World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/ *World J Gastroenterol* 2017 February 21; 23(7): 1189-1202

DOI: 10.3748/wjg.v23.i7.1189 ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Basic Study

Dysregulation of mRNA profile in cisplatin-resistant gastric cancer cell line SGC7901

Xiao-Que Xie, Qi-Hong Zhao, Hua Wang, Kang-Sheng Gu

Xiao-Que Xie, Hua Wang, Kang-Sheng Gu, Department of Oncology, the First Affiliated Hospital of Anhui Medical University, Hefei 230032, Anhui Province, China

Qi-Hong Zhao, Department of Food and Nutrition Hygiene, School of Public Health, Anhui Medical University, Hefei 230032, Anhui Province, China

Author contributions: Xie XQ performed experiments, prepared the manuscript and analyzed data; Zhao QH performed select experiments; Zhao QH and Wang H read the manuscript and gave important intellectual suggestion; Wang H and Gu KS designed and supervised the project.

Supported by Projects of Foreign Science and Technology Cooperation of Anhui Province, No. 1604b0602027; New Century Excellent Talents in University, Ministry of Education of China, No. NCET-13-0644; and Wanjiang Scholars Program of Anhui Province of China.

Institutional review board statement: The study was reviewed and approved by the First Affiliated Hospital of Anhui Medical University Institutional Review Board.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors declared no conflict of interest.

Data sharing statement: Technical appendix and dataset available from the corresponding author at 13805692145@163.com. Participants gave informed consent for data sharing.

Manuscript source: Unsolicited manuscript

Correspondence to: Kang-Sheng Gu, PhD, Professor, Department of Oncology, the First Affiliated Hospital of Anhui Medical University, 218 Jixi Road, Hefei 230032, Anhui Province, China. 13805692145@163.com
Telephone: +86-551-62923504

Received: October 9, 2016
Peer-review started: October 10, 2016
First decision: November 9, 2016
Revised: November 24, 2016
Accepted: December 16, 2016
Article in press: December 19, 2016
Published online: February 21, 2017

Abstract

AIM

To explore novel therapeutic target of cisplatin resistance in human gastric cancer.

METHODS

The sensitivity of SGC7901 cells and cisplatin-resistant SGC7901 cells (SGC7901/DDP) for cisplatin were detected by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) assay. High-quality total RNA which isolated from SGC7901/DDP cells and SGC7901 cells were used for mRNA microarray analysis. Results were analyzed bioinformatically to predict their roles in the development of cisplatin resistance and the expression of 13 dysregulated mRNAs we selected were validated by quantitative real-time polymerase chain reaction (qRT-PCR).

RESULTS

SGC7901/DDP cells highly resistant to cisplatin demonstrated by MTT assay. A total of 1308 mRNAs (578 upregulated and 730 downregulated) were

differentially expressed (fold change ⩾ 2 and *P*-value < 0.05) in the SGC7901/DDP cells compared with SGC7901 cells. The expression of mRNAs detected by qRT-PCR were consistent with the microarray results. Gene Ontology, Kyoto Encyclopedia of Genes and Genomes pathway and protein-protein interaction analysis demonstrated that the differentially expressed mRNAs were enriched in *PI3K-Akt*, *Notch*, *MAPK*, *ErbB*, *Jak-STAT*, *NF-kappaB* signaling pathways which may be involved in cisplatin resistance. Several genes such as *PDE3B*, *VEGFC*, *IGFBP3*, *TLR4*, *HIPK2* and *EGF* may associated with drug resistance of gastric cancer cells to cisplatin.

CONCLUSION

Exploration of those altered mRNAs may provide more promising strategy in diagnosis and therapy for gastric cancer with cisplatin resistance.

Key words: Gastric cancer; Dysregulate; Cisplatin resistance; Microarray; Biology

Core tip: We tested the sensitivity of human gastric cancer cells SGC7901/DDP and SGC7901 for cisplatin and compared their mRNA expression profile using a human mRNA microarray, and then performed bioinformatics analysis to depict comprehensively the properties of the differentially expressed mRNAs. Results demonstrated that the dysregulated mRNA were enriched in functions and pathways that may be involved in cisplatin resistance. Exploration of the dysregulated genes could suggest a promising strategy in diagnosis and therapy of gastric cancer with cisplatin resistance.

Xie XQ, Zhao QH, Wang H, Gu KS. Dysregulation of mRNA profile in cisplatin-resistant gastric cancer cell line SGC7901. *World J Gastroenterol* 2017; 23(7): 1189-1202 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i7/1189.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i7.1189

INTRODUCTION

Gastric cancer is the fourth most common cancer and the second leading cause of cancer death globally[1], and more than two thirds of patients when diagnosed with unresectable disease[2]. The 5-year overall survival rate of patients with advanced gastric cancer approximately 25%[3]. Currently, platinum-based chemotherapy regimen is the standout chemotherapy frequently used for advanced gastric cancer[4,5], and median overall survival and progression free survival was significantly longer in cisplatin-containing combination therapy compared to non-cisplatin containing regimens[6,7]. However, cisplatin-based chemotherapeutic agents are often limited in chemotherapy due to drug resistance[8,9].

Cisplatin resistance of gastric cancer is multi-factorial, accumulating evidence have suggested that the aberrant expression of proteins which associated with decreased cellular accumulation, increased DNA repair capacity, increased drug inactivation[10] play important role in the acquisition of cisplatin resistance. Previous researches have shown that abnormal expression of copper transporter 1 (CTR1) and MRP2 lead to cisplatin resistance by reducing the concentration of cisplatin in cells[11-13]. Moreover, the upregulation of excision repair cross complementing 1 (*ERCC1*)[14], X-ray repair cross complementing 1 (*XRCC1*)[15] and breast cancer 1 (*BRCA1*)[16] have shown to be involved in cisplatin resistance by removal of Pt-DNA adducts[17,18]. Other studies have shown that downregulation of the human epidermal growth factor receptor II (ErbB2) can significantly enhanced the apoptosis-inducing effects of cisplatin in gastric cancer[19,20].

The mechanisms of cisplatin resistance are quite complex and have not been fully revealed till now, so investigation of the molecular mechanisms and biomarkers is urgently needed. This study aims to analyze mRNA expression profiles in SGC7901/DDP cells to explore more chemotherapeutic molecular targets and to guide appropriate chemotherapy for gastric cancer with cisplatin resistance.

MATERIALS AND METHODS

Cell lines and culture

The human cisplatin-resistant gastric cancer cell line SGC7901/DDP and its parental cells SGC7901 were purchased from KeyGEN Biotechnology Company (Nanjing, Jiangsu, China). Cells were cultured in RPMI-1640 medium (Gibco, Grand Island, NY, United States) containing 10% fetal calf serum (Gibco, NY, United States) supplemented with 100 U/mL penicillin and 100 μg/mL streptomycin. Cells were cultured in a humidified atmosphere with 5% CO_2 at 37 ℃. Cisplatin (Sigma, CA, United States) with final concentration of 800 ng/mL was added to the culture media for SGC7901/DDP cells to maintain the cisplatin-resistant phenotype.

MTT method assay for SGC7901/DDP and SGC7901 cells viability

SGC7901/DDP and SGC7901 cells were suspended at a density of 1×10^5 cells/mL and planted into 96-well culture plate. After 24 hours, the cells were treated with freshly prepared DDP. The final concentrations were 133.34 μmol /L, 66.67 μmol/L, 6.67 μmol/L, 0.67 μmol/L and 0.067 μmol/L, because the human peak plasma concentration for DDP has been reported

as 6.67 μmol/L[21]. Cell viability was examined after 48 h and was determined by adding 20 μL MTT (5 mg/mL) to each well and incubated for a further 4 h. The resulting formazan crystal was dissolved by addition of 150 μL dimethyl sulfoxide (DMSO) (sigma, Germany) each well, and then plates were shaken for 10 minutes. The absorbance at 490 nm was measured by spectrophotometer (ELx 800; BioTek; Winooski, VT, United States). The inhibition of growth (IC50) for DDP was calculated by the cells relative viability. Each experiment was performed in triplicate.

Total RNA extraction and mRNA microarray

Cells were harvested when they had grown to 80%-90% confluency and were still in logarithmic phase. Total RNA was extracted from the three matched pairs of SGC7901/DDP and SGC7901 cells using TRIzol reagent (Invitrogen, Carlsbad, CA, United States) according to the manufacturer's instructions. The quality of total RNA was measured by NanoDrop ND-2000 spectrophotometer (Thermo Scientific, Waltham, MA, United States). Total RNA from three paired samples were amplified and transcribed into fluorescent cDNA, and then the fluorescent labeled samples were hybridized to the Agilent LncRNA-mRNA Human Gene Expression Microarray V4.0 (Capital Bio Corp, Beijing, China) which contains 25069 human mRNA according to the manufacturer's recommendations. The microarray was scanned by an Agilent Microarray Scanner. Image processing was conducted using Agilent Feature Extraction software and raw microarray signals normalized using Agilent Gene-Spring software. The normalized mRNA expression profiles data output was received in Excel spreadsheets. The two group of samples data were analyzed by *t*-test to get the *P*-values. FC values representing the differently expressed mRNAs between SGC7901/DDP and their parental cells. Cluster 3.0 software was performed to show differential expression patterns of mRNAs.

Bioinformatics analysis

Bioinformatics analysis were generated using KOBAS software and STRING 9.1 software. KOBAS software was used to analyze Ontology, Disease and pathways of the dysregulated mRNAs. KOBAS associated with 1 ontology database (Gene Ontology), 5 disease databases (OMIM, KEGG DISEASE, PID Reactome, FunDO, GAD, NHGRI) and 7 pathway databases (KEGG PATHWAY, PID Curated, PID BioCarta, BioCyc, eactome, Panther). The entire analysis process includes two steps: first, bring the input gene ID map to the gene in the databases, and then annotate pathways, disease and function of these genes involved in. Second step, compare the first step results with background (usually the entire genome of the gene, or the entire probe on the chip), and unearth statistically significant enrichment pathways, disease or function. Fisher's exact test and χ^2 test were used as statistical tests and the FDR was performed to correct the *P*-value[22]. Additionally, we used STRING 9.1 software to decipher the protein-protein interaction (PPI) network of the differentially expressed proteins. The PPI network may help in understanding the molecular mechanism of cisplatin resistance. All mRNA microarray data were given by Capital Bio Corp.

Quantitative real-time PCR validation of microarray results

To validate the reliability of microarray analysis, we performed quantitative real-time PCR (qRT-PCR). The reverse transcription production cDNA was synthesized using oligo-dT primers and Superscript II reverse transcriptase. PCR was performed with SYBR® Premix Ex Taq™ (TaKaRa Bio; Japan) by a Light Cycler PCR system (Agilent Technologies, Palo Alto, CA, United States) according to the manufacturer's instructions. After amplification, melting curves were analyzed. Beta-actin snRNA used as endogenous control, each sample was done in triplicate. The relative expression levels of target mRNAs were calculated using the $2^{-\Delta\Delta Ct}$ method (where ΔΔCt is the difference in threshold cycles for the ΔCt of SGC7901/DDP sample and SGC7901 sample, and ΔCt is the difference between the target gene and endogenous control beta-actin). Sequences of primers for qRT-PCR are provided in supporting Table 1.

Statistical analysis

MTT test and qRT-PCR statistical analysis was performed using GraphPad Prism software (v. 5.0a; GraphPad Software, La Jolla, CA, United States). We used one-way analysis of variance (ANOVA) followed by Student's *t*-test to assess the statistical significance of differences between different cell groups. The threshold for statistical significance was *P*-values < 0.05. Fold changes of mRNAs validated by qRT-PCR in SGC7901/DDP cells compared with SGC7901 cells are shown as mean ± SD.

RESULTS

Sensitivity of SGC7901/DDP and SGC7901 cells to DDP

To determine the chemotherapy sensitivity of SGC7901/DDP and SGC7901 cell line to cisplatin, varying concentrations of cisplatin were added into the 96-well plates and incubated for 48 h. From these data, half maximal inhibitory concentration (IC50) cisplatin dose was calculated. IC50 cisplatin doses for SGC7901/DDP and SGC7901 (after 48 h in DDP-containing media) were 43.47 ± 0.21 μmol/L and 1.24 ± 0.02 μmol/L, respectively, and the resistance index for SGC7901/DDP cell lines was 35.12, confirming that these cells are refractory to cisplatin. Cell viability was checked by MTT assay (Figure 1).

Table 1 Primer of quantitative real-time polymerase chain reaction

ID	Primer	Sequence (5'to3')	Base (bp)	Tm (℃)	GC
HIPK2	Forward	CCCCGTGTACGAAGGTATGG	20	59.90	60%
	Reverse	GGGATGTTCTTGCTCTGGCT	20	60.03	55%
PDE3B	Forward	TGAGAGTTATGGCTGCCTGT	20	58.72	50%
	Reverse	CTGAGGGGCATTTGTAGCCA	20	60.30	55%
FGF2	Forward	TCCACCTATAATTGGTCAAAGTGGT	25	59.99	40%
	Reverse	CATCAGTTACCAGCTCCCCC	20	59.82	60%
TWIST1	Forward	ATTCAAAGAAACAGGGCGTGG	21	59.39	47.6%
	Reverse	CAGAGGTGTGAGGATGGTGC	20	60.39	40%
ZEB2	Forward	GCCTCTGTAGATGGTCCAGTGA	22	61.21	54.6%
	Reverse	ATCGCGTTCCTCCAGTTTTCT	21	60.00	47.6%
VEGFC	Forward	CCCGCCTCTCCAAAAAGCTA	20	60.04	55%
	Reverse	CGGGTGTCAGGTAAAAGCCT	20	59.96	55%
SPHK1	Forward	GCTGCGAAGTTGAGCGAAAA	20	60.04	50%
	Reverse	CGTTCCCTACAGTGGCCTG	19	60.08	63.2%
BAX	Forward	GCCCTTTTGCTTCAGGGTTT	20	59.24	50%
	Reverse	CATCCTCTGCAGCTCCATGT	20	59.82	55%
PTEN	Forward	CAGGATACGCGCTCGGC	17	60.73	70.6%
	Reverse	ACAGCGGCTCAACTCTCAAA	20	57.89	50%
HTRA1	Forward	AGCCAAAGAGCTGAAGGACC	20	59.96	55%
	Reverse	GACATCATTGGCGGAGACCA	20	60.11	55%
CCL5	Forward	TGCTGCTTTGCCTACATTGC	20	59.76	50%
	Reverse	CTTGTTCAGCCGGGAGTCAT	20	60.04	55%
TGM2	Forward	CCTCTGTCTCTCCGGGAACC	20	61.32	65%
	Reverse	TGGCAACCAGGGGTCCTAT	19	60.23	57.9%
TLR4	Forward	CTCGGTCAGACGGTGATAGC	20	59.97	60%
	Reverse	TTTAGGGCCAAGTCTCCACG	20	59.68	55%
ACTB	Forward	CTCACCATGGATGATGATATCGC	23	59.13	47.8%
	Reverse	AGGAATCCTTCTGACCCATGC	21	59.79	52.4%

GC: Gastric cancer.

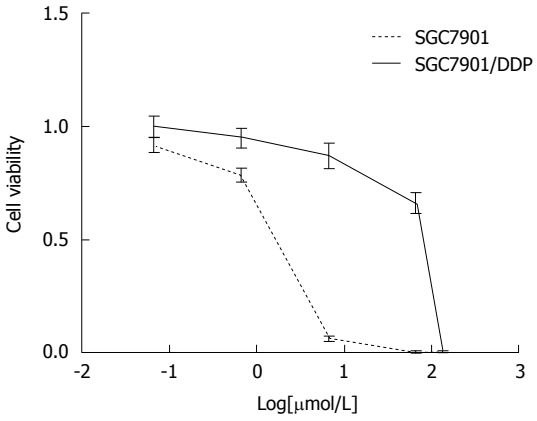

Figure 1 Cell viability treated with different concentrations of cisplatin for 48 h. MTT assay for SGC7901 cells and SGC7901/DDP cells treated with cisplatin (133.34, 66.67, 6.67, 0.67 and 0.067 μmol/L, respectively).

Expression profile of mRNAs in SGC7901/DDP cells

To show mRNA expression profile in cisplatin-resistant SGC7901/DDP cells, we used a stringency cutoff to identify significantly differently mRNAs ($P < 0.05$, FC $\geqslant 2$) and two-dimensional hierarchical clustering 3.0 to represent expression profiles between samples (Figure 2). The results indicated that 1308 mRNAs were significantly differentially expressed in SGC7901/DDP cells compared with SGC7901 cells. Among these transcripts, 578 mRNAs were upregulated, and 730 mRNAs were downregulated.

Validation of microarray results by qRT-PCR of 13 mRNAs

First, we concentrated on validating the microarray results. From the abnormally expressed ($P < 0.05$) mRNAs obtained from the microarray analyses, we selected 8 upregulated mRNAs (*HIPK2, PDE3B, FGF2, TWIST1, ZEB2, VEGFC, SPHK1, BAX*) and 5 downregulated (*PTEN, HTRA1, CCL5, TGM2, TLR4*) mRNAs for qRT-PCR validation. The relative fold-changes (SGC7901/DDP *vs* SGC7901) detected by qRT-PCR were consistent with the microarray results (Figure 3), indicating the dependability of our microarray platform.

Statistical analysis

To depict comprehensively the properties of the differentially expressed mRNA in SGC7901/DDP cells, GO annotation and enrichment analysis was performed to evaluate which cellular components, molecular functions and biological processes may be are affected by this dysregulation. The GO enrichment analysis showed that the differentially expressed genes were involved in a variety of functions, including locomotion, chemotaxis, cell adhesion, regulation of cell migration, extracellular matrix disassembly, response to xenobiotic chemotaxis, localization of cell adhesion and blood vessel morphogenesis (Figure 4A).

Additionally, 59 human diseases were significant enriched ($P < 0.05$) in five human disease databases

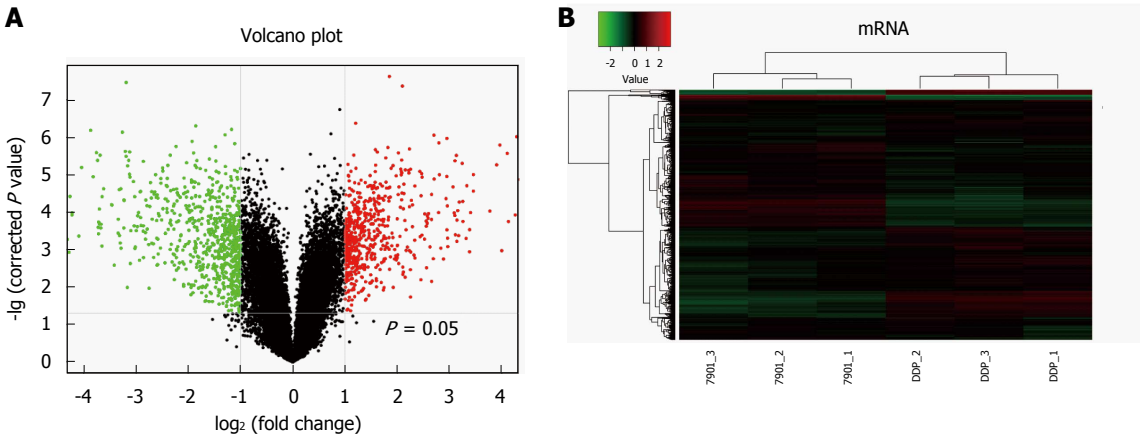

Figure 2 mRNA expression levels from microarray. A: The volcano plot image showed the mRNA expression levels of microarray in SGC7901/DDP cells compared with SGC7901 cells. Black dots: equally expressed mRNAs between SGC7901/DDP cells and SGC7901 cells (FC ⩽ 2); red dots: mRNAs were over-expressed in SGC7901/DDP cells compared with SGC7901 cells (FC ⩾ 2); green dots: mRNAs in SGC7901/DDP cells were down-expressed compared to SGC7901 cells (*P*-values < 0.05, FC ⩾ 2). Fold changes of these mRNAs in SGC7901/DDP cells compared with SGC7901 cells are shown as mean ± SD; B: Two-dimensional hierarchical clustering image of the 1308 dysregulated mRNAs in the SGC7901/DDP cells compared with the SGC7901 cells, each row represents an mRNA, each column represents a sample. 7901-1, 7901-2 and 7901-3 represent the three samples of SGC7901 cells, DDP-1, DDP-2 and DDP-3 represent the three samples of SGC7901/DDP cells. Red: Higher expression levels; green: Lower expression levels.

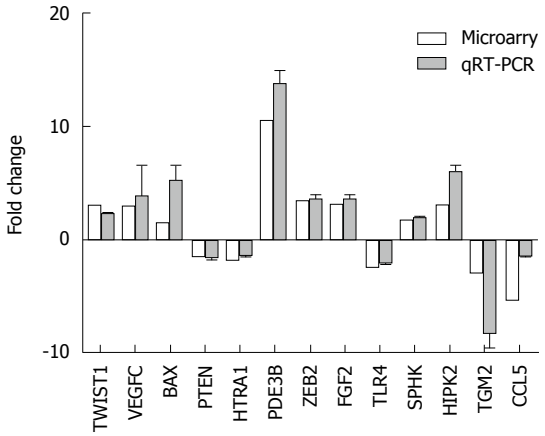

Figure 3 Quantitative real-time polymerase chain reaction validation of the microarray results of the 13 mRNAs. Relative fold changes in expression between SGC7901/DDP cells and SGC7901 cells were in agreement with microarray.

(KEGG DISEASE, FunDO, GAD, NHGRI GWAS Catalog and OMIM) (Figure 4B, Table 2). Furthermore, it is worth noting that in KEGG disease database, gastric cancer is the most highly enriched disease, and the input genes include *DCC, CD44, CDH1, VEGFC, EGF, TGFA.*

To determine which pathway might be involved in drug resistance formation, KEGG pathway analysis was used to authenticate pathways and understand biological functions of significantly differentially expressed genes. The result indicated that the differentially expressed mRNAs were enriched for 233 pathways, including the *Rap1* signaling pathway, *PI3K-Akt* signaling pathway, *ECM*-receptor interaction, *TNF* signaling pathway, and pathways in cancer, among others (Figure 5, Table 3). Cluster 3.0 software were performed the heat-map.This finding identified many candidate pathways and input genes that may play an important role in resistance mechanism.

Interaction network analysis

The STRING 9.1 software (Search Tool for the Retrieval of Interacting Genes) was used to perceive functional relations and generate networks of differential expression of proteins (Figure 6). For all of the 1002 differentially expressed proteins, we extracted a network containing 443 upregulated and 559 downregulated proteins which functionally associated with each other. We found that interacting proteins which participate in angiogenesis, toll-like receptor signaling pathway and cell adhesion had a high level of co-expression.

DISCUSSION

Cisplatin is widely used against a variety of solid neoplasms, including testicular, ovarian, colorectal, bladder, head and neck cancers and gastric cancer[23]. However, the repeated clinical expose to cisplatin often results in the tumor cells evading the apoptosis program initiated by cisplatin. Therefore, there is a need to explore the molecular mechanisms of cisplatin resistance, in order to overcome drug resistance in tumor therapy. Recently, several studies have indicated that many proteins are involved in the recognition of Pt-DNA adducts and cisplatin-induced apoptosis program[24,25]. In this study, we used microarray, GO, KEGG pathway and protein-protein interaction (PPI) analysis to explore the roles of differentially expressed mRNAs in cisplatin resistance and to support other studies.

Many genes which shown differentially expression in the microarray analysis have been demonstrated to be associated with cisplatin resistance in human cancer

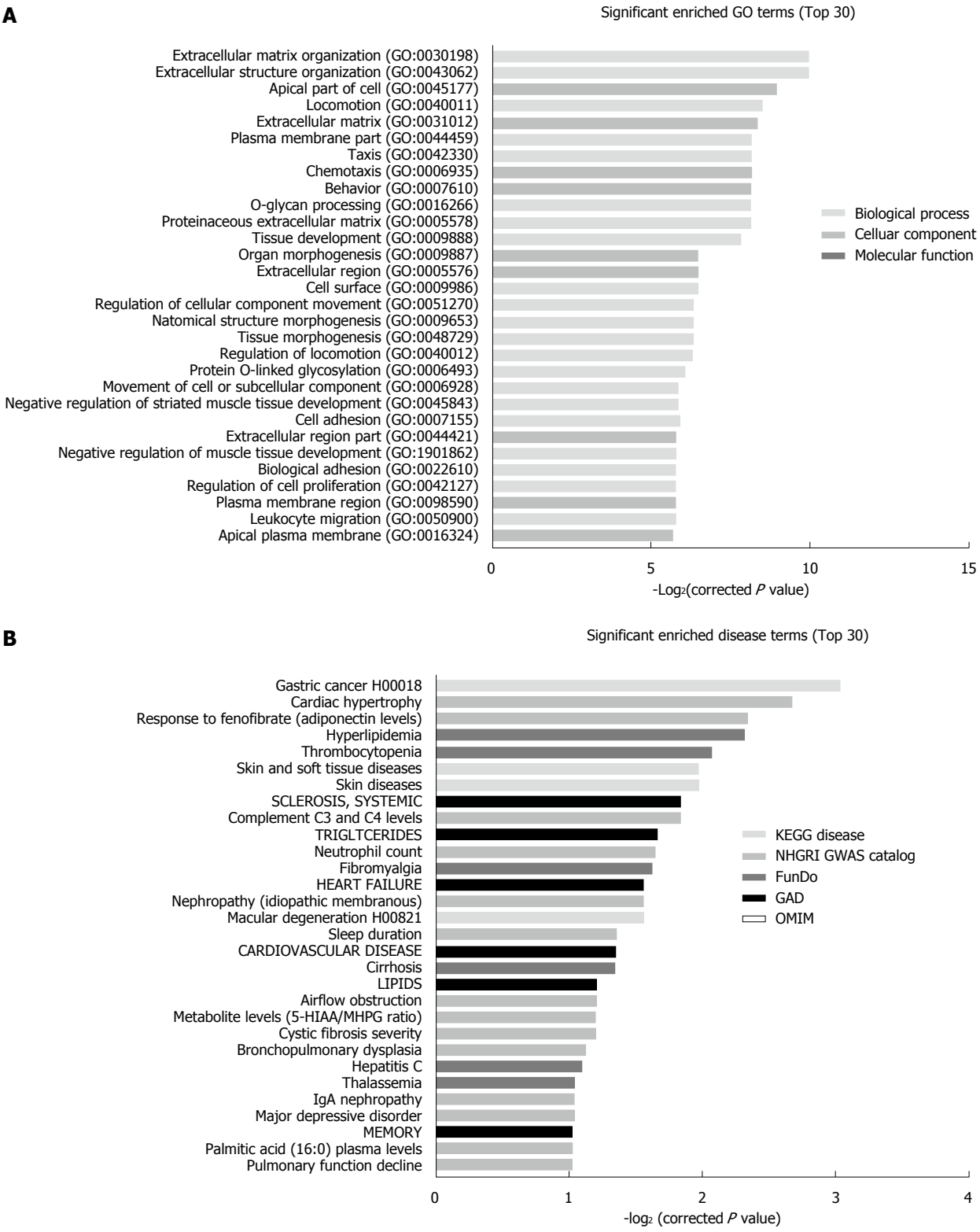

Figure 4 Bioinformatic analysis of differentially expressed mRNAs. Gene ontology analysis of mRNAs dysregulated in SGC7901/DDP cells compared with SGC7901 cells. A: Top 30 molecular functions of the dysregulated mRNAs may associated with. Gene ontology analysis include biological processes, cellular components and molecular function; B: Gene ontology enriched diseases. Top 30 diseases annotations of dysregulated mRNAs may involve in. The disease enrich system include 5 disease databases: OMIM, KEGG disease, FunDO, GAD and NHGRI GWAS Catalog.

(Table 4), such as *PDE3B*, which was substantially upregulated (*P* value = 0.00029, Fold Chang (FC) = 10.45) in SGC7901/DDP cells. Treatment with a combination of a *PDE3B* inhibitor and DDP can significantly increase the number of apoptotic and cell growth-suppressive cancer cells in cisplatin resistant

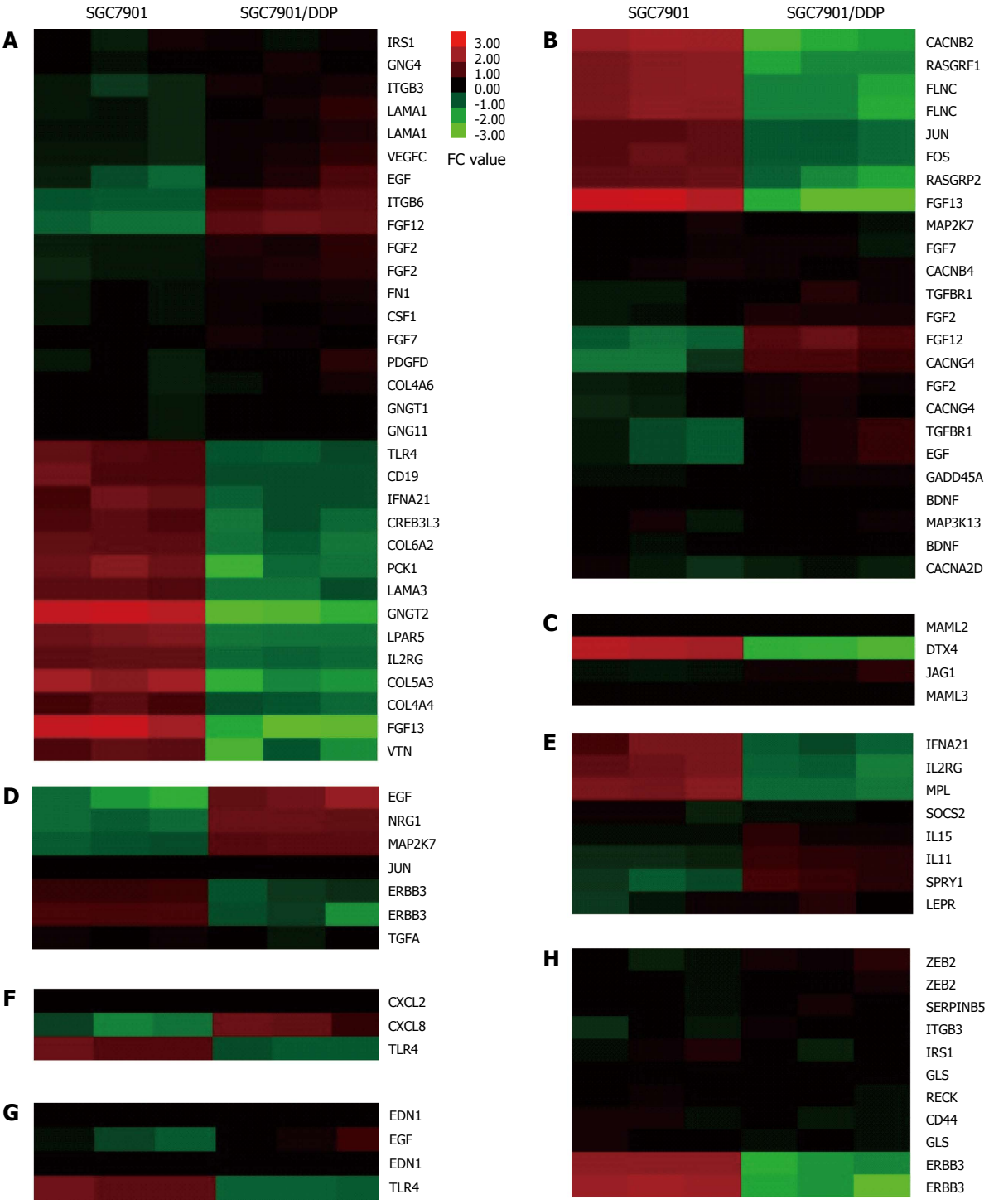

Figure 5 Heat-map of gene ontology enriched cisplatin resistance pathways and input mRNAs which significantly altered in SGC7901/DDP cells compared with SGC7901 cells. A: PI3K-Akt signaling pathway and input genes; B: MAPK signaling pathway and input genes; C: Notch signaling pathway and input genes; D: ErbB signaling pathway and input genes; E: Jak-STAT signaling pathway and input genes; F: NF-kappa B signaling pathway and input genes; G: HIF-1 signaling pathway and input genes; H: MicroRNAs in cancer and input genes. Each row represents an mRNA, and each column represents a sample. The intensity of the color indicates the relative levels of mRNAs. Red: Higher expression levels; green: Lower expression levels. The name of the input mRNAs which significantly altered ($P < 0.05$, FC $\geqslant 2$) is present at the right of the figure.

squamous cell carcinoma (SCC) and Hela cells[26]. Research shows that *VEGFC*, which is upregulated in our data (*P* value = 0.00013 FC = 2.93), enhanced cell invasion and cisplatin resistance in gastric cancer[27]. In non-small cell lung cancer, loss of *IGFBP-3* expression may activate the *PI3K/AKT* pathway and induce resistance to cisplatin[28]. In support of this association, our results showed that this mRNA is downregulated (*P* = 0.00007, FC = 2.93) in SGC7901/DDP cells.

GO enrichment analysis exhibits many functions which the differently expressed mRNAs are involved in, including locomotion, chemotaxis, cell adhesion,

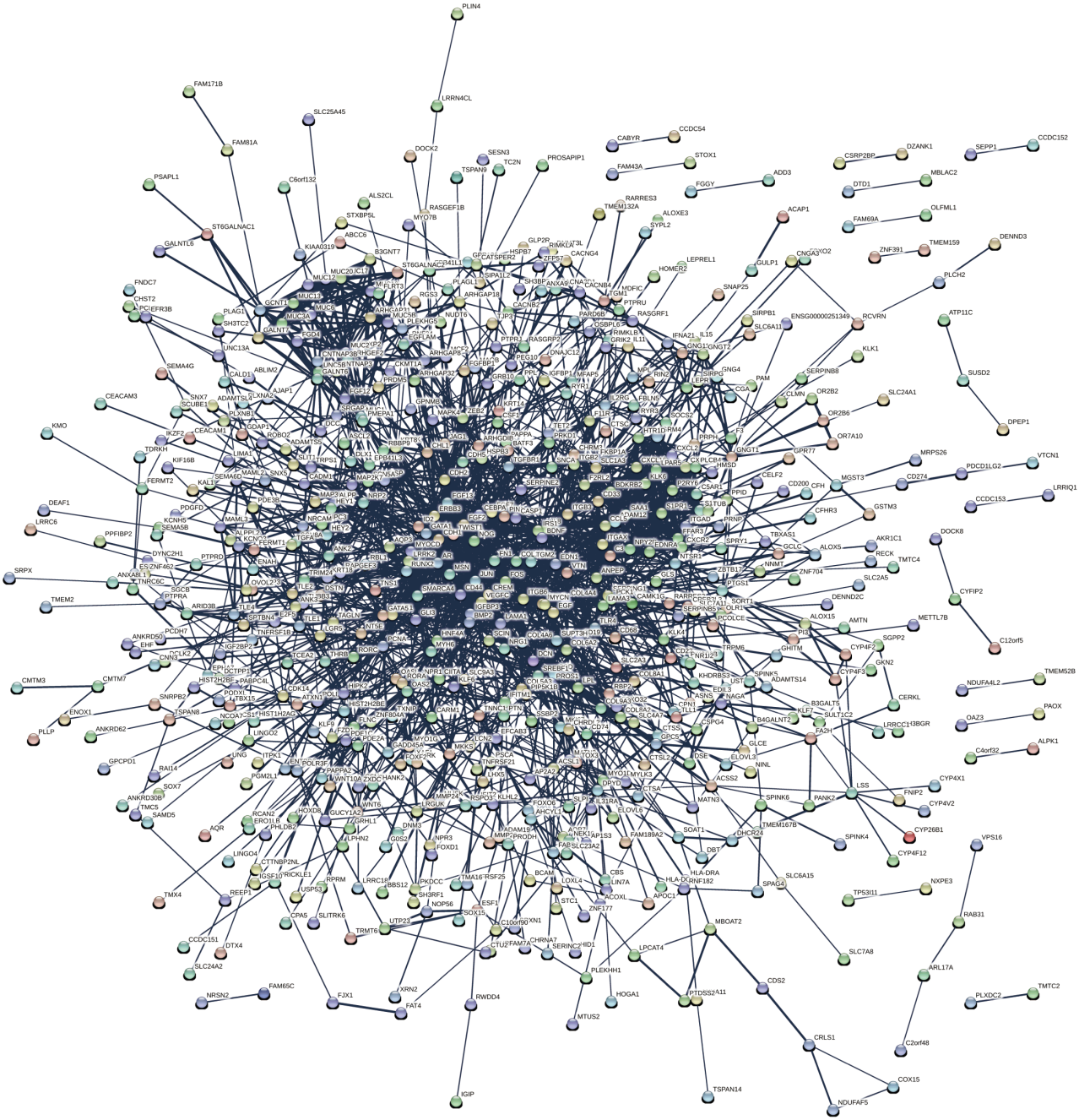

Figure 6 Interaction network analyses of differentially express proteins. In the network, nodes represents proteins, lines as functional associations between the abnormal expressed proteins and the thickness of the lines indicates the level of confidence in association reported.

regulation of cell migration, extracellular matrix disassembly, response to xenobiotic chemotaxis, localization of cell adhesion and blood vessel morphogenesis. Functional annotation showed that the differently expressed mRNAs mainly regulate cellular biological behaviors in the progress of regulation of transcription. How the underlying targets of each GO term are implicated in the cisplatin resistance needs further investigation in the future.

Our KEGG pathway analysis showed that the differently expressed mRNAs are enriched in pathways of *ECM*-receptor interaction, *PI3K-Akt, Rap1, MAPK, Notch1, ErbB, ABC* transporters, *Jak-STAT, NF-κB, HIF-1* and *TGF-β*. All of those pathways have been confirmed to be involved in cisplatin resistance in different experiments described previously. For example, the inhibition of *PI3K-Ak*t signaling pathway may increase the sensitivity of gastric cancer cells to cisplatin chemotherapy[29]. Another study found that Janus kinase 2 (*JAK2*) signal transducer and activator of transcription 3 (*STAT3*) signaling pathways were activated by overexpressed *AKT* in cisplatin resistant human gastric cancer cells[30]. A study revealed that the canonical *NF-κB* signaling pathway was involved in APRIL-mediated cisplatin resistance in gastric cancer[31]. Our data are consistent with these previous

Table 2 Different expressed mRNAs enriched by KOBAS

Term	Database	*P* value	Input gene symbols
Gastric cancer	KEGG DISEASE	0.0016	*DCC, CD44, CDH1, VEGFC, EGF, TGFA*
Skin diseases	KEGG DISEASE	0.0078	*DSP, TGM1, CCL5, IL31RA, SPINK5, HLA, FERMT1, KRT14, CTSC, COL17A1, LAMA3, REEP1, RIN2, ALOXE3, ABCC6, WNT10A, FBLN5*
Skin and soft tissue diseases	KEGG DISEASE	0.0078	*DSP, TGM1, CCL5, IL31RA, SPINK5, HLA, FERMT1, KRT14, CTSC, COL17A1, LAMA3, REEP1, RIN2, ALOXE3, ABCC6, WNT10A, FBLN5*
Macular degeneration	KEGG DISEASE	0.0140	*C3, FBLN5, CFH, TLR4*
Cancers of the digestive system	KEGG DISEASE	0.0439	*DCC, CD44, CDH1, VEGFC, EGF, TGFA*
Familial thoracic aortic aneurysm and dissection (TAAD)	KEGG DISEASE	0.0459	*MYLK, TGFBR1*
Hypomagnesemia	KEGG DISEASE	0.0459	*TRPM6, EGF*
Multiple epiphyseal dysplasia (MED)	KEGG DISEASE	0.0459	*COL9A3, MATN3*
Transient neonatal diabetes mellitus (TNDM)	KEGG DISEASE	0.0459	*PLAGL1, ZFP57*
Non-syndromic autosomal dominant mental retardation	KEGG DISEASE	0.0461	*EPB41L1, DOCK8, PACS1, SMARCA4*
Cardiac hypertrophy	NHGRI GWAS Catalog	0.0028	*PLXNA2, GRIK2, COL17A1, JAG1, SNAP25, BTBD3, SLX4IP*
Response to fenofibrate (adiponectin levels)	NHGRI GWAS Catalog	0.0046	*OAS2, PMEPA1, SHANK2, SCUBE1, SLC30A4, PCK1*
Complement C3 and C4 levels	NHGRI GWAS Catalog	0.0094	*HLA, CFHR3, CFH, C3*
Neutrophil count	NHGRI GWAS Catalog	0.0119	*PLCB4, TGFA, FGGY, PDGFD, PSD3*
Nephropathy(idiopathic membranous)	NHGRI GWAS Catalog	0.0137	*HLA, ITGB6, PLA2R1*
Sleep duration	NHGRI GWAS Catalog	0.0195	*PLLP, TMC5, ADAMTS14*
Airflow obstruction	NHGRI GWAS Catalog	0.0259	*HYKK, LEF1, SERPINB8, GPR126, MAP3K13, PTPRD*
Cystic fibrosis severity	NHGRI GWAS Catalog	0.0265	*HLA, EHF, AHRR*
Metabolite levels (5-HIAA/ MHPG Ratio)	NHGRI GWAS Catalog	0.0265	*PIEZO2, ROBO2, ADAM12*
Bronchopulmonary dysplasia	NHGRI GWAS Catalog	0.0296	*PLXDC2, ZNF770, SPOCK1, TRPS1, RASGRF1, HIVEP3*
Major depressive disorder	NHGRI GWAS Catalog	0.0346	*PCLO, SLC6A15, ENOX1, SYPL2, IGFBP1, IGFBP3, C12orf5, ATXN1, PIEZO2, TRPS1, RASGEF1B, FGF12, KCNH5*
IgA nephropathy	NHGRI GWAS Catalog	0.0346	*HLA, ACOXL, TNFSF13*
Pulmonary function decline	NHGRI GWAS Catalog	0.0368	*MUSK, CSMD1, RORA, FLRT2*
Palmitic acid (16:0) plasma levels	NHGRI GWAS Catalog	0.0368	*SCD, CNN3, GRIK2, PTPRD*
Male-pattern baldness	NHGRI GWAS Catalog	0.0439	*AUTS2, EDA2R, AR*
Response to citalopram treatment	NHGRI GWAS Catalog	0.0439	*LAMA1, RORA, EGFLAM*
Hyperlipidemia	FunDO	0.0050	*IRS1, CCL5, C3, PAPPA, TXNIP, APOC1, F3, SCD*
Thrombocytopenia	FunDO	0.0068	*GATA1, CCL5, ITGB3, IL11, CXCL8, MPL*
Fibromyalgia	FunDO	0.0126	*MAOB, CXCL8, BDNF, IGFBP3*
Cirrhosis	FunDO	0.0209	*RBP4, KRT18, IGFBP3, KRT8, EGF, F3, FGF2IGFBP1*
Hepatitis C	FunDO	0.0321	*CD274, CCL5, RBP4, MKI67, CXCL8, KRT18, TLR4, KRT8, FGF2*
Thalassemia	FunDO	0.0345	*LCN2, CXCL8, ANK2, KIR3DL1, MUC1*
Gingival overgrowth	FunDO	0.0417	*EDN1, IL15, FGF7*
Pulmonary fibrosis	FunDO	0.0474	*CSF1, BDNF, MMP7, EDN1, CCL5, ERBB3*
Ovary cancer	FunDO	0.0477	*LCN2, IL15, CXCL8, FGF7, CASP1*
Esophageal tumor	FunDO	0.0477	*CD274, TSPAN8, FRAT1, PDCD1LG2, FGF7*
Hyperlipidemia	GAD	0.0093	*CCL5, HLA, CXCL8, CD22, TNFRSF1B, CD19*
Thrombocytopenia	GAD	0.0114	*CSMD1, DOCK4, GALNTL6, SOBP, PLXDC2, SESN3, ADAMTS5, EHF, TMC5, LPL, CD109, FAM117B, PDE1C, TAGLN, PTN, FGD4, DYNC2H1, GNG4, MUSK, FBLN5, CCDC54, TTC9, PMEPA1, TLR4, ANK3, EDA2R, APOC1, BMP2, TOX3, NRG1, ITPK1, PTPRD, KLF6, PAM, PTPRU, LEPR, IKZF2, LHX5, MCTP2, ANKRD50, SEMA6D, PLXNA2, DPYD, GRIK2, SRGAP3, ACOXL, TDRKH, FAM135B, VEGFC, CHST2*
Fibromyalgia	GAD	0.0136	*GLI3, CELF2, VWA3B, PLXDC2, EDNRA, EDN1, JUN, DOCK8, DCLK2, BTBD3, DCN, CD74, EGFLAM, TLL1, TLR4, BMP2, PTPRD, ANK2, PTPRU, JADE2, IGF2BP2, PAPPA, DOCK2, KLK4, FAM49A, RGS3, AATK, FN1, IGSF10, NCOA7, SCIN, TNS1, FAM135B, MUC16, ADAM19, ATXN1, MTUS2, NXNL2, KCNQ3, ANPEP, CDH2*
Cirrhosis	GAD	0.0204	*IRS1, CCL5, ITGB3, NPR1, NPR3, APOC1, LPL*
Hepatitis C	GAD	0.0258	*DPYD, CELF4, CELF2, FAM117B, TDRKH, LPCAT4, FBLN5, SOBP, PMEPA1, CSMD1, STOX1, CACNB2, CADM1, VEGFC, SLC7A11, LPL, CD109, MCTP2, SLC24A2, PTPRD, ITPK1*
Thalassemia	GAD	0.0362	*MCTP2, PSD3, CCDC54, ROBO2, ELOVL6*
Gingival overgrowth	GAD	0.0419	*PLXNA2, ATXN1, IGF2BP2, ABCA13, FN1*
Pulmonary fibrosis	GAD	0.0420	*CREG2, GALNTL6, LINC01550, KIF16B, SH3BGR, TRPS1, PDE1C, NCKAP5, TNFRSF21, RYR3, MAGEC2, EDIL3, CXCL16, MCF2, DTD1, GPC5, KLF6, IKZF2, KCNH5, AJAP1, BTBD3, PHACTR2, ITPK1, IGSF10, SRGAP3, C12orf75, ABI3BP, FOS, SCUBE1*

Ovary cancer	GAD	0.0426	*CELF4, TRPS1, TWIST1, PQLC2L, MAL2, PSD3, RCAN2, SUPT3H, TGFA, TMEM131L, HIVEP3, CSMD1, ROBO2, CCDC54, PRNP, APOC1, HRK, GPC5, AR, FN1, ABCA13, F2RL2, KLF6, IGF2BP2, LEPREL1, GNG4, SNAP25, MCTP2, FAM49A, ANKRD50, CACNA2D1, PLXNA2, ELOVL6, RUNX2, SCN8A, ATXN1, ID2, SLC24A2, CMTM7, LINGO2*
Esophageal tumor	GAD	0.048	*CACNA2D1, SLC46A3, CHST2, PKDCC, PPID, CDH2*

Table 3 Cisplatin resistance pathway and input gene ($P < 0.05$, FC $\geqslant$ 2.0)

Pathway	Input gene	Fold change	Regulation	Genomic coordinates	Cyto band
PI3K-Akt signaling pathway	*LAMA1*	2.60826	Up	Chr18:6958512-6956742	hs|18p11.31
	LAMA1	2.75269	Up	Chr18:6942035-6941976	hs|18p11.31
	GNG4	2.09356	Up	Chr1:235714443-235714384	hs|1q42.3
	ITGB3	2.96629	Up	Chr17:45389027-45389086	hs|17q21.32
	ITGB6	7.72783	Up	Chr2:160964233-160958330	hs|2q24.2
	VEGFC	2.92538	Up	Chr4:177604882-177604823	hs|4q34.3
	PDGFD	2.42861	Up	Chr11:103778445-103778386	hs|11q22.3
	IRS1	2.00967	Up	Chr2:227596677-227596618	hs|2q36.3
	GNGT1	2.04779	Up	Chr7:93536149-93540155	hs|7q21.3
	CSF1	2.25620	Up	Chr1:110466137-110466196	hs|1p13.3
	EGF	4.76437	Up	Chr4:110932689-110932748	hs|4q25
	FGF2	3.02437	Up	Chr4:123819331-123819390	hs|4q28.1
	FGF2	2.99240	Up	Chr4:123819317-123819376	hs|4q28.1
	FN1	2.31254	Up	Chr2:216288895-216288217	hs|2q35
	COL4A6	2.08497	Up	Chrx:107399109-107399050	hs|Xq22.3
	FGF12	10.99211	Up	Chr3:191860574-191860515	hs|3q28
	GNG11	2.01984	Up	Chr7:93555764-93555823	hs|7q21.3
	FGF7	2.19252	Up	Chr15:49776810-49776869	hs|15q21.2
	LAMA3	2.56116	Down	Chr18:21534735-21534794	hs|18q11.2
	IFNA21	2.30808	Down	Chr9:21166331-21166272	hs|9p21.3
	CREB3L3	2.40183	Down	Chr19:4172219-4172278	hs|19p13.3
	TLR4	2.13271	Down	Chr9:120476856-120476915	hs|9q33.1
	COL6A2	2.89458	Down	Chr21:47546086-47546145	hs|21q22.3
	CD19	2.09302	Down	Chr16:28950600-28950659	hs|16p11.2
	LPAR5	3.83177	Down	Chr12:6728794-6728735	hs|12p13.31
	COL4A4	2.11177	Down	Chr2:227867523-227867464	hs|2q36.3
	PCK1	4.49558	Down	Chr20:56141030-56141089	hs|20q13.31
	VTN	3.82587	Down	Chr17:26694806-26694747	hs|17q11.2
	GNGT2	16.48365	Down	Chr17:47284034-47283975	hs|17q21.32
	IL2RG	2.87954	Down	Chrx:70328539-70328480	hs|Xq13.1
	COL5A3	7.53410	Down	Chr19:10070602-10070543	hs|19p13.2
	FGF13	17.08866	Down	Chrx:137713947-137713888	hs|Xq26.3
MAPK signaling pathway	*FLNC*	4.57879	Down	Chr7:128498538-128498597	hs|7q32.1
	FLNC	4.81302	Down	Chr7:128498476-128498535	hs|7q32.1
	CACNB2	7.83293	Down	Chr10:18787305-18787364	hs|10p12.31
	RASGRF1	4.87152	Down	Chr15:79254554-79254495	hs|15q25.1
	FOS	2.17501	Down	Chr14:75748214-75748273	hs|14q24.3
	JUN	2.04000	Down	Chr1:59246570-59246511	hs|1p32.1
	RASGRP2	3.10358	Down	Chr11:64508971-64508912	hs|11q13.1
	FGF13	17.08866	Down	Chrx:137713947-137713888	hs|Xq26.3
	TGFBR1	2.93035	Up	Chr9:101916322-101916381	hs|9q22.33
	TGFBR1	4.76437	Up	Chr4:110932689-110932748	hs|4q25
	EGF	4.76437	Up	Chr4:110932689-110932748	hs|4q25
	FGF12	10.99211	Up	Chr3:191860574-191860515	hs|3q28
	MAP3K13	2.25019	Up	Chr3:185161379-185165590	hs|3q27.2
	FGF2	3.02437	Up	Chr4:123819331-123819390	hs|4q28.1
	FGF2	2.99240	Up	Chr4:123819317-123819376	hs|4q28.1
	MAP2K7	2.08267	Up	Chr19:7979302-7979361	hs|19p13.2
	FGF7	2.19252	Up	Chr15:49776810-49776869	hs|15q21.2
	CACNG4	8.83585	Up	Chr17:65028139-65028198	hs|17q24.2
	CACNG4	2.94145	Up	Chr17:65029115-65029174	hs|17q24.2
	CACNB4	2.14311	Up	Chr2:152694239-152694180	hs|2q23.3
	GADD45A	2.56659	Up	Chr1:68153371-68153430	hs|1p31.3
	BDNF	2.32411	Up	Chr11:27679959-27679900	hs|11p14.1
	BDNF	2.30323	Up	Chr11:27677072-27677013	hs|11p14.1
	CACNA2D1	2.09452	Up	Chr7:81579504-81579445	hs|7q21.11

Notch signaling pathway	*MAML2*	2.03379	Up	Chr11:95712434-95712375	hs|11q21
	JAG1	3.20086	Up	Chr20:10619120-10619061	hs|20p12.2
	MAML3	2.57919	Up	Chr4:140810806-140810747	hs|4q31.1
	DTX4	9.99859	Down	Chr11:58975615-58975674	hs|11q12.1
ErbB signaling pathway	*EGF*	4.76437	Up	Chr4:110932689-110932748	hs|4q25
	NRG1	2.77996	Up	Chr8:32474390-32585512	hs|8p12
	MAP2K7	2.08267	Up	Chr19:7979302-7979361	hs|19p13.2
	JUN	2.04000	Down	Chr1:59246570-59246511	hs|1p32.1
	ERBB3	5.29571	Down	Chr12:56482380-56482439	hs|12q13.2
	ERBB3	8.12050	Down	Chr12:56496160-56496219	hs|12q13.2
	TGFA	2.37427	Down	Chr2:70675378-70675319	hs|2p13.3
Jak-STAT signaling pathway	*IL11*	4.21849	Up	Chr19:55875847-55875788	hs|19q13.42
	IL15	2.92970	Up	Chr4:142654431-142654490	hs|4q31.21
	SOCS2	2.00180	Up	Chr12:93969799-93969858	hs|12q22
	SPRY1	5.95682	Up	Chr4:124324494-124324553	hs|4q28.1
	LEPR	2.90187	Up	Chr1:66102129-66102188	hs|1p31.3
	IL2RG	2.87954	Down	Chrx:70328539-70328480	hs|Xq13.1
	MPL	3.41581	Down	Chr1:43819826-43819885	hs|1p34.2
NF-kappaB signaling pathway	*CXCL2*	2.03846	Up	Chr4:74963044-74962985	hs|4q13.3
	CXCL8	9.97781	Up	Chr4:74609265-74609324	hs|4q13.3
	TLR4	2.13271	Down	Chr9:120476856-120476915	hs|9q33.1
HIF-1 signaling pathway	*EDN1*	2.39081	Up	Chr6:12296672-12296731	hs|6p24.1
	EDN1	2.46437	Up	Chr6:12296218-12296277	hs|6p24.1
	EGF	4.76437	Up	Chr4:110932689-110932748	hs|4q25
	TLR4	2.13271	Down	Chr9:120476856-120476915	hs|9q33.1
MicroRNAs in cancer	*IRS1*	2.00967	Up	Chr2:227596677-227596618	hs|2q36.3
	ZEB2	3.32563	Up	Chr2:145146320-145146261	hs|2q22.3
	ZEB2	2.70558	Up	Chr2:145182422-145182363	hs|2q22.3
	CD44	2.02409	Up	Chr11:35253812-35253871	hs|11p13
	RECK	2.25018	Up	Chr9:36124319-36124378	hs|9p13.3
	ITGB3	2.96629	Up	Chr17:45389027-45389086	hs|17q21.32
	SERPINB5	2.61864	Up	Chr18:61172218-61172277	hs|18q21.33
	GLS	2.36144	Up	Chr2:191829716-191829775	hs|2q32.2
	GLS	2.07371	Up	Chr2:191827822-191827881	hs|2q32.2
	ERBB3	5.29571	Down	Chr12:56482380-56482439	hs|12q13.2
	ERBB3	8.12050	Down	Chr12:56496160-56496219	hs|12q13.2

Table 4 Dysregulated mRNAs ($P < 0.05$, FC $\geq$ 2.0) associated with cisplatin resistance

Gene symbol	*P* value	FC (abs)	Regulation	Genename	Ref.
FGF7	0.00035	2.19252	Up	Fibroblast growth factor 7	PMID: 22990650
HIPK2	2.63E-06	4.06213	Up	Homeodomain interacting protein kinase 2	PMID: 24846322
EDN1	9.94E-05	2.46437	Up	Endothelin 1	PMID: 21220476
CBS	0.00108	2.29340	Up	Cystathionine-beta-synthase	PMID: 24236104
PDE3B	0.00029	10.44998	Up	Phosphodiesterase 3B, cgmp-inhibited	PMID: 24133626
E2F5	0.00041	2.42888	Up	E2F transcription factor 5, p130-binding	PMID: 22193543
PIN1	0.00104	2.13293	Up	Peptidylprolyl cis/trans isomerase, NIMA-interacting 1	PMID: 26820938
EGF	0.00346	4.76437	Up	Epidermal growth factor	PMID: 27086487
CSF1	0.00025	2.25620	Up	Colony stimulating factor 1 (macrophage)	PMID: 22005523
PCNA	0.00103	2.17028	Up	Proliferating cell nuclear antigen	PMID: 24474685
HIPK2	2.63E-06	4.06213	Up	Homeodomain interacting protein kinase 2	PMID: 24846322
ENTPD6	0.00011	2.43726	Up	Ectonucleoside triphosphate diphosphohydrolase 6 (putative)	PMID: 21519793
AKR1C1	0.00097	2.29646	Up	Aldo-keto reductase family 1, member C1	PMID: 23165153, PMID: 17266043
ASNS	0.00172	2.19491	Up	Asparagine synthetase (glutamine-hydrolyzing)	PMID: 23956056, PMID: 17409444
BDNF	0.00062	2.32411	Up	Brain-derived neurotrophic factor	PMID: 22276165, PMID: 17044982
CABYR	0.01089	2.55664	Up	Calcium binding tyrosine-(Y)-phosphorylation regulated	PMID: 24362251
FGF2	2.15E-06	2.99240	Up	Fibroblast growth factor 2 (basic)	PMID: 12894531
SLC7A11	1.95E-05	2.93256	Up	Solute carrier family 7 member 11	PMID: 24516043
TUBB3	0.00046	2.00213	Up	Tubulin, beta 3 class III	PMID: 25107571
TWIST1	0.00180	2.96340	Up	Twist family bhlh transcription factor 1	PMID: 22673193, PMID: 22245869
JAG1	9.41E-05	3.20086	Up	Jagged 1	PMID: 24659709
ANXA11	0.00031	2.36619	Down	Annexin A11	PMID: 19484149, PMID: 17982121

CCL5	2.67E-05	5.05630	Down	Chemokine (C-C motif) ligand 5	PMID: 26983899
FGF13	0.00044	17.08866	Down	Fibroblast growth factor 13	PMID: 24113164
IGFBP3	7.48E-05	2.92508	Down	Insulin-like growth factor binding protein 3	PMID: 20023704
KLK6	0.00066	2.24596	Down	Kallikrein-related peptidase 6	PMID: 23307575
SLC7A8	4.50E-05	5.36735	Down	Solute carrier family 7 member 8	PMID: 23462296
TGM2	2.88E-05	6.24520	Down	Transglutaminase 2	PMID: 21424127, PMID: 24828664
TLR4	0.00114	2.13271	Down	Toll-like receptor 4	PMID: 21616060, PMID: 22583829
XAF1	0.02405	3.20613	Down	XIAP associated factor 1	PMID: 25824780, PMID: 25240826
TCEA2	0.00061	3.65969	Down	Transcription elongation factor A (SII), 2	PMID: 16142353

studies, and these pathways and input genes deserve our attention in gastric cancer cisplatin resistance.

Although protein expression is generally stable when organs mature, under various pathological and physiological conditions, gene expression may change and ultimately result in aberrant protein levels. Therefore, research on proteomics is helpful to illustrate some biological mechanisms, including cisplatin resistance. Protein-protein interaction network analysis might uncover previously unknown molecular mechanisms of cisplatin resistance. Hub proteins of subnetworks which interact with many partners might associate with drug resistance. For example, studies have shown that dysregulation of the genes *PDE3B, TLR4*, and *HIPK2* is associated with cisplatin resistance in human SCC cells, ovarian granulosa tumor cells and bladder cancer cells, respectively[26,32,33]. Moreover, hub proteins and their partners may have similar biological functions. Since downregulation of EGF has been shown to substantially overcome resistance to cisplatin in ovarian cancer[34], we predict that the proteins EDN1 and DCN, whose hub protein is EGF, may contribute to cisplatin resistance in a similar fashion. We also found that ZEB2, which over-expressed in SGC7901/DDP compared with SGC7901 has a similar expression profile to TWIST1, suggesting that ZEB2 may play an important role in cisplatin resistance by regulating the expression of TWIST1. Nevertheless, more evidence and research is needed.

In conclusion, our study identified mRNAs differentially expressed between gastric cancer cell lines SGC7901/DDP and SGC7901. These results provide a global view of the function of the differentially expressed mRNAs. Several molecular and pathway abnormalities detected in our study have previously been reported to be associated with drug resistance in gastric cancer. The dysregulated mRNAs identified participate in cisplatin resistance through diverse mechanisms, and further investigation is required to confirm the role in drug resistance of these transcripts, pathways and the interaction networks of the proteins they code for.

COMMENTS

Background

Cisplatin-contained chemotherapy is one of the most frequently used for advanced gastric cancer; however, this chemotherapeutic agent is often limited due to drug resistance and result unsatisfactory prognosis. Research increasingly suggests that abnormal expression of biological pathway and proteins associated with cisplatin resistance. This demonstrated that more bioinformatics study is needed to predict targets for gastric cancer with cisplatin.

Research frontiers

Bioinformatics analysis demonstrated that some mRNAs which related to the biological behavior abnormal expression in SGC7901/DDP cells. These mRNAs have already been shown to play important roles in the process of cisplatin resistance of various cancers, including gastric cancer.

Innovations and breakthroughs

The authors performed bioinformatics analysis of mRNA expression profile in SGC7901/DDP cells compared with SGC7901 cells, and found that many mRNAs and pathways in SGC7901/DDP cells expressed abnormally, these may participate in and predict cisplatin resistance in gastric cancer.

Applications

These results suggest that targeting the differently expression mRNA may provide more selective approaches to reverse cisplatin resistance of therapeutic targets.

Terminology

The definition of cisplatin resistance: in the clinic, if a patient who have disease recurrence within the first months after the recent cisplatin dose, the patient is considered cisplatin resistance; in cells, generally, resistance index > 20 exhibited high resistance, resistance index 5-15 is moderate resistance, resistance index < 5 represent low or no resistance. Correct *P*: Using Benjamini Hochberg FDR method for correction of p values. Fold change (FC): gene expression in SGC7901 / DDP cells compared with SGC7901 cells.

Peer-review

The paper is a good study on mRNAs expression profile in SGC7901/DDP cells. The investigators shown that many mRNAs was abnormal expressed in SGC7901/DDP cells and these mRNAs enriched in many biological process which have already been shown to play important roles in the process of cisplatin resistance in human cancer.

REFERENCES

1 **Ferro A**, Peleteiro B, Malvezzi M, Bosetti C, Bertuccio P, Levi F, Negri E, La Vecchia C, Lunet N. Worldwide trends in gastric cancer mortality (1980-2011), with predictions to 2015, and incidence by subtype. *Eur J Cancer* 2014; **50**: 1330-1344 [PMID: 24650579 DOI: 10.1016/j.ejca.2014.01.029]

2 **Wöhrer SS**, Raderer M, Hejna M. Palliative chemotherapy for advanced gastric cancer. *Ann Oncol* 2004; **15**: 1585-1595 [PMID: 15520058 DOI: 10.1093/annonc/mdh422]

3 **Jemal A**, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010; **60**: 277-300 [PMID: 20610543 DOI: 10.3322/caac.20073]

4 **Al-Batran SE**, Hartmann JT, Probst S, Schmalenberg H,

Hollerbach S, Hofheinz R, Rethwisch V, Seipelt G, Homann N, Wilhelm G, Schuch G, Stoehlmacher J, Derigs HG, Hegewisch-Becker S, Grossmann J, Pauligk C, Atmaca A, Bokemeyer C, Knuth A, Jäger E. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol* 2008; **26**: 1435-1442 [PMID: 18349393 DOI: 10.1200/jco.2007.13.9378]

5 **Kang YK**, Kang WK, Shin DB, Chen J, Xiong J, Wang J, Lichinitser M, Guan Z, Khasanov R, Zheng L, Philco-Salas M, Suarez T, Santamaria J, Forster G, McCloud PI. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. *Ann Oncol* 2009; **20**: 666-673 [PMID: 19153121 DOI: 10.1093/annonc/mdn717]

6 **Koizumi W**, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Nagaie T, Takagi S, Yamamura Y, Yanaoka K, Orita H, Takeuchi M. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008; **9**: 215-221 [PMID: 18282805 DOI: 10.1016/s1470-2045(08)70035-4]

7 **Wagner AD**, Unverzagt S, Grothe W, Kleber G, Grothey A, Haerting J, Fleig WE. Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev* 2010; **(3)**: CD004064 [PMID: 20238327 DOI: 10.1002/14651858.CD004064.pub3]

8 **Rabik CA**, Dolan ME. Molecular mechanisms of resistance and toxicity associated with platinating agents. *Cancer Treat Rev* 2007; **33**: 9-23 [PMID: 17084534 DOI: 10.1016/j.ctrv.2006.09.006]

9 **Garcia JA**, Dreicer R. Systemic chemotherapy for advanced bladder cancer: update and controversies. *J Clin Oncol* 2006; **24**: 5545-5551 [PMID: 17158540 DOI: 10.1200/jco.2006.08.0564]

10 **Wilson TR**, Longley DB, Johnston PG. Chemoresistance in solid tumours. *Ann Oncol* 2006; **17** Suppl 10: x315-x324 [PMID: 17018746 DOI: 10.1093/annonc/mdl280]

11 **Borst P**, Evers R, Kool M, Wijnholds J. A family of drug transporters: the multidrug resistance-associated proteins. *J Natl Cancer Inst* 2000; **92**: 1295-1302 [PMID: 10944550]

12 **Hioki M**, Gotohda N, Konishi M, Nakagohri T, Takahashi S, Kinoshita T. Predictive factors improving survival after gastrectomy in gastric cancer patients with peritoneal carcinomatosis. *World J Surg* 2010; **34**: 555-562 [PMID: 20082194 DOI: 10.1007/s00268-010-0396-5]

13 **Yang T**, Chen M, Chen T, Thakur A. Expression of the copper transporters hCtr1, ATP7A and ATP7B is associated with the response to chemotherapy and survival time in patients with resected non-small cell lung cancer. *Oncol Lett* 2015; **10**: 2584-2590 [PMID: 26622894 DOI: 10.3892/ol.2015.3531]

14 **Metzger R**, Leichman CG, Danenberg KD, Danenberg PV, Lenz HJ, Hayashi K, Groshen S, Salonga D, Cohen H, Laine L, Crookes P, Silberman H, Baranda J, Konda B, Leichman L. ERCC1 mRNA levels complement thymidylate synthase mRNA levels in predicting response and survival for gastric cancer patients receiving combination cisplatin and fluorouracil chemotherapy. *J Clin Oncol* 1998; **16**: 309-316 [PMID: 9440758]

15 **Xu W**, Chen Q, Wang Q, Sun Y, Wang S, Li A, Xu S, Røe OD, Wang M, Zhang R, Yang L, Zhou J. JWA reverses cisplatin resistance via the CK2-XRCC1 pathway in human gastric cancer cells. *Cell Death Dis* 2014; **5**: e1551 [PMID: 25476899 DOI: 10.1038/cddis.2014.517]

16 **Shim HJ**, Yun JY, Hwang JE, Bae WK, Cho SH, Lee JH, Kim HN, Shin MH, Kweon SS, Lee JH, Kim HJ, Chung IJ. BRCA1 and XRCC1 polymorphisms associated with survival in advanced gastric cancer treated with taxane and cisplatin. *Cancer Sci* 2010; **101**: 1247-1254 [PMID: 20331623 DOI: 10.1111/j.1349-7006.2010.01514.x]

17 **Liu J**, Deng N, Xu Q, Sun L, Tu H, Wang Z, Xing C, Yuan Y. Polymorphisms of multiple genes involved in NER pathway predict prognosis of gastric cancer. *Oncotarget* 2016; **7**: 48130-48142 [PMID: 27340861 DOI: 10.18632/oncotarget.10173]

18 **Sargent RG**, Meservy JL, Perkins BD, Kilburn AE, Intody Z, Adair GM, Nairn RS, Wilson JH. Role of the nucleotide excision repair gene ERCC1 in formation of recombination-dependent rearrangements in mammalian cells. *Nucleic Acids Res* 2000; **28**: 3771-3778 [PMID: 11000269]

19 **Funato T**, Kozawa K, Fujimaki S, Miura T, Kaku M. Increased sensitivity to cisplatin in gastric cancer by antisense inhibition of the her-2/neu (c-erbB-2) gene. *Chemotherapy* 2001; **47**: 297-303 [PMID: 11399867]

20 **Zhou N**, Qu Y, Xu C, Tang Y. Upregulation of microRNA-375 increases the cisplatin-sensitivity of human gastric cancer cells by regulating ERBB2. *Exp Ther Med* 2016; **11**: 625-630 [PMID: 26893657 DOI: 10.3892/etm.2015.2920]

21 **Sileni VC**, Fosser V, Maggian P, Padula E, Beltrame M, Nicolini M, Arslan P. Pharmacokinetics and tumor concentration of intraarterial and intravenous cisplatin in patients with head and neck squamous cancer. *Cancer Chemother Pharmacol* 1992; **30**: 221-225 [PMID: 1628371]

22 **Zhou C**, Zhang T, Liu F, Zhou J, Ni X, Huo R, Shi Z. The differential expression of mRNAs and long noncoding RNAs between ectopic and eutopic endometria provides new insights into adenomyosis. *Mol Biosyst* 2016; **12**: 362-370 [PMID: 26662114 DOI: 10.1039/c5mb00733j]

23 **Muggia FM**, Bonetti A, Hoeschele JD, Rozencweig M, Howell SB. Platinum Antitumor Complexes: 50 Years Since Barnett Rosenberg's Discovery. *J Clin Oncol* 2015; **33**: 4219-4226 [PMID: 26503202 DOI: 10.1200/jco.2015.60.7481]

24 **Ge X**, Liu X, Lin F, Li P, Liu K, Geng R, Dai C, Lin Y, Tang W, Wu Z, Chang J, Lu J, Li J. MicroRNA-421 regulated by HIF-1α promotes metastasis, inhibits apoptosis, and induces cisplatin resistance by targeting E-cadherin and caspase-3 in gastric cancer. *Oncotarget* 2016; **7**: 24466-24482 [PMID: 27016414 DOI: 10.18632/oncotarget.8228]

25 **Sakai W**, Swisher EM, Karlan BY, Agarwal MK, Higgins J, Friedman C, Villegas E, Jacquemont C, Farrugia DJ, Couch FJ, Urban N, Taniguchi T. Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers. *Nature* 2008; **451**: 1116-1120 [PMID: 18264087 DOI: 10.1038/nature06633]

26 **Uzawa K**, Kasamatsu A, Baba T, Usukura K, Saito Y, Sakuma K, Iyoda M, Sakamoto Y, Ogawara K, Shiiba M, Tanzawa H. Targeting phosphodiesterase 3B enhances cisplatin sensitivity in human cancer cells. *Cancer Med* 2013; **2**: 40-49 [PMID: 24133626 DOI: 10.1002/cam4.56]

27 **Cho HJ**, Kim IK, Park SM, Baek KE, Nam IK, Park SH, Ryu KJ, Choi J, Ryu J, Hong SC, Jeong SH, Lee YJ, Ko GH, Kim J, Won Lee C, Soo Kang S, Yoo J. VEGF-C mediates RhoGDI2-induced gastric cancer cell metastasis and cisplatin resistance. *Int J Cancer* 2014; **135**: 1553-1563 [PMID: 24585459 DOI: 10.1002/ijc.28801]

28 **Cortés-Sempere M**, de Miguel MP, Pernía O, Rodriguez C, de Castro Carpeño J, Nistal M, Conde E, López-Ríos F, Belda-Iniesta C, Perona R, Ibanez de Caceres I. IGFBP-3 methylation-derived deficiency mediates the resistance to cisplatin through the activation of the IGFIR/Akt pathway in non-small cell lung cancer. *Oncogene* 2013; **32**: 1274-1283 [PMID: 22543588 DOI: 10.1038/onc.2012.146]

29 **Fu X**, Feng J, Zeng D, Ding Y, Yu C, Yang B. PAK4 confers cisplatin resistance in gastric cancer cells via PI3K/Akt- and MEK/Erk-dependent pathways. *Biosci Rep* 2014; Epub ahead of print [PMID: 24471762 DOI: 10.1042/bsr20130102]

30 **Zhang LL**, Zhang J, Shen L, Xu XM, Yu HG. Overexpression of AKT decreases the chemosensitivity of gastric cancer cells to cisplatin in vitro and in vivo. *Mol Med Rep* 2013; **7**: 1387-1390 [PMID: 23546174 DOI: 10.3892/mmr.2013.1400]

31 **Zhi X**, Tao J, Xiang G, Cao H, Liu Z, Yang K, Lv C, Ni S. APRIL induces cisplatin resistance in gastric cancer cells via activation of the NF-κB pathway. *Cell Physiol Biochem* 2015; **35**: 571-585 [PMID: 25612651 DOI: 10.1159/000369720]

32 **Lin J**, Zhang Q, Lu Y, Xue W, Xu Y, Zhu Y, Hu X. Downregulation of HIPK2 increases resistance of bladder cancer cell to cisplatin by regulating Wip1. *PLoS One* 2014; **9**: e98418 [PMID: 24846322

DOI: 10.1371/journal.pone.0098418]

33 **Woods DC**, White YA, Dau C, Johnson AL. TLR4 activates NF-κB in human ovarian granulosa tumor cells. *Biochem Biophys Res Commun* 2011; **409**: 675-680 [PMID: 21616060 DOI: 10.1016/j.bbrc.2011.05.063]

34 **Tang XH**, Li M, Deng S, Lu MS. Cross-reacting material 197, a heparin-binding EGF-like growth factor inhibitor, reverses the chemoresistance in human cisplatin-resistant ovarian cancer. *Anticancer Drugs* 2014; **25**: 1201-1210 [PMID: 25115341 DOI: 10.1097/cad.0000000000000155]

P- Reviewer: Ghosh RD **S- Editor**: Qi Y **L- Editor**: A
E- Editor: Wang CH

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327