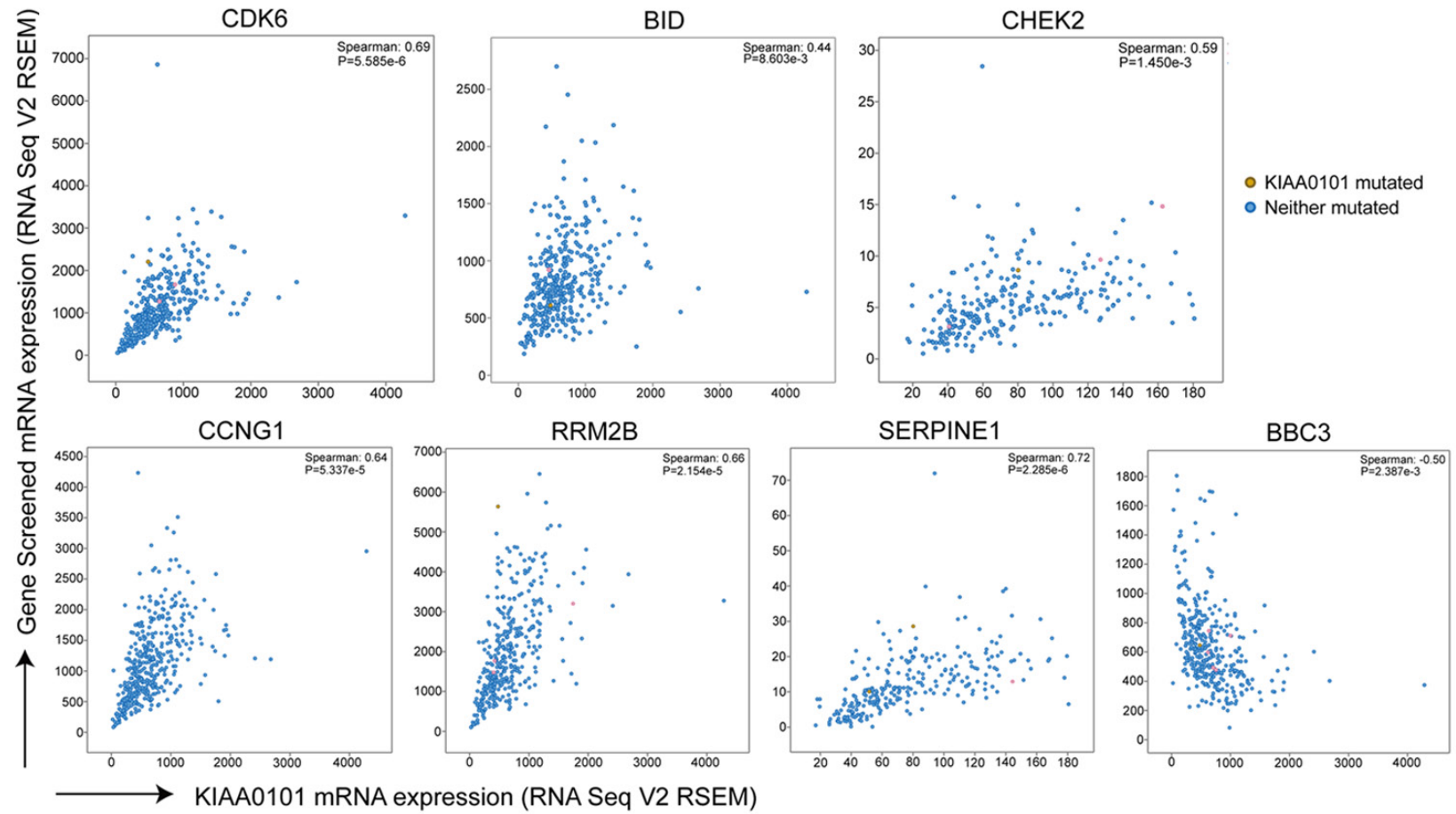
ssed genes showed good consistency (**Figure 2D**). The affected genes in the p53 pathway were RRM2B, BID, CDK6, SERPINE1, CHEK2, BBC3, IGFBP3 and CCNG1. We uploaded the KIAA0101 gene information into the cBioPortal analysis platform in the Cancer Genomic Atlas (TCGA). By systematic analysis of the expression strength of all gene probes, 7 of 8 genes, except IGFBF3, screened in enrichment analysis of the p53 pathway were confirmed to be related to the expression level of KIAA0101 gene in gastric cancer (**Figure 3**).

#### Bioinformatics analysis suggested SERPINE-1 is related to p53 signalling pathway

To identify the regulatory mechanism of KIAA0101 expression in the p53 pathway, we entered related genes into the KEGG pathway-related site to generate pathway maps. The relevant genes in the pathway were marked with red circles.

On the access map drawn via KEGG website, we found that SERPINE identified by enri-

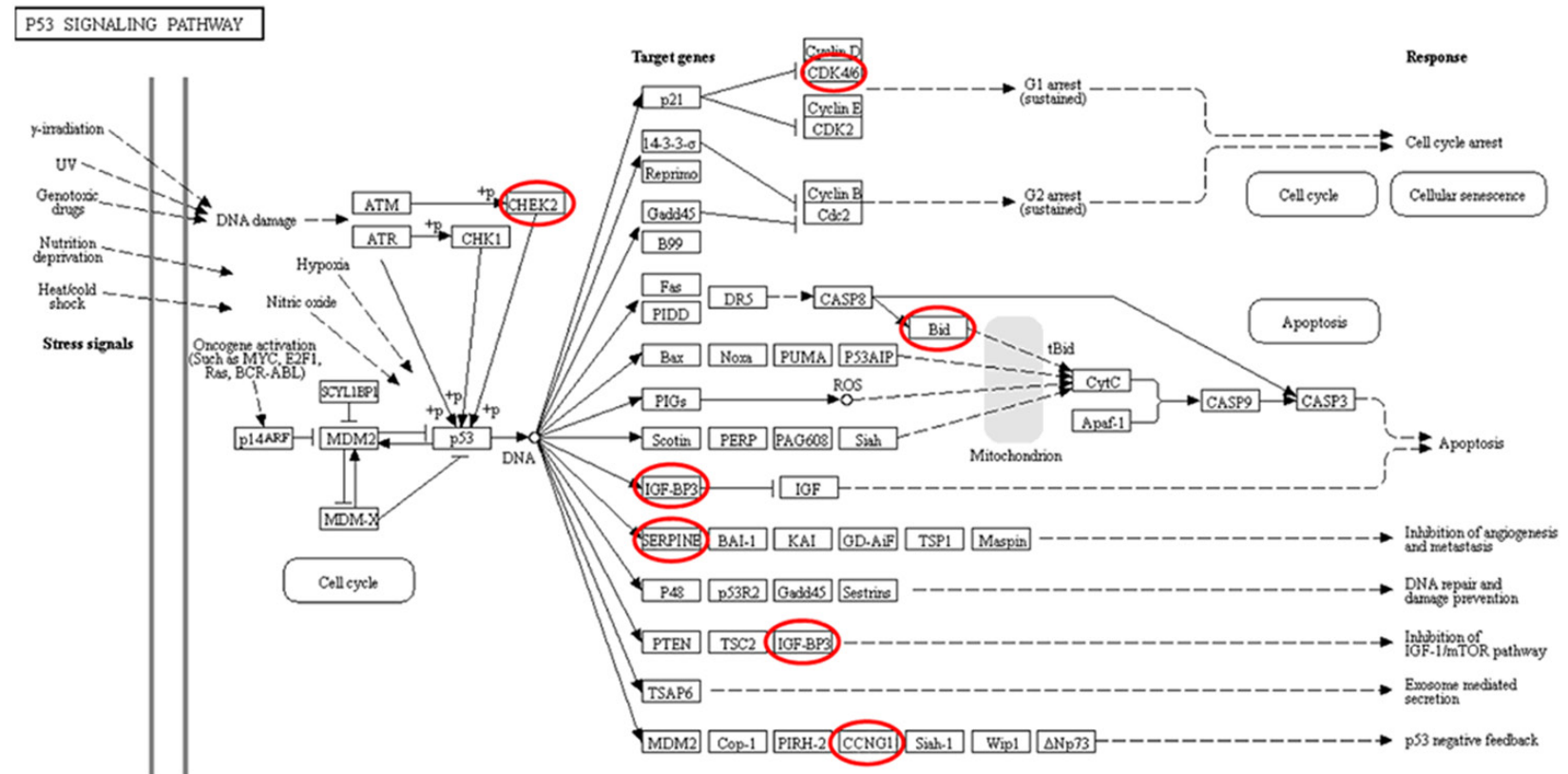
# KIAA0101 up-regulates SERPINE-1 in p53 signalling pathway



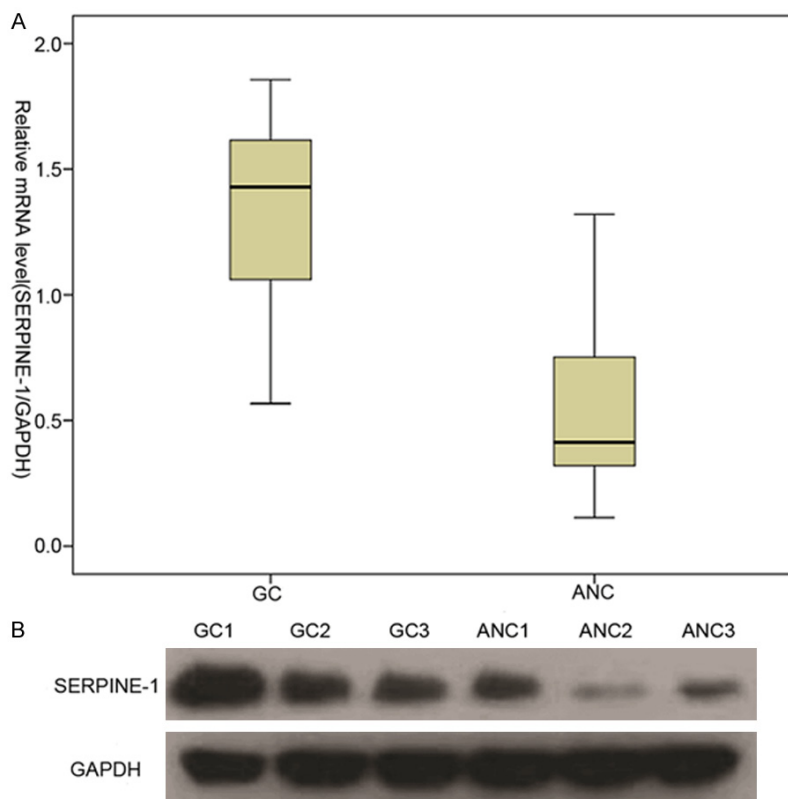
**Figure 3.** KIAA0101-related genes in p53 pathway analyzed by Cancer Genomic Atlas (TCGA). CDK6, BID, CHEK2, CCNG1, RRM2B, SERPINE1, BBC3 genes in the p53 pathway were related to the expression level of KIAA0101 gene in gastric cancer.



# KIAA0101 up-regulates SERPINE-1 in p53 signalling pathway



**Figure 4.** Position of SERPINE (PAI) in the p53 signaling pathway on access map. SERPINE is in an important position in the p53 signaling pathway and is related to inhibition of angiogenesis and metastasis. As a member of SERPINE family, SERPINE-1 could also be involved in this process.



**Figure 5.** RT-PCR and western blot analysis of SERPINE-1 levels in gastric cancer and matched adjacent non-cancerous tissues. A. The relative SERPINE-1 mRNA expression levels in 80 gastric cancer tissues were  $1.338 \pm 0.448$ , significantly higher than the values in matched adjacent non-cancerous tissues ( $0.537 \pm 0.299$ ;  $P < 0.05$ ). B. A significant up-regulation effect was observed using western blot. SERPINE-1 protein level was significantly elevated compared with the ANC group in 3 matched human gastric cancer tissues and adjacent non-cancerous gastric tissues. GC: gastric cancer tissue; ANC: adjacent non-cancerous tissue. The numbers represent 3 matched tissues.

chment analysis in an important position in the p53 signalling pathway is also related to inhibition of angiogenesis and metastasis (**Figure 4**). As a member of the SERPINE family, SERPINE-1 could also be involved in this process.

#### *SERPINE-1 mRNA was significantly correlated with KIAA0101 mRNA*

Because microarray analysis suggested that KIAA0101 expression influences changes in SERPINE-1 expression, and bioinformatics analysis suggested a role of SERPINE-1 in the p53 signalling pathway, we separately assessed SERPINE-1 at the mRNA and protein levels. RT-PCR showed that relative SERPINE-1 mRNA expression levels in gastric cancer were significantly higher than in 80 matched adjacent non-cancerous tissues. Western blot analysis showed that the SERPINE-1 protein level was sig-

nificantly elevated compared to the control group (**Figure 5**). Spearman correlation analysis showed that SERPINE-1 mRNA was significantly correlated with KIAA0101 mRNA expression ( $P = 0.005$ ) [8].

#### **Discussion**

Plasminogen activator inhibitor-1 (PAI-1), also known as serpin peptidase inhibitor, clade E, member-1 (SERPINE-1), belongs to the urokinase-type plasminogen activator (uPA) system and plays a key role in tumour genesis as a primary inhibitor of plasminogen activators [13]. SERPINE-1 is activated during the initial synthesis stage, and then rapidly inactivated into serum [14]. SERPINE-1 is also associated with angiogenesis, that is, the formation of new blood vessels from existing blood vessels is essential for normal growth and the development of tissues and organs [15, 16]. It has also been demonstrated by

immunohistochemical analysis that SERPINE-1 is associated with lymphatic metastasis [17, 19].

P53 is the most important tumour suppressor and is inactivated by mutations or deletions in approximately 50% of all malignancies [18]. Mutation of p53 is the most-common biological process in human malignancies including gastric cancer. Regulatory relationships between p53 and SERPINE-1 have been illustrated in previous studies. It has been reported that p53 is required for gene expression of p21, MMP2, and SERPINE-1 [19]. p53-dependent regulation of SERPINE-1 gene expression by TGF- $\beta$  has also been revealed [20].

p53 is required for TGF- $\beta$ -induced cytostatic activity, and SERPINE-1 is also involved in its effects in several cell lines. These findings suggest that SERPINE-1 is involved in many important p53-related cytostatic activities.

Although the relationship between KIAA0101 and p53 and regulation of SERPINE-1 by p53 were reported by some studies, there is little conclusive evidence to demonstrate the clinical significance of the relationship between KIAA0101 and SERPINE-1. An explanation for this could be that the action of numerous downstream genes in multiple pathways may change after up-regulation or down-regulation of one gene. Therefore, we aimed to investigate the relationship of these three factors in gastric cancer by a high-flux gene microarray and bioinformatics analysis.

In a microarray analysis, we compared the gene expression profiles between three KIAA0101-overexpressing gastric adenocarcinoma tissues and normally expressing adjacent non-cancerous gastric tissues using Gene Chip Prime View Human. Based on the selected differentially expressed genes, a pathway enrichment analysis was performed. According to the genetic information of all the pathways in KEGG and BIOCARTA, the differentially expressed genes were enriched and analysed. The results showed that RRM2B, BID, CDK6, SERPINE1, CHEK2, BBC3, IGFBP3 and CCNG1 were enriched in the p53 pathway in KIAA0101-overexpressing gastric cancer tissues.

After systematically analysing the expression changes of related genes and pathways caused by the up-regulation of KIAA0101 gene expression in gastric cancer tissues, we further applied public data resources to investigate the status of KIAA0101 expression in non-interfered gastric cancer and normal gastric tissues by bioinformatics analysis. The corresponding upstream or downstream regulatory gene expression data was expected to provide further reliable information on gastric cancer. The results showed that 7 out of 8 genes screened in enrichment analysis in the p53 pathway were confirmed to be related to the expression level of KIAA0101 gene in gastric cancer by cBioPortal analysis platform in the Cancer Genomic Atlas (TCGA). On the KEGG access map, the SERPINE-1 could also be associated with the p53 signalling pathway map, which is related to the inhibition of angiogenesis and metastasis.

Combining the microarray analysis and bioinformatics analysis, the results strongly suggested that the SERPINE-1 could play an important role in the mechanism of KIAA0101 action on

the p53 pathway. RT-PCR and western blot analysis validated that the SERPINE-1 mRNA and protein were relatively overexpressed in gastric cancer tissues compared with matched adjacent non-cancerous gastric tissues. Correlation analysis showed that SERPINE-1 mRNA was significantly correlated with KIAA0101 mRNA expression, which confirmed our hypothesis.

Invasion and metastasis are critical determinants of cancer morbidity [21, 22]. Gene and molecular factors participating in these steps must be considered as potential prognostic biomarkers. We found that KIAA0101 was frequently overexpressed in gastric cancer and significantly associated with pathological stages of cancer, suggesting that its expression in gastric cancer is related to tumour progression and may be useful as a marker for invasive gastric cancer [23]. Many studies in the past have also proved that SERPINE-1 was associated with lymphatic metastasis and cancer invasion [24-27]. In this study, we illustrated for the first time that SERPINE-1 is a downstream mediator of the KIAA0101-related action on the p53 pathway in gastric cancer, which could be a completely unknown function for KIAA0101 in the p53 pathway.

In conclusion, the correlation of KIAA0101 and SERPINE-1 gene expression in the p53 signalling pathway could be an unknown mechanism related to proliferation, invasion, lymphatic metastasis and poor prognosis for gastric cancer. Patients may benefit from elucidation of this mechanism for better selection of therapeutic targets.

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## Disclosure of conflict of interest

None.

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