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Bioinformatic Analysis of *GLI1* and Related Signaling Pathways in Chemosensitivity of Gastric Cancer

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: This study assessed the prognostic value of *GLI1* in gastric cancer and analyzed the possible *GLI1*-related signaling network in chemosensitivity.

Material/Methods: Bioinformatic data mining was performed by using data in the TCGA-Stomach Cancer (TCGA-STAD) and the Kaplan-Meier plotter. *GLI1* co-expressed genes in TCGA-STAD were subjected to KEGG pathway analysis. The genes enriched in the KEGG pathways were further subjected to Protein-Protein Interaction (PPI) analysis.

Results: In TCGA-STAD, high *GLI1* gene/exon expression was associated with significantly worse survival (p=0.016 and 0.0023 respectively). In the Kaplan-Meier plotter, high *GLI1* expression was associated with unfavorable overall survival (OS) (HR: 1.68, 95%CI: 1.42–2, p<0.0001) and first progression-free survival (FPS) (HR: 1.72, 95%CI: 1.4–2.11, p<0.0001). In TCGA-STAD, 600 *GLI1* co-expressed genes were identified (absolute Pearson's r ≥0.5). The most significant pathways were pathways in cancer (p=230.0E-12) and the Hedgehog signaling pathway (p=6.9E-9). PI3K-AKT pathway (p=17.0E-9) has the largest proportion of gene enrichment. Some *GLI1* co-expressed genes in the PI3K-AKT pathway are central nodes in the PPI network and also play important roles in chemosensitivity of gastric cancer. Nevertheless, the mechanisms underlying their co-expression are still largely unexplored.

Conclusions: High *GLI1* expression is associated with unfavorable OS and FPS in patients with gastric cancer. As a member of the Hedgehog signaling pathway, *GLI1* co-expressed genes are also largely enriched in PI3K/AKT pathway in gastric cancer, which is closely related to chemoresistance. The underlying mechanisms are still largely unexplored and need further study.

MeSH Keywords: Antineoplastic Agents • Phosphatidylinositol 3-Kinases • Stomach Neoplasms

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Background

Sonic Hedgehog (Shh), as a member of the Hedgehog family, is usually activated in several types of tumors [1]. Shh proteins can bind to the transmembrane receptor Patched (Ptch) and enhance the activity of transmembrane protein Smoothened (SMO), then lead to activated transcription of *GLI1, GLI2,* and *GLI3*, which are 3 transcription factor genes [2]. Recent studies reported that dysregulated *GLI1* is an important mechanism leading to malignant phenotypes and chemoresistance of multiple types of cancer, such as glioma [3], pancreatic cancer [4], melanoma [5], large B-cell lymphoma [5], and gastric cancer [7].

As a transcriptional factor, *GLI1* can turn on its target genes via epigenetic mechanisms and enhance chemoresistance. For example, in gastric cancer, GLI1 protein can interact with the promoter fragment of ATP-binding cassette sub-family G member 2 (*ABCG2*) through a Gli-binding consensus site and upregulate its expression in large B-cell lymphoma cells[6] and gastric cancer cells [8]. ABCG2 is a well-characterized multidrug resistance-associated transporter [9]. In glioma cells, GLI1 can modulate stem cell self-renewal through epigenetically activating *BMI1* and *SOX2* genes [10], thereby conferring chemoresistance to the cells [11]. In pancreatic cancer cells, GLI1 can upregulate *IGFBP6* and *BCL2* through promoter binding and enhance cell survival [12], and can also upregulate a new gene, *S100A4,* to facilitate epithelial-to-mesenchymal transition [13]. These findings suggest that the regulative effect of GLI1 is cancer-specific.

Recent studies also found *GLI1* expression has a prognostic value in some cancers. Patients with nuclear *GLI1*-expressing basal-like breast tumors had a significantly shorter survival time than those without nuclear *GLI1* expression [14]. Elevated *GLI1* expression is also correlated with poor prognosis in patients with non-small cell lung cancer [14,15]. Although recent data suggest that *GLI1* is a key mediator of chemoresistance in gastric cancer [7,8], its regulative network and its association with survival in the patients are still not well understood. In this study, by bioinformatic analysis, we studied the prognostic value of *GLI1* in gastric cancer and also analyzed the possible *GLI1*-related signaling network in chemosensitivity of gastric cancer.

Material and Methods

Data mining in TCGA-Stomach Cancer (TCGA-STAD)

RNA and exon expression of *GLI1* in patients with primary gastric cancer in TCGA-STAD were reviewed by using the UCSC Xena browser (*http://xena.ucsc.edu/*), which is an online tool to analyze data provided by TCGA. Kaplan-Meier curves of survival were also generated by splitting the patients into high/low gene or exon expression groups. Median gene/exon expression was used as the cutoff. Log-rank test was performed to determine the significance of difference between the curves.

Data mining in the Kaplan-Meier plotter

The association between *GLI1* expression and overall survival (OS) or first progression-free survival (FPS) was studied by data mining in the Kaplan-Meier plotter (http://kmplot.com/analysis/), which is an online database that enables cross-validation of survival associated biomarkers in gastric cancer using transcriptomic data of 1065 patients [16]. The patients were grouped by median *GLI1* expression. The hazard ratio (HR) with 95% confidence intervals (CI) and log-rank *p* value were calculated. The number-at-risk is indicated below the survival curves.

Bioinformatic analysis using the cBioPortal for Cancer Genomics and ClueGo

The genes co-expressed with *GLI1* in TCGA-STAD (absolute Pearson's r ≥0.5) were identified using the cBioPortal for Cancer Genomics (*http://www.cbioportal.org/*). Then, the genes were loaded into ClueGo in Cytoscape [17] for analysis of KEGG pathways. Only pathways with *p* value ≤0.05 were included.

Protein-Protein interaction (PPI) network

To identify the known PPI network among *GLI1* and its co-expressed genes, they are loaded into the Search Tool for the Retrieval of Interacting Genes (STRING) (*http://string-db.org/*) database for analysis. Evidence threshold was set to >0.7, which indicates experimentally validated interactions.

Statistical analysis

The significance of difference between survival curves was assessed by the log-rank test. $p<0.05$ was considered as statistically significant.

Results

High *GLI1* expression is associated with poor OS in patients with gastric cancer

A series of previous studies found that *GLI1* upregulation contributes to tumorigenesis and development of chemoresistance of gastric cancer 8,18,19]. In this study, by data mining in TCGA-STAD, we further studied the prognostic value of *GLI1* in patients with gastric cancer. Using the UCSC Xena browser, we characterized *GLI1* gene and exon expression in 415 patients with primary gastric cancer in TCGA-STAD (Figure 1A). Log-rank test of

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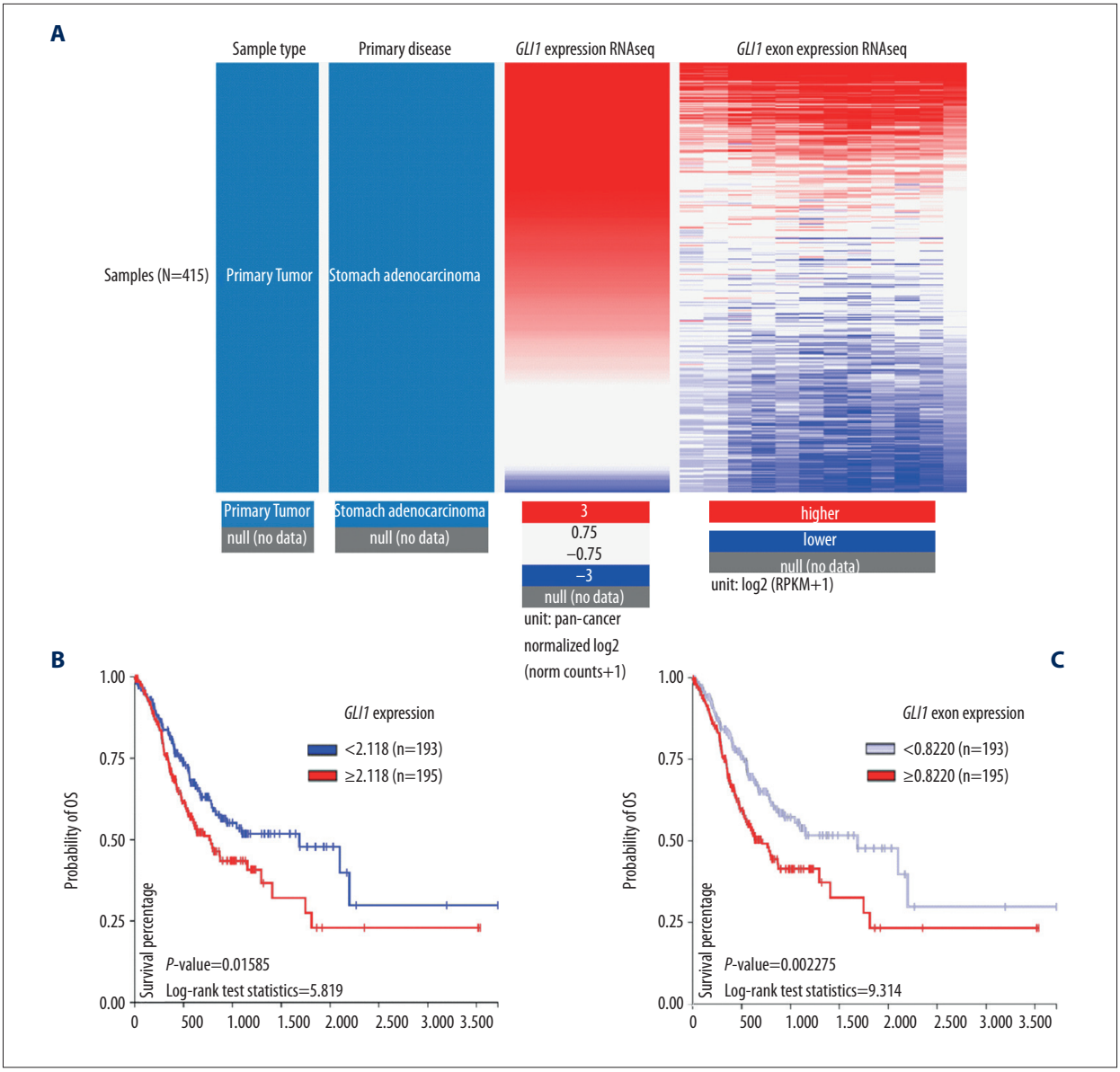

Figure 1. High *GLI1* expression is associated with poor OS in patients with gastric cancer. (**A**) Heatmap of *GLI1* gene and exon expression in 415 patients with primary gastric cancer in TCGA-STAD. (**B, C**) Kaplan-Meier curves of OS in gastric cancer patients with high/low *GLI1* gene (**B**) or exon (**C**) expression. The analysis was performed by using the UCSC Xena browser.

Kaplan-Meier curves of OS showed that high *GLI1* gene expression was associated with significantly worse survival (Figure 1B, p=0.016). Since *GLI1* is a protein coding gene, we also studied the association between *GLI1* exon expression and survival. Results of log-rank test confirmed that high *GLI1* exon expression was also associated with unfavorable survival (Figure 1C, p=0.0023).

High *GLI1* expression is associated with poor FPS in patients with gastric cancer

To further study the association between *GLI1* expression and survival outcomes in patients with gastric cancer, data mining was also performed using the Kaplan-Meier plotter. Results indicated that high *GLI1* expression was associated with unfavorable OS (HR: 1.68, 95%CI: 1.42-2, p<0.0001) (Figure 2A, up) and FPS (HR: 1.72, 95%CI: 1.4-2.11, p<0.0001) (Figure 2B, up) in patients with gastric cancer. In the low *GLI1* expression group, median OS and FPS were 46.8 and 42.37 months, respectively (Figure 2A, 2B, down). In comparison, median OS and FPS drastically dropped to 23.4 and 12.8 months in the high *GLI1* expression group (Figure 2A, 2B, down).

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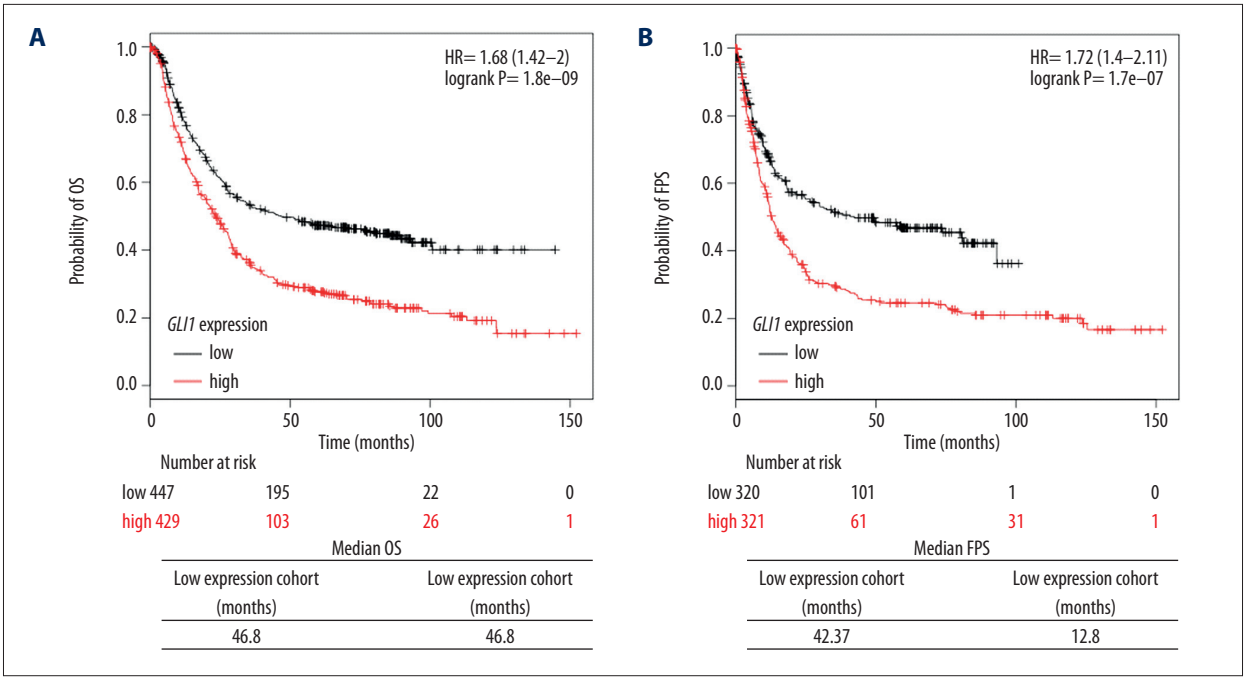

Figure 2. High *GLI1* expression is associated with poor FPS in patients with gastric cancer. (**A, B**) Kaplan-Meier curves of OS (**A**) and FPS (**B**) in gastric cancer patients with high/low *GLI1* expression. Median OS and FPS were also calculated and given below in the survival graphs. The analysis was performed using the Kaplan-Meier plotter. Patients were grouped by median *GLI1* expression.

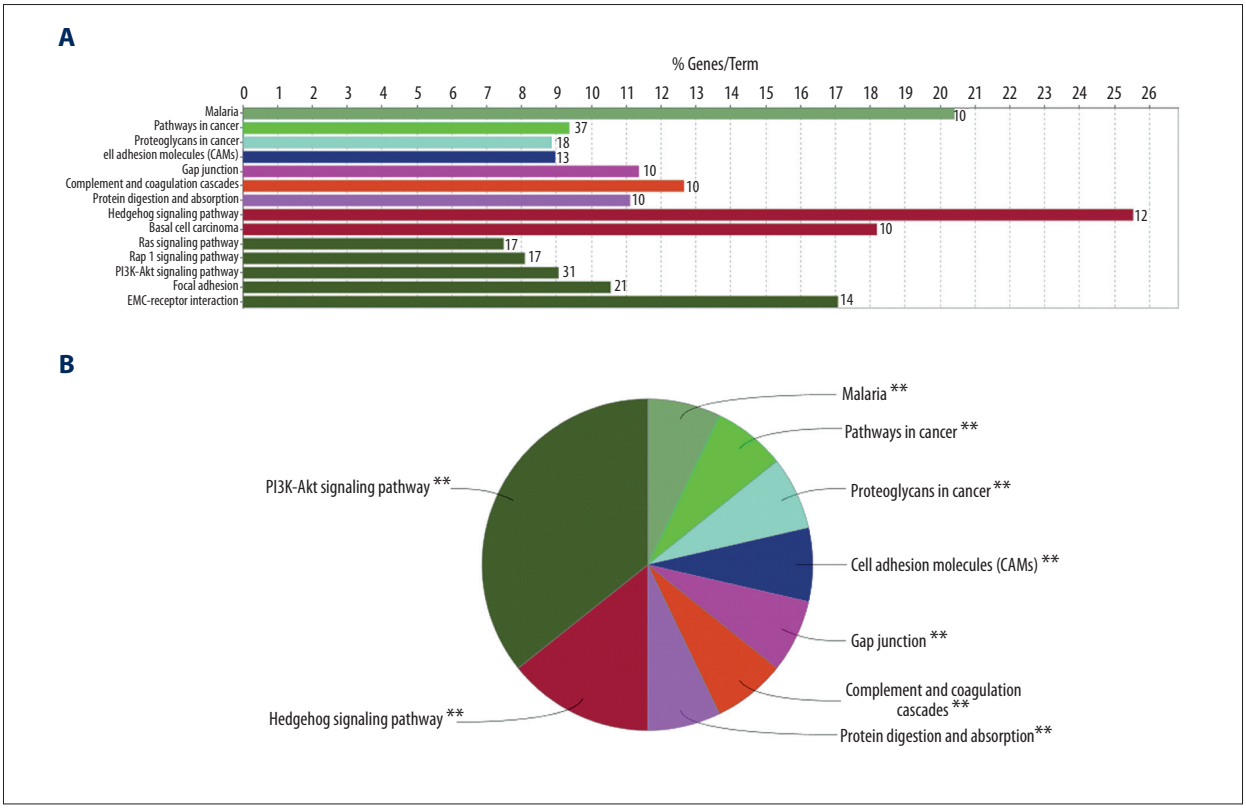

Figure 3. The enrichment of *GLI1* and its co-expressed genes in KEGG pathways. (**A, B**) Bar chart (**A**) and pie chart (**B**) of the enrichment of *GLI1* and its co-expressed genes in KEGG pathways.

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Table 1. KEGG pathway analysis of GLI1 and its co-expressed genes in TCGA-STAD.

GOID	GO term	Term P value	Group P value	% Associated genes	Nr. genes	Associated genes found
GO: 0005144	Malaria	1.2E-6	1.2E-6	20.41	10.00	[ACKR1, GYPC, HGF, LRP1, SELP, TGFB1, TGFB3, THBS2, THBS3, THBS4]
GO: 0005200	Pathways in cancer	230.0E-12	230.0E-12	9.37	37.00	[ADCY4, AKT3, BCL2, EDNRA, F2R, FGF14, FGF7, FZD1, FZD4, GLI1, GLI2, GLI3, GNAI2, GNB4, GNG11, HGF, IGF1, LAMA2, LAMA4, LAMB2, LPAR1, LPAR4, MAPK10, PDGFRA, PDGFRB, PTCH1, PTCH2, PTGER3, RASGRP4, RUNX1T1, STAT5B, SUFU, TGFB1, TGFB3, VEGFC, WNT2B, WNT9B]
GO: 0005205	Proteoglycans in cancer	28.0E-6	28.0E-6	8.87	18.00	[AKT3, COL21A1, DCN, FZD1, FZD4, HGF, HSPB2, HSPG2, IGF1, ITPR1, LUM, MRAS, PTCH1, TGFB1, TIMP3, TWIST2, WNT2B, WNT9B]
GO: 0004514	Cell adhesion molecules (CAMs)	340.0E-6	340.0E-6	8.97	13.00	[CADM3, CD34, CDH5, CNTNAP1, ITGA9, JAM2, JAM3, NLGN2, NLGN3, NRXN2, PTPRM, SELP, VCAN]
GO: 0004540	Gap junction	250.0E-6	250.0E-6	11.36	10.00	[ADCY4, GNAI2, GUCY1A3, GUCY1B3, HTR2A, ITPR1, LPAR1, PDGFRA, PDGFRB, TUBA1A]
GO: 0004610	Complement and coagulation cascades	100.0E-6	100.0E-6	12.66	10.00	[A2M, C1R, C1S, C3, C7, CFH, F2R, F8, SERPING1, VWF]
GO: 0004974	Protein digestion and absorption	300.0E-6	300.0E-6	11.11	10.00	[COL14A1, COL15A1, COL1A2, COL21A1, COL3A1, COL5A1, COL6A1, COL6A2, COL6A3, ELN]
GO: 0004340	Hedgehog signaling pathway	6.9E-9	8.5E-9	25.53	12.00	[BCL2, BOC, CDON, DHH, EVC, EVC2, GLI1, GLI2, GLI3, PTCH1, PTCH2, SUFU]
GO: 0005217	Basal cell carcinoma	3.8E-6	8.5E-9	18.18	10.00	[FZD1, FZD4, GLI1, GLI2, GLI3, PTCH1, PTCH2, SUFU, WNT2B, WNT9B]
GO: 0004014	Ras signaling pathway	380.0E-6	1.1E-6	7.49	17.00	[AKT3, FGF14, FGF7, GNB4, GNG11, HGF, IGF1, MAPK10, MRAS, NGFR, PDGFRA, PDGFRB, RASA4, RASGRP4, RGL1, TEK, VEGFC]
GO: 0004015	Rap1 signaling pathway	150.0E-6	1.1E-6	8.10	17.00	[ADCY4, AKT3, F2R, FGF14, FGF7, GNAI2, HGF, IGF1, LPAR1, LPAR4, MRAS, NGFR, PDGFRA, PDGFRB, PRKD1, TEK, VEGFC]
GO: 0004151	PI3K-Akt signaling pathway	17.0E-9	1.1E-6	9.06	31.00	[AKT3, BCL2, COL1A2, COL6A1, COL6A2, COL6A3, F2R, FGF14, FGF7, GHR, GNB4, GNG11, HGF, IGF1, IL3RA, ITGA9, LAMA2, LAMA4, LAMB2, LPAR1, LPAR4, NGFR, PDGFRA, PDGFRB, TEK, THBS2, THBS3, THBS4, TNXB, VEGFC, VWF]
GO: 0004510	Focal adhesion	350.0E-9	1.1E-6	10.55	21.00	[AKT3, BCL2, COL1A2, COL6A1, COL6A2, COL6A3, HGF, IGF1, ITGA9, LAMA2, LAMA4, LAMB2, MAPK10, PDGFRA, PDGFRB, THBS2, THBS3, THBS4, TNXB, VEGFC, VWF]
GO: 0004512	ECM-receptor interaction	96.0E-9	1.1E-6	17.07	14.00	[COL1A2, COL6A1, COL6A2, COL6A3, HSPG2, ITGA9, LAMA2, LAMA4, LAMB2, THBS2, THBS3, THBS4, TNXB, VWF]

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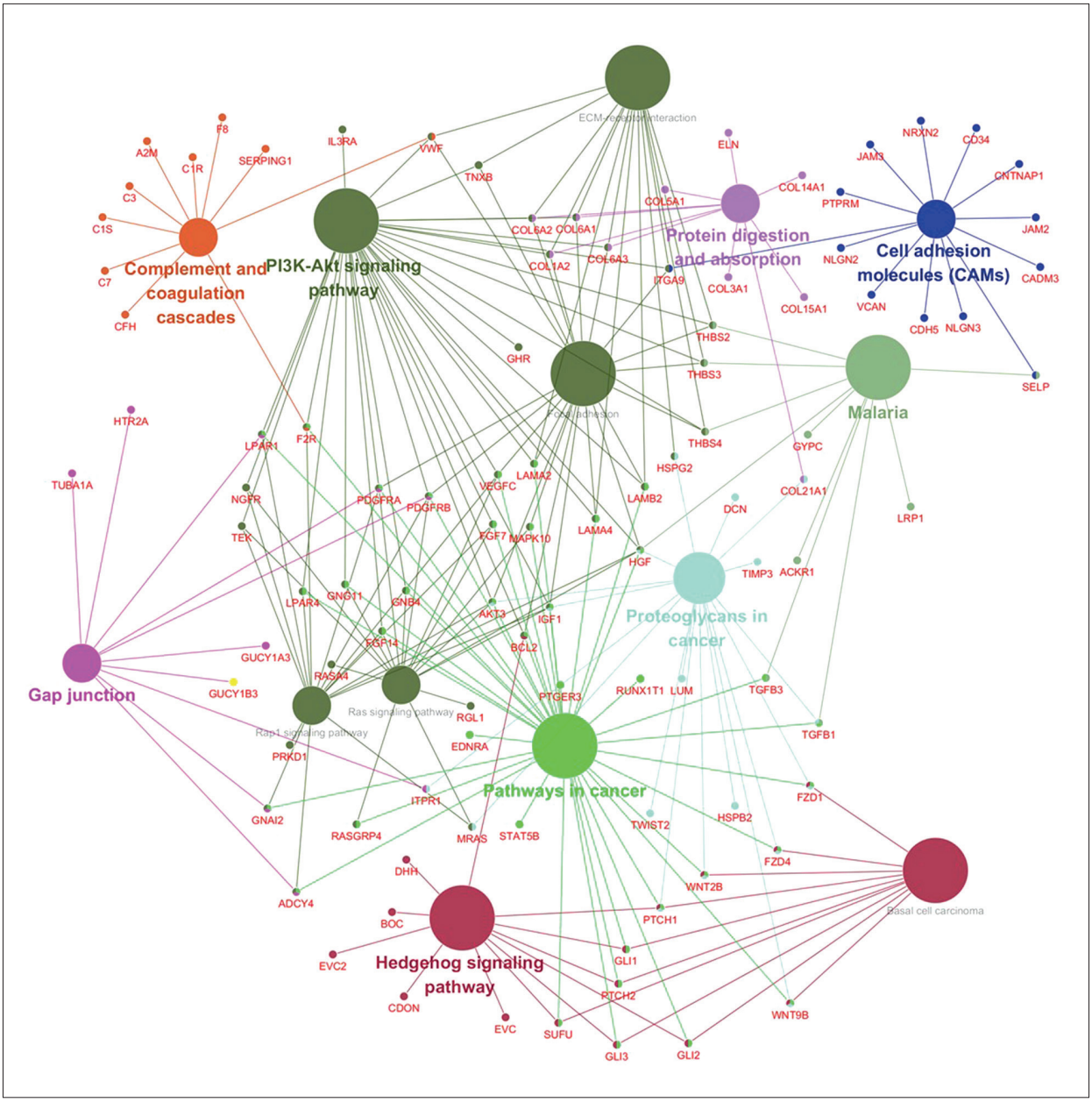

Figure 4. The network of *GLI1* and its co-expressed genes in KEGG pathways.

KEGG pathway analysis of *GLI1* and its co-expressed genes in TCGA-STAD

Via data mining using cBioPortal for Cancer Genomics, we identified the genes significantly co-expressed with *GLI1* in TCGA-STAD. There were 600 genes identified by setting absolute Pearson's r ≥0.5 as a threshold. Then, the genes were subjected to enrichment in KEGG pathways. Results indicated that the genes were enriched in Malaria, Pathways in cancer, Proteoglycans in cancer, Cell adhesion molecules (CAMs), Gap junction, Complement and coagulation cascades, Protein digestion and absorption, Hedgehog signaling pathway, Basal cell carcinoma, Ras signaling pathway, Rap1 signaling pathway, PI3K-Akt signaling pathway, Focal adhesion, and ECM-receptor interaction (Figure 3A, Table 1). The most significant pathways were pathways in cancer (p=230.0E-12) and Hedgehog signaling pathway (p=6.9E-9) (Table 1). Interestingly, although *GLI1* itself is a member of the Hedgehog signaling pathway, the highest level of gene enrichment was in the PI3K-AKT pathway (Figures 3A, 3B, 4). By performing PPI analysis, we further summarized the known interactions among the *GLI1* co-expressed genes (Figure 5). Some proteins involved in the PI3K-AKT pathway, such as BCL2, GNB4, GNG11, F2R, LPAR1, LPAR4, IGF1, HGF, VEGFC, PDGFRA, PDGFRB, COL5A1, COL6A1, COL6A2,

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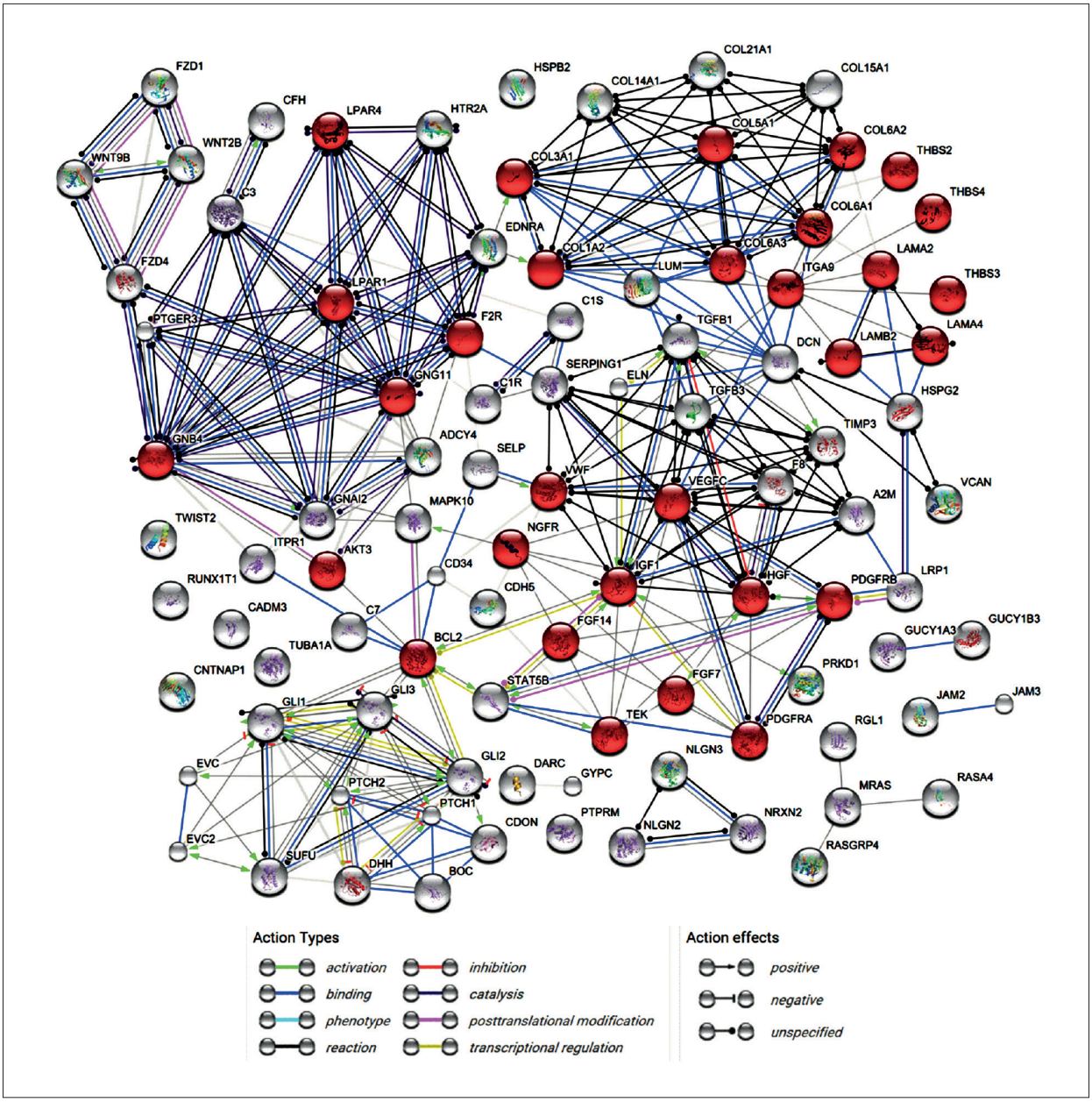

Figure 5. The PPI network of *GLI1* co-expressed genes in KEGG pathways.

and COL6A3, are central nodes in the network (Figure 5). The known direct interaction between GLI1 and PI3K-AKT pathway is its connection with BCL2 (Figure 5).

Discussion

A series of factors can influence the survival of gastric cancer [20–23]. *GLI1* upregulation is common in gastric cancer and is associated with malignant behaviors of the tumor. Previous studies reported that *GLI1* upregulation is positively correlated with the epithelial-to-mesenchymal transition of gastric cancer cells and with lymph node metastasis [18,24]. Mechanistically, Shh-activated *GLI1* can directly increase transcription of *PTCH1, FOXM1,* and *CCND2*, leading to enhanced cell proliferation through cell cycle regulation [25]. In addition, *GLI1* can upregulate *ABCG2* expression, which is associated with increased tumor sphere formation, side population, and cell surface markers for putative cancer stem cells [8]. This mechanism directly leads to the resistance of gastric cancer stem cells to doxorubicin-induced apoptosis [8,26]. More importantly, high *ABCG2* expression was associated with poor survival in gastric cancer patients who underwent chemotherapy [8]. In the present study, by data mining in 2 large databases (TCGA-STAD and

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Kaplan-Meier plotter), we further assessed the association between *GLI1* expression and survival outcomes in gastric cancer patients. Results indicated that high *GLI1* expression is associated with unfavorable OS and FPS.

GLI1 is a transcription factor and its epigenetic regulative effect on gene expression might be cancer-specific. To support future exploration of the regulative mechanisms of *GLI1* in chemoresistance of gastric cancer, we identified its co-expressed genes and analyzed their enrichment in the KEGG pathway. Among the pathways identified, Pathways in cancer, Proteoglycans in cancer, Cell adhesion molecules (CAMs), and Hedgehog signaling pathway are all related to chemosensitivity of gastric cancer. As a member of the Hedgehog signaling pathway, *GLI1* co-expressed genes are also largely enriched in the PI3K/AKT pathway in gastric cancer.

Activation of the PI3K-AKT pathway is among the most important mechanisms of enhanced chemoresistance in gastric cancer [27,28]. Inhibition of PI3K can suppress propagation of drug-tolerant gastric cancer cell subpopulations enriched by 5-fluorouracil [29] and also strengthen their response to multiple chemotherapeutic reagents [30,31]. *GLI1*-mediated activation of PI3K/AKT pathway was observed in colorectal cancer [32], ovarian cancer [33], and hepatocellular carcinoma [34]. Among *GLI1* co-expressed genes in TCGA-STAD, 30 genes were enriched in the PI3K-AKT pathway (Figures 4, 5, genes in red). However, few studies have reported their association. The known mechanisms of GLI1-mediated activation of the PI3K/AKT pathway is its trans-activating effect on *BCL2* [35,36]. Among the central nodes in the PPI network, several genes have well-characterized influences on chemoresistance in some cancers, including gastric cancer. *BCL2* is a well-known anti-apoptosis gene in multiple cancers [37,38]. The IGF axis-pathway SNPs can influence FOLFOX chemotherapy in patients with advanced gastric cancer [39]. Secreted VEGFC can enhance gastric cancer cell invasion and conferred cisplatin resistance to Rho GDP dissociation inhibitor 2 (RhoGDI2)-overexpressing cells [40]. The expression of NGFR might be associated with chemoresistance in glioblastoma multiforme [41] and is also a potential cancer stem cell marker associated with chemoresistance and metastatic capacity in esophageal squamous cell carcinoma [42]. The mechanisms underlying the co-expressed between *GLI1* and the central nodes in the PPI network and their regulative effects on chemoresistance in gastric cancer are still largely unexplored. These are potential research directions of our future studies.

Conclusions

High *GLI1* expression is associated with unfavorable OS and FPS in patients with gastric cancer. As a member of the Hedgehog signaling pathway, *GLI1* co-expressed genes are also largely enriched in the PI3K/AKT pathway in gastric cancer, which is closely related to chemoresistance. The underlying mechanisms are still largely unexplored and need further study.

Conflict of interest

None.

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