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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

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 bioinformation 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 December 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 ± 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_2 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'-GATATCGATGACTTGGGATAGGATTGAAA-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 Lipoectamine 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.

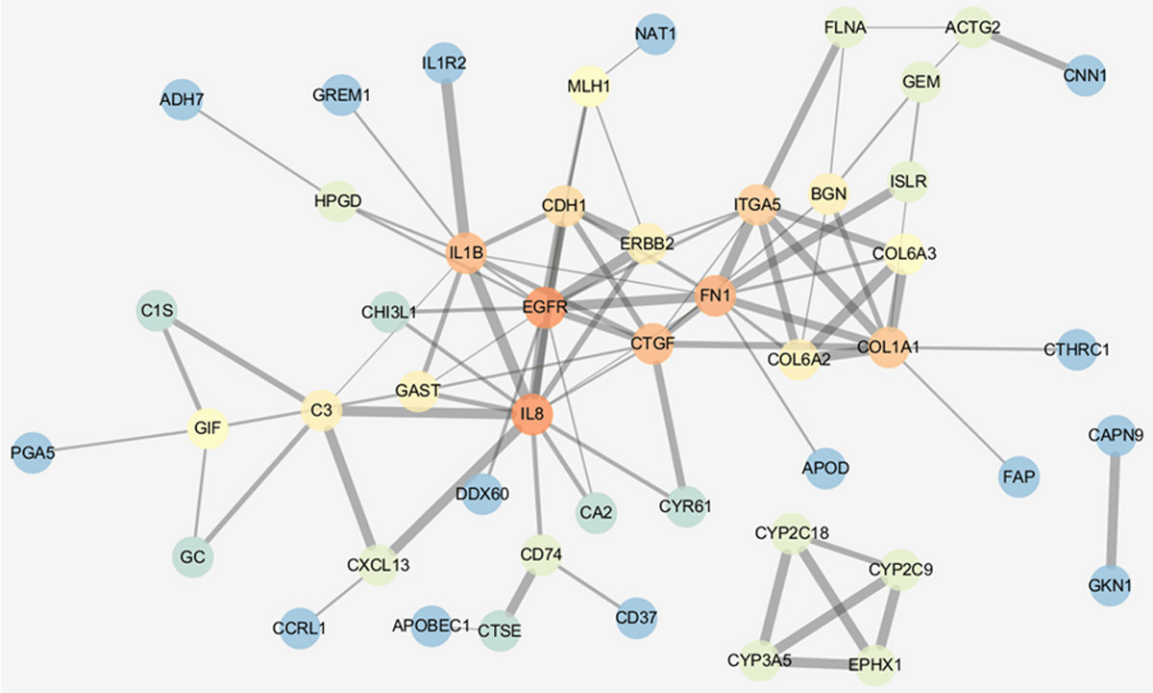

Figure 1. Interaction network of differentially expressed genes. Data in the protein-protein interaction network were obtained via STRING and it was found that IL1R2 was associated with known GC-related genes. This indicated that ILR2 was involved in development of GC. GC, gastric cancer.

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'-CGTCTGTGCATCCATATTCCC-3'. The primers of reference gene β-actin: upstream primer: 5'-GCCTCCCGCGCGCGCACTAG-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 × 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 uL 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 CantoII 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

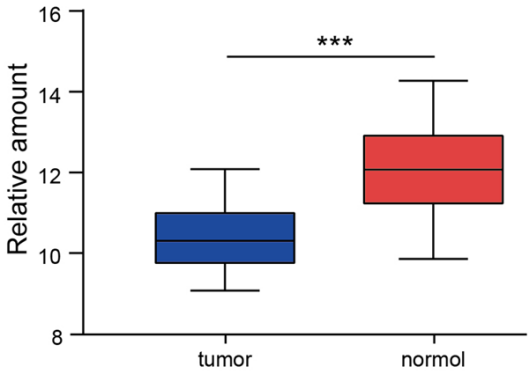

Figure 2. IL1R2 expression in tissue samples. IL1R2 expression in 56 patient tissue samples was detected by quantitative polymerase chain reaction. It was found that IL1R2 mRNA expression in GC tissues was remarkably higher than that in adjacent tissues detected by t-test. ***, $P < 0.001$. Blue, GC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

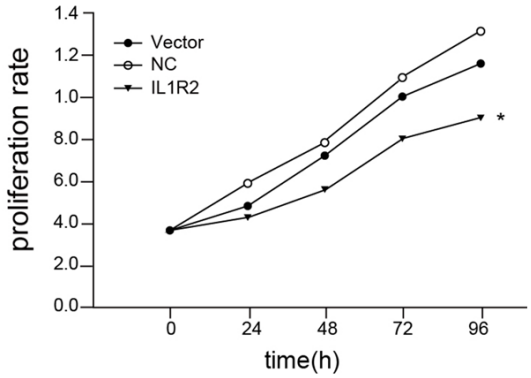

Figure 3. Cell proliferation detected by CCK-8 method. GC cells were inoculated in 96-well plates. The optical density at 450 nm was detected via ELIASA. *, $P < 0.05$. ELISA, enzyme-linked immunesorbent assay; GC, gastric cancer.

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

Statistical methods

Measurement data are expressed as mean ± 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 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

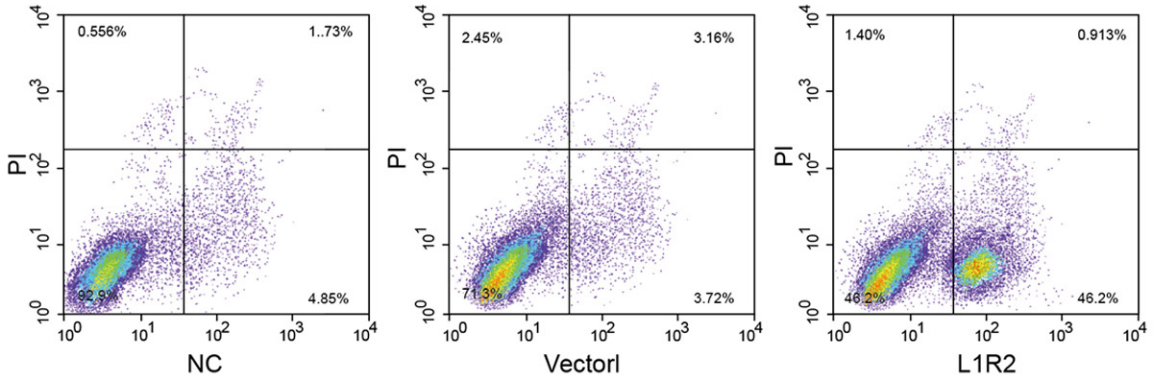

Figure 4. Cell apoptosis detected by flow cytometry. IL1R2 overexpression plasmids and corresponding empty vectors were transfected into SGC7901 cells. Compared with negative control and empty vector groups, IL1R2 overexpression significantly promoted apoptosis of SGC7901 cells.

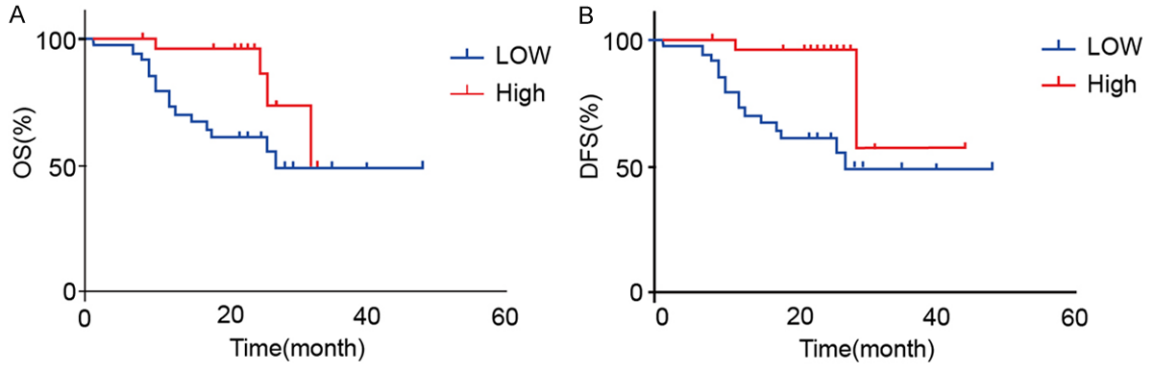

Figure 5. Relationship between IL1R2 expression and prognosis of GC patients. The relationship between patient prognosis and IL1R2 expression was detected by Kaplan-Meier. Blue, IL1R2 low expression; red, IL1R2 low expression; GC, gastric cancer.

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 indicated 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

from PolySearch2.0 (http://polysearch.cs.ualberta.ca/), a web-based text mining bioinformation 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.

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Disclosure of conflict of interest

None.

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References

[1] Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF, Allen C, Hansen G, Woodbrook R, Wolfe C, Hamadeh RR, Moore A, Werdecker A, Gessner BD, Te Ao B, McMahon B, Karimkhani C, Yu C, Cooke GS, Schwebel DC, Carpenter DO, Pereira DM, Nash D, Kazi DS, De Leo D, Plass D, Ukwaja KN, Thurston GD, Yun Jin K, Simard EP, Mills E, Park EK, Catalá-López F, deVeber G, Gotay C,

Khan G, Hosgood HD 3rd, Santos IS, Leasher JL, Singh J, Leigh J, Jonas JB, Sanabria J, Beardsley J, Jacobsen KH, Takahashi K, Franklin RC, Ronfani L, Montico M, Naldi L, Tonelli M, Geleijnse J, Petzold M, Shrime MG, Younis M, Yonemoto N, Breitborde N, Yip P, Pourmalek F, Lotufo PA, Esteghamati A, Hankey GJ, Ali R, Lunevicius R, Malekzadeh R, Dellavalle R, Weintraub R, Lucas R, Hay R, Rojas-Rueda D, Westerman R, Sepanlou SG, Nolte S, Patten S, Weichenthal S, Abera SF, Fereshtehnejad SM, Shiue I, Driscoll T, Vasankari T, Alsharif U, Rahimi-Movaghar V, Vlassov VV, Marcenes WS, Mekonnen W, Melaku YA, Yano Y, Artaman A, Campos I, MacLachlan J, Mueller U, Kim D, Trillini M, Eshrati B, Williams HC, Shibuya K, Dandona R, Murthy K, Cowie B, Amare AT, Antonio CA, Castañeda-Orjuela C, van Gool CH, Violante F, Oh IH, Deribe K, Soreide K, Knibbs L, Kereselidze M, Green M, Cardenas R, Roy N, Tillmann T, Li Y, Krueger H, Monasta L, Dey S, Sheikhbahaei S, Hafezi-Nejad N, Kumar GA, Sreeramareddy CT, Dandona L, Wang H, Vollset SE, Mokdad A, Salomon JA, Lozano R, Vos T, Forouzanfar M, Lopez A, Murray C, Naghavi M. The global burden of cancer 2013. JAMA Oncol 2015; 1: 505-27.

[2] Jung HY. [Current status of endoscopic resection of early gastric cancer in Korea]. Korean J Gastroenterol 2017; 70: 121-127.

[3] Kim SH, Hong SJ. [Treatment strategies after non-curative endoscopic resection of early gastric cancer]. Korean J Gastroenterol 2017; 70: 128-133.

[4] Chen W, Zheng R, Zeng H, Zhang S. The updated incidences and mortalities of major cancers in China, 2011. Chin J Cancer 2015; 34: 502-7.

[5] Jiang B, Chen JH, Yuan WZ, Ji JT, Liu ZY, Wu L, Tang Q, Shu XG. Prognostic and clinical value of Sirt1 expression in gastric cancer: a systematic meta-analysis. J Huazhong Univ Sci Technolog Med Sci 2016; 36: 278-84.

[6] Mizel SB. The interleukins. Faseb J 1989; 3: 2379-88.

[7] Sims JE, Dower SK. Interleukin-1 receptors. Eur Cytokine Netw 1994; 5: 539-46.

[8] Peters VA, Joesting JJ, Freund GG. IL-1 receptor 2 (IL-1R2) and its role in immune regulation. Brain Behav Immun 2013; 32: 1-8.

[9] Li H, Wang X, Fang Y, Huo Z, Lu X, Zhan X, Deng X, Peng C, Shen B. Integrated expression profiles analysis reveals novel predictive biomarker in pancreatic ductal adenocarcinoma. Oncotarget 2017; 8: 52571-52583.

[10] Yang T, Chen M, Yang X, Zhang X, Zhang Z, Sun Y, Xu B, Hua J, He Z, Song Z. Down-regulation of KLF5 in cancer-associated fibroblasts inhibit gastric cancer cells progression by CCL5/CCR5 axis. Cancer Biol Ther 2017; 18: 806-815.

[11] Zhao BW, Chen S, Li YF, Xiang J, Zhou ZW, Peng JS, Chen YB. Low expression of CDK10 correlates with adverse prognosis in gastric carcinoma. J Cancer 2017; 8: 2907-2914.

[12] Cai Y, Zheng M, Zhao Z, Huang H, Fu W, Xu X. Expression of Tspan-1 gene in patients with advanced gastric cancer. Oncol Lett 2017; 14: 2996-3000.

[13] Dong T, Peng Y, Zhong N, Liu F, Zhang H, Xu M, Liu R, Han M, Tian X, Jia J, Chang LK, Guo LH, Liu S. Perfluorodecanoic acid (PFDA) promotes gastric cell proliferation via sPLA2-IIA. Oncotarget 2017; 8: 50911-50920.

[14] Xu X, Wei Y, Wang S, Luo M, Zeng H. Serine-arginine protein kinase 1 (SRPK1) is elevated in gastric cancer and plays oncogenic functions. Oncotarget 2017; 8: 61944-61957.

[15] Pi J, He Y, Bortner C, Huang J, Liu J, Zhou T, Qu W, North SL, Kasprzak KS, Diwan BA, Chignell CF, Waalkes MP. Low level, long-term inorganic arsenite exposure causes generalized resistance to apoptosis in cultured human keratinocytes: potential role in skin co-carcinogenesis. Int J Cancer 2005; 116: 20-6.

[16] Oliveira C, Pinheiro H, Figueiredo J, Seruca R, Carneiro F. Familial gastric cancer: genetic susceptibility, pathology, and implications for management. Lancet Oncol 2015; 16: e60-70.

[17] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136: E359-86.

[18] Guin D, Mishra MK, Talwar P, Rawat C, Kushwaha SS, Kukreti S, Kukreti R. A systematic review and integrative approach to decode the common molecular link between levodopa response and Parkinson's disease. BMC Med Genomics 2017; 10: 56.

[19] Wu X, Miao J, Jiang J, Liu F. Analysis of methylation profiling data of hyperplasia and primary and metastatic endometrial cancers. Eur J Obstet Gynecol Reprod Biol 2017; 217: 161-166.

[20] Li L, Lei Q, Zhang S, Kong L, Qin B. Screening and identification of key biomarkers in hepatocellular carcinoma: evidence from bioinformatic analysis. Oncol Rep 2017; 38: 2607-2618.

[21] Zhou Z, Zhang J, Li X, Xia C, Han Y, Chen H. Protein microarray analysis identifies key cytokines associated with malignant middle cerebral artery infarction. Brain Behav 2017; 7: e00746.

[22] Niu G, Wang D, Pei Y, Sun L. Systematic identification of key genes and pathways in the development of invasive cervical cancer. Gene 2017; 618: 28-41.

[23] Alonso S, Mayol X, Nonell L, Salvans S, Pascual M, Pera M; Colorectal Cancer Research Group (Hospital del Mar Medical Research Institute). Peripheral blood leucocytes show differential expression of tumour progression-related genes in colorectal cancer patients who have a postoperative intra-abdominal infection: a prospective matched cohort study. Colorectal Dis 2017; 19: O115-O125.

[24] Mar AC, Chu CH, Lee HJ, Chien CW, Cheng JJ, Yang SH, Jiang JK, Lee TC. Interleukin-1 receptor type 2 acts with c-Fos to enhance the expression of interleukin-6 and vascular endothelial growth factor a in colon cancer cells and induce angiogenesis. J Biol Chem 2015; 290: 22212-24.

[25] Aceto N, Duss S, MacDonald G, Meyer DS, Roloff TC, Hynes NE, Bentires-Alj M. Co-expression of HER2 and HER3 receptor tyrosine kinases enhances invasion of breast cells via stimulation of interleukin-8 autocrine secretion. Breast Cancer Res 2012; 14: R131.

[26] Ma XJ, Wang Z, Ryan PD, Isakoff SJ, Barmettler A, Fuller A, Muir B, Mohapatra G, Salunga R, Tuggle JT, Tran Y, Tran D, Tassin A, Amon P, Wang W, Wang W, Enright E, Stecker K, Estepa-Sabal E, Smith B, Younger J, Balis U, Michaelson J, Bhan A, Habin K, Baer TM, Brugge J, Haber DA, Erlander MG, Sgroi DC. A two-gene expression ratio predicts clinical outcome in breast cancer patients treated with tamoxifen. Cancer Cell 2004; 5: 607-16.

[27] Ishiguro T, Takeda J, Fang X, Bronson H, Olson DM. Interleukin (IL)-1 in rat parturition: IL-1 receptors 1 and 2 and accessory proteins abundance in pregnant rat uterus at term - regulation by progesterone. Physiol Rep 2016; 4.

[28] He C, Tu H, Sun L, Xu Q, Gong Y, Jing J, Dong N, Yuan Y. SNP interactions of Helicobacter pylori-related host genes PGC, PTPN11, IL1B, and TLR4 in susceptibility to gastric carcinogenesis. Oncotarget 2015; 6: 19017-26.

[29] Jiang Z, Yu T, Fan Z, Yang H, Lin X. Kruppel-like factor 7 is a marker of aggressive gastric cancer and poor prognosis. Cell Physiol Biochem 2017; 43: 1090-1099.