

## Original Article

# Prognostic value of IL1R2 expression in gastric cancer patients undergoing gastrectomy

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**Abstract:** *Objective:* Our aim was to explore new oncogenes in gastric cancer (GC), after gastrectomy, by the bioinformatics method and to investigate the underlying mechanism. *Methods:* GC-related core genes were determined by construction of an interaction network based on bioinformatics. IL1R2 expression in GC tissues and paired adjacent tissues was examined by quantitative polymerase chain reaction (q-PCR). Effects of IL1R2 expression on proliferation and apoptosis of GC cell SGC-7901 were, respectively, tested by CCK-8 method and flow cytometry. The difference between patient overall survival (OS) and disease-free survival (DFS) was observed. *Results:* IL1R2 presented lower expression in cancer tissues than in adjacent tissues. Compared with both the negative control and blank groups, proliferation and apoptosis of the GC cell line SGC-7901 were decreased and increased in the experimental group, respectively ( $P < 0.05$ ). There was no significant difference between negative control and blank groups ( $P < 0.05$ ). OS and DFS in low IL1R2 expression group were lower than those in the high IL1R2 expression group. *Conclusion:* Our results show that a new oncogene, ILR2, affects proliferation and apoptosis of GC and is associated with patient prognosis.

**Keywords:** Gastric cancer, IL1R2, proliferation, apoptosis, prognosis

## Introduction

Gastric cancer (GC) is one of the most common malignant tumors worldwide. Although treatment on gastrointestinal tumors has made rapid progress, it is still the second leading cause of cancer-related deaths [1]. Currently, treatments for early GC include endoscopic mucosal resection, radiotherapy, and chemotherapy [2, 3]. However, in China, most GC patients are diagnosed at an advanced stage, failing to improve efficacy and prognosis after gastrectomy [4]. GC progression involves the activation of oncogenes and inactivation of tumor suppressor genes. Therefore, recognition of tumors from the molecular perspective is an important way to identify cancer genes and to illustrate development of malignant tumors. It is important to determine the mechanism of carcinogenesis in gastric cancer and study the biomarkers of early diagnosis, clinically [5]. Due to development of high-throughput biotechnology, scholars at home and abroad have obtained enormous biological

data and have made significant progress in understanding the role of gene function. Discovery of tumor markers provides a reliable basis for diagnosis, prediction, and prognosis of cancers.

Occurrence of GC is a multi-gene and multi-step process involving activation of multiple oncogenes and inactivation of tumor suppressor genes. Interleukin-1 (IL1) is a key mediator of autoimmune and inflammatory diseases and can be produced by multiple cell types such as monocytes, activated macrophages, and endothelial cells [6]. IL1 is related to many immune diseases because it affects coagulation mechanism and the immune system. IL1 gene family includes IL1A, IL1B, and IL1RN genes. IL1R2, a kind of decoy receptor, is an important mediator of immune and inflammatory responses induced by various cytokines [7] and expressed by neutrophils, B cells, macrophages, and monocytes [8]. Scholars have analyzed expression data of pancreatic ductal adenocarcinoma, through the bioinformatics method, and

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found that IL1R2 presented significantly lower expression in cancer tissues than in adjacent tissues. These are found in 4 microarray databases, laying the foundation for research on the mechanism of drug resistance and prognosis of pancreatic ductal adenocarcinoma. Based on this, it is thought that IL1R2 has a certain correlation with cancers. In clinical study, molecular markers of GC tissue mainly include KLF5 [10], CDK10 [11], Tspan-1 [12], PFDA [13], and SRPK1 [14]. Scholars have observed and proven the function of molecular markers in predicting efficacy and prognosis of GC through experiments and clinical samples. At present, there is no study on the mechanism of IL1R2 in GC after gastrectomy. In our study, we analyzed correlation between expression levels of IL1R2 and prognosis in GC, after gastrectomy, and explored its mechanism in GC, providing a basis for targeted therapy.

### Methods and materials

#### *GEO chip data processing*

Gene expression data were downloaded from NCBI Gene Expression Omnibus (GEO), with “gastric cancer” and “gastrectomy” as keywords (<http://www.Ncbi.nlm.Gov/geo>). GSE54-129 was selected as gene expression data for analysis. The platform of this database was GPL: 570 [hg-u133\_plus\_2] Affymetrix Human Genome U133 Plus 2.0 Array, which included 111 cases of GC tissues and 21 cases of non-cancerous tissues. In this study, 21 cases of paired adjacent tissues and GC tissues, respectively, were included for gastrectomy.

#### *Known GC-related genes*

PolySearch2.0 (<http://polysearch.cs.ualberta.ca/>) is a web-based text mining bioinformatics database which supports retrieval of related genes/proteins, single nucleotide polymorphisms, gene mutations, drugs, and their metabolites of diseases, tissues, and cells. It easily allows viewing of disease-related hot genes/proteins. With “gastric cancer” as a keyword, GC-related genes were retrieved and selected according to Z-score.

#### *Sample collection*

A total of 56 GC patients, undergoing gastrectomy, were received from January 2013 to De-

ember 2014, at the Department of Oncology, the first Affiliated Hospital of Bengbu Medical College. The patients included 31 males and 25 females with an average age of  $61.01 \pm 5.13$  years old. Inclusion criteria: (1) Diagnosed with GC through pathological examination; (2) Perfect clinical data; and (3) Signed informed consent. Exclusion criteria: (1) No death occurred during the whole operation; (2) Combination of severe organ diseases; and (3) Lactating and pregnant women. Specimens with a diameter of 0.5 cm were taken from GC and paired normal adjacent tissues (5 cm from GC tissues), respectively. After gastrectomy, fresh specimens were immediately frozen in liquid nitrogen.

#### *GC cell line and cell culture*

GC cell line SGC7901 was purchased from American Type Culture Collection (ATCC) and preserved in our laboratory. After recovery, cells were cultured at 37°C in 5% CO<sub>2</sub> in Dulbecco's Modified Eagle's Medium (DMEM) (Sigma-Aldrich Chemical Company, St Louis MO, USA) containing 10% fetal bovine serum (FBS) (Sigma-Aldrich Chemical Company, St Louis MO, USA), 100 U/mL penicillin and 100 µg/mL streptomycin.

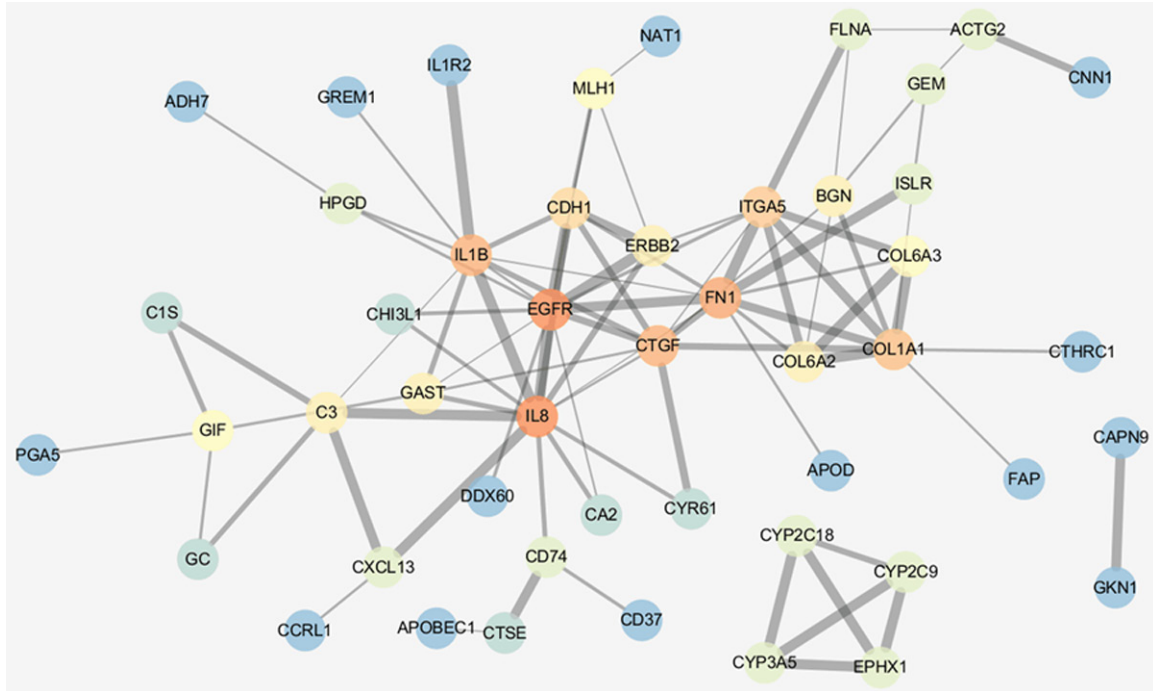
#### *Vector construction and cell transfection*

Primers were designed and the full-length cDNA sequences were amplified according to IL1R2 gene sequence. Upstream primer was 5'-GGAAGATCTGATGTTGCGCTTGTACGTGTTG-3' and downstream primer was 5'-GATATCGA-TGACTTGGGATAGGATTGAAA-3'. Then, cDNA of genes was subcloned into vector pCDH-CopGFP to construct overexpression plasmids and the plasmids were transfected into GC cell line SGC7901 using Lipoelectamine 3000, with an empty vector as control. After that, cells were cultured for 48 hours and then screened with DMEM medium containing 400 µg/mL G418 for a month. Subsequently, cells continued to be cultured and frozen in DMEM + 10% FBS + penicillin and streptomycin (P/S) medium.

#### *Total RNA extraction and quantitative polymerase chain reaction*

Total RNA was extracted from GC tissues using TRIzol Reagent (Invitrogen, Carlsbad, California, USA), according to manufacturer instructions.

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**Figure 1.** Interaction network of differentially expressed genes. Data in the protein-protein interaction network were obtained via STRING and it was found that IL1R2 was associated with known GC-related genes. This indicated that IL1R2 was involved in development of GC. GC, gastric cancer.

The first chain of cDNA (TaKaRa Biotechnology, Dalian, China) was synthesized with reverse transcription using First Strand cDNA synthesis Kit. Expression of genes was detected by q-PCR using SYBR Premix Ex Taq kit (TaKaRa Biotechnology, Dalian, China) on an ABI Prism 7500 Fast Real-Time PCR system (Applied Biosystems), in accordance with the manufacturer's instructions. q-PCR primers of IL1R2: upstream primer: 5'-CTACGCACCACAGTCAAGGAAG-3' and downstream primer: 5'-CGTCTGTGCATC-CATATCCCC-3'. The primers of reference gene  $\beta$ -actin: upstream primer: 5'-GCCTCCCGCGC-GCGCACTAG-3' and downstream primer: 5'-AAAGGCAAACGCTGGCCCGG-3'. Expression of genes was calculated by  $2^{-\Delta\Delta Ct}$  method.

### Cell proliferation

Cell proliferation was detected by cell counting Kit-8 (CCK8) method. Cells were inoculated at  $3 \times 10^3$  cells/well in 96-well plates and cultured in DMEM medium containing 10% FBS for 4 days. During cell culturing, CCK8 solutions were added at different times (1 d, 2 d, 3 d, and 4 d), respectively. A total of 10  $\mu$ L CCK8 solutions were added to each plate and then cells were cultured at 37°C for 2 hours. Cell viability was

detected by absorbance that was measured at 450 nm.

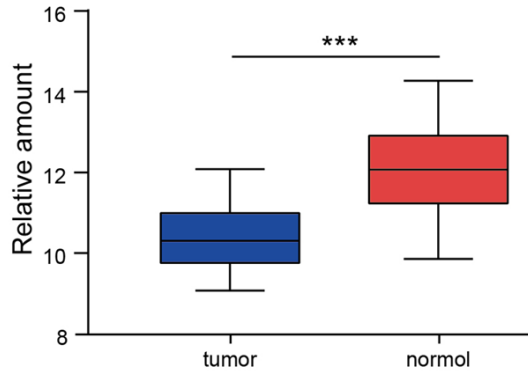
### Cell apoptosis

SGC7901 cells, transfected with IL1R2 overexpression plasmids or vectors, were inoculated in 6-well plates and grown to about 70% confluence. Apoptotic and necrotic cells were determined by flow cytometry (FACS Cantoll with HTS option, BD Biosciences) using TACS Annexin V-FITC Apoptosis Detection Kit (Trevigen, Gaithersburg, MD) [15]. A total of 10,000 cells were examined. Statistical analysis of the various dot plots was performed to determine the percentage of apoptotic and necrotic cells using CellQuest software (Diva 6.0, BD Biosciences).

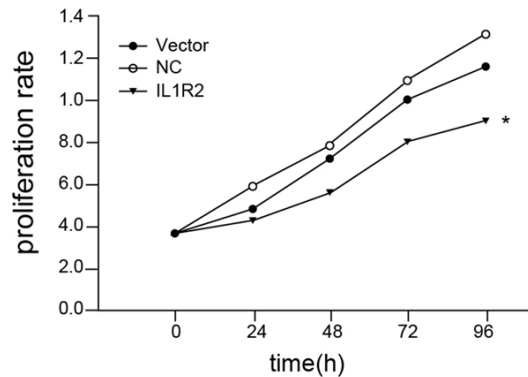
### Follow up

A total of 56 patients were followed up via telephone and outpatient services, with a follow up rate of 100% and 0 patients were lost to follow up. Patients were followed up at the first, third, sixth, and twelfth month after gastrectomy and then every 6 months for observation of their overall survival (OS) and disease-free survival

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**Figure 2.** IL1R2 expression in tissue samples. IL1R2 expression in 56 patient tissue samples was detected by quantitative polymerase chain reaction. It was found that IL1R2 mRNA expression in GC tissues was remarkably higher than that in adjacent tissues detected by t-test. \*\*\*,  $P < 0.001$ . Blue, GC tissues; red, adjacent tissues. GC, gastric cancer.



**Figure 3.** Cell proliferation detected by CCK-8 method. GC cells were inoculated in 96-well plates. The optical density at 450 nm was detected via ELIASA. \*,  $P < 0.05$ . ELISA, enzyme-linked immunosorbent assay; GC, gastric cancer.

(DFS). Follow up was ceased in December 2016.

### Statistical methods

Measurement data are expressed as mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ) and analyzed by t-test. Enumeration data were presented as case numbers and percentages and analyzed by Pearson's Chi-square test. IL1R2 expression, OS, and recurrence rates of patients were analyzed by Kaplan-Meier method and survival time difference was tested using log-rank method.  $P < 0.05$  was considered statistically significant.

## Results

### Analysis of differentially expressed genes

Microarray data were analyzed using R software and normalization between samples was performed using the "Normalize Between Arrays" function from the Limma package. Microarray data were analyzed by paired t-test and multiple inspections were performed. Genes from GSE54129 with adj  $P < 0.01$  and  $|\log \text{fold change (FC)}| > 3$  were identified as differentially expressed genes (DEGs) (Supplementary Table 1).

### Known GC-related genes

Advanced GC-related genes were downloaded from the PolySearch2.0 database for subsequent analysis. A total of 12 GC hot genes (Supplementary Table 2) were selected according to Z-score.

### Interaction network of DEGs

Cluster analysis was carried out using K-means clustering method to identify association between known GC-related genes and DEGs (Figure 1). It could be seen that IL1R2 interacted with known GC-related gene IL1B. Thus, IL1R2 was determined as pre-analysis gene after referring to relevant literatures and databases.

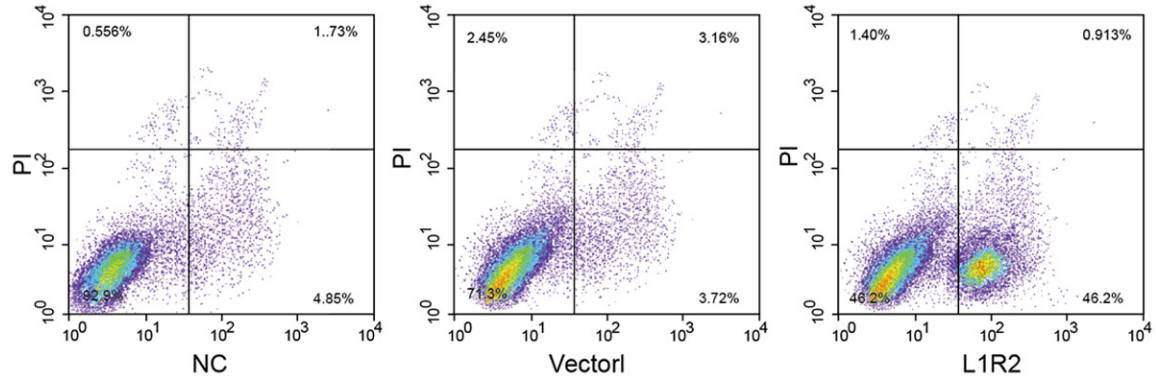
### IL1R2 expression in GC tissues and normal adjacent tissues

IL1R2 expression in GC tissues and normal adjacent tissues was detected. As shown in Figure 2, IL1R2 expression in GC tissues was significantly lower than in normal adjacent tissues and the difference was statistically significant ( $P < 0.05$ ). Patients were divided into high expression ( $n = 23$ ) and low IL1R2 expression groups ( $n = 33$ ), according to IL1R2 expression.

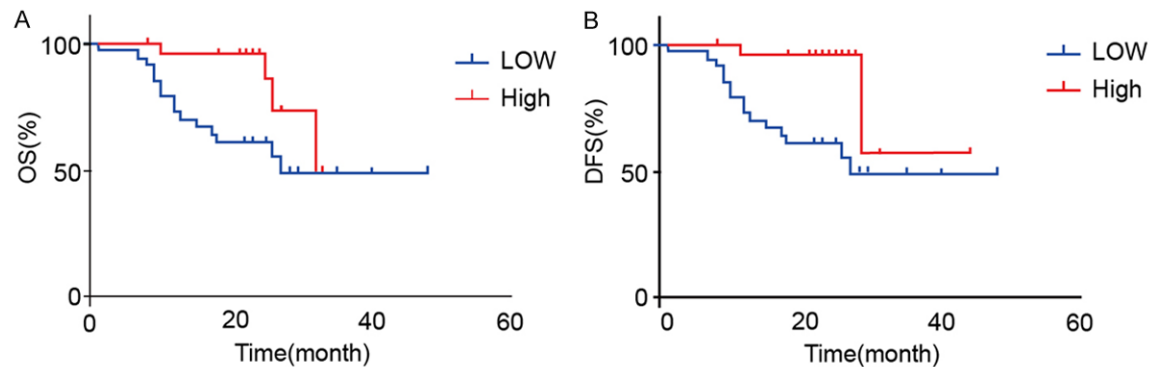
### Cell proliferation detected by CCK-8 method

Absorbance values of three groups of cells were detected by CCK-8 method. Compared with control and blank groups, cell proliferation in the experimental group decreased with time and the difference was statistically significant ( $P < 0.05$ ). Comparison between control and blank groups showed that there was no obvious

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**Figure 4.** Cell apoptosis detected by flow cytometry. IL1R2 overexpression plasmids and corresponding empty vectors were transfected into SGC7901 cells. Compared with negative control and empty vector groups, IL1R2 overexpression significantly promoted apoptosis of SGC7901 cells.



**Figure 5.** Relationship between IL1R2 expression and prognosis of GC patients. The relationship between patient prognosis and IL1R2 expression was detected by Kaplan-Meier. Blue, IL1R2 low expression; red, IL1R2 high expression; GC, gastric cancer.

change in cell growth with time and the difference was statistically significant ( $P > 0.05$ , **Figure 3**).

### Apoptosis rate of transfected cells detected by flow cytometry

After 48 hours, transfected cells were detected by flow cytometry. Our results showed that the apoptosis rate of experimental group was significantly higher than negative control and blank groups. The difference was statistically significant ( $P < 0.05$ ). There was no significant difference between the control and blank groups ( $P > 0.05$ , **Figure 4**).

### Relationship between IL1R2 expression and prognosis of GC patients

IL1R2 expression and OS and DFS of patients were analyzed by Kaplan-Meier. Results indi-

cated that both OS and DFS in low IL1R2 expression group were lower than in high IL1R2 expression group (**Figure 5**).

### Discussion

Over one million patients suffer from GC yearly and 70%-85% of patients have died within 5 years of being diagnosed [16, 17]. Bioinformatics integrates a variety of technologies such as informatics, computer science, and statistics to analyze enormous biodata and make speculations using existing data for subsequent experiments and clinical verifications, providing a basis for guiding occurrence, development, and treatment of diseases. In this study, GC data after gastrectomy were excavated based on GEO database from NCBI. A total of 123 DEGs were screened, among which 55 and 68 genes were downregulated and upregulated, respectively. Known GC genes were retrieved

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from PolySearch2.0 (<http://polysearch.cs.ualberta.ca/>), a web-based text mining bioinformatics database. IL1R2 was obtained using STRING in the gene-protein interaction network to construct a protein-protein interaction (PPI) network [18-21]. Thus, we speculated that IL1R2 was involved in development of GC after gastrectomy.

Studies on association between IL1R2 and cancer have shown that IL1R2 significantly changed in high-grade squamous intraepithelial lesions (HSIL) and invasive squamous cell carcinoma (ISCC), after analyzing genes in cervical cancer (CC). These results indicated that IL1R2 might be involved in development of CC [22]. Through studying the effect of abdominal infections on peripheral blood leukocyte expression after colorectal cancer surgery, it was found that IL1R2 expression was upregulated in patients with abdominal infection, suggesting that IL1R2 might promote growth of residual cancer cells after surgery and cause poor prognosis [23]. In colorectal cancer (CRC) cells, IL1R2 was highly expressed and correlated with IL-6. IL1R2 also promoted vascular regeneration [24]. IL1R2 overexpression was involved in tumor progression and resulted in decreased recurrence-free survival (RFS) in breast cancer [25]. After tamoxifen treatment, IL1R2 presented high expression in patients with breast cancer recurrence [26]. All of these results indicate that IL1R2 is highly expressed in most human malignant tumors. This study found that IL1R2 was associated with known GC gene IL1B via PPI analysis. IL1B is an effective inhibitor of gastric acid secretion [27] and a host gene of helicobacter pylori infection, while the host gene is involved in occurrence and development of GC. So, IL1B is related to susceptibility of GC [28]. It is speculated that IL1R2 plays a critical role in GC. Various experiments have shown that IL1R2 expression in GC tissues was lower than in adjacent tissues, after gastrectomy. It has been found that IL1R2 inhibits proliferation and promotes apoptosis of GC cells. All of these results suggest that IL1R2 could act as a tumor suppressor gene.

Analysis of patient prognosis has been the focus in clinical research. Expression of biomarkers and patient prognosis has been studied by most scholars. In our study, IL1R2 was retrieved by bioinformatics method and its mechanism in GC was investigated, combined

with experiments. Then, correlation between IL1R2 expression and prognosis of GC was analyzed based on clinical samples. OS and DFS of patients with different expression were depicted through Kaplan-Meier survival curve, showing that OS and DFS of patients with low expression were lower than that of patients with high expression. Relevant research has proven that molecular marker KLF7 is correlated with patient prognosis, using Kaplan-Meier survival curve to compare survival rates of patients [29]. In our study, we have reached a similar conclusion.

In conclusion, our study verifies the role of IL1R2 in GC and correlation between IL1R2 and patient prognosis. This was achieved through a combination of basic experiments and clinical samples, providing an experimental and theoretical basis for revealing the effect of IL1R2 on GC. Based on known GC genes, we found a new GC gene IL1R2 via PPI. We verified that IL1R2 is involved in development of GC and is related to patient prognosis.

### Acknowledgements

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### Disclosure of conflict of interest

None.

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