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ORIGINAL ARTICLE

Analyzing the molecular mechanism of the tissue specificity of gastrointestinal stromal tumors by using bioinformatics approaches

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Summary

Purpose: *Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. About 70% of GIST occur in the stomach, 20% in the small intestine and less than 10% in the esophagus. This study aimed to explore the difference of gene expression profile of GIST between different tumor sites.*

Methods: *Microarray data GSE8167 (accession number of the microarray data) were available from Gene Expression Omnibus (GEO) which included 23 gastric and 9 small intestine untreated GIST samples, and then the differentially expressed genes (DEGs) between these samples were identified using t-test. Furthermore, pathway enrichment analysis was performed to these DEGs and one protein-protein interaction network was constructed by STRING. Additionally, BioNet in R was used to establish a sub-network with false discovery rate < 0.001, and genes in this sub-network were further subjected to gene ontology (GO) and pathway analyses.*

Results: *A total 730 genes were differentially expressed between gastric samples and small intestine samples, indicating the tissue specifity of GIST. Pathway analysis suggested these DEGs disturbed ECM-receptor interaction, gap junction and colorectal cancer. Moreover, some nodes (such as PLAT, VEGFC, PGF and CHD7) in the sub-network were significantly enriched in blood vessel development (p=4.58E-06), appendage development (p=9.54E-06) and skeletal system development (p=2.40E-04), respectively. Finally, several DEGs in the sub-network, including VEGFC and PGF, mainly affected pathways in cancer, focal adhesion, bladder cancer and cytokine-cytokine receptor interaction.*

Conclusions: *Our results suggest that molecular mechanisms of GIST originating in different site were different. Our findings are helpful for physicians and researchers to study the tissue specificity of GIST.*

Key words: *differential expressed genes, functional analysis, gastrointestinal stromal tumor, protein-protein interaction network*

Introduction

GISTs are reported to arise from the interstitial cells of Cajal (ICC) and are tumors with connective tissue, such as sarcomas. Generally, less than 10% GISTs are found in the esophagus, 20% in the small intestine and about 70% are found in the stomach [1]. GISTs occur mostly in 50-70-year old people and the signs and symptoms of the disease are gastrointestinal hemorrhage, troubles in swallowing or metastases [2]. Typically, the disease is defined as tumor with mutations of the *KIT* gene or platelet-derived growth factor-alpha (*PDGFRA*) gene [3]. Therefore, there is an urgent need to explore the molecular mechanism of GISTs' initiation and progression in different tissues.

Up to now, with the development of bio-molecular technology, many researchers have investigated the pathogenesis of GISTs. In a previous paper, hypomethylation of SPP1 is discovered as an

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independent prognostic factor for GISTs [4]. Moreover, Ma et al. have found that CTHRC1 acts as a prognostic factor which has the ability to promote invasiveness of GISTs by activating Wnt/PCP-Rho signaling [5]. Additionally, several researchers have demonstrated that the loss of function of succinate dehydrogenase (SDH) is an alternative molecular mechanism of GISTs [6]. Many other papers revealing the pathogenesis of GIST have been published; however, few papers have explored the different mechanism of GISTs of different tumor sites [7,8].

In the present study, microarray data were downloaded and DEGs were identified. Then, the functions of these DEGs were predicted by pathway and GO enrichment analyses. Furthermore, one protein-protein interaction (PPI) network and a sub-network were established by bioinformatics approaches. Importantly, functional analysis was performed to the nodes in the sub-network; therefore, the roles of these genes in GIST tissue specificity were investigated. Our research and findings might provide new insight in the GISTs' pathogenesis and treatment, which may be helpful for physicians and researchers.

Methods

Affymetrix chip data

The Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo/) database in the National Center for Biotechnology Information (NCBI) is currently the largest fully public gene expression resource, which includes 214268 samples and 4500 platforms [9]. GSE8167 data were available from GEO, which included 23 gastric and 9 small intestine untreated GIST samples [10]. Total RNA was extracted from these 32 tumor samples and their expression was analyzed based on GPL570 (HG-U133_Plus_2) Affymetrix Human Genome U133 Plus 2.0 Array.

Data preprocessing and DEGs identifying

The microarray data and annotation files were downloaded, and then GCRMA in Affy was used to preprocess the mRNA expression data [11]. The original CEL file data were transformed to probe-level data, and then converted to gene symbols by perl procedure. Regarding the gene corresponding to several probes, expression values of these probes were averaged to be the expression value of the gene. Then t-test was utilized to identify DEGs between 9 small intestinal and 23 gastric GIST samples and p values were adjusted using Benjamini & Hochberg method [12]. Finally, genes with $|\log_2$ fold change$|$ ($|\log_2$ FC$|$) > 1 and false discovery rate (FDR) < 0.05 were screened out as DEGs.

Functional enrichment analysis

In the present study, DAVID (Database for Annotation, Visualization and Integrated Discovery) was applied to conduct Kyoto encyclopedia of genes and genomes (KEGG) pathway analysis to DEGs. DAVID bioinformatics resource consists of an integrated biological knowledge base and analytic tools aimed at systematically extracting the biological meaning from large gene or protein lists [13]. KEGG is a knowledge base for systematic analysis of gene functions [14]. In our work, the significant KEGG pathways with p<0.05 and Classification Stringency=Medium were selected for further analysis.

PPI network constructing

It has been discovered that functional links between proteins can be inferred from genomic associations between the genes that encode them and the genes are often located in close proximity on the genome [15]. STRING database (http://www.bork.embl-heidelberg.de/STRING/) [16] is a precomputed global resource for the exploration and analysis of these associations. STRING is updated continuously and currently contains 261033 orthologs in 89 fully sequenced genomes. In the present study, STRING 9.0 was used to screen the PPIs with Required Confidence (combined score) > 0.4 and then the PPI network was constructed using Cytoscape [17]. In a network, the degree of a node is the number of connections or edges the node has to other nodes [18]. Moreover, according to Connectivity Degree in PPI network, the nodes with higher degrees than others were selected as Hub genes which may play important roles in the progression of GISTs in different tissues. In our study, nodes with Connectivity Degree not less than 10 were selected as hub genes.

BioNet analysis

As previous papers have reported, the BioNet package provides an extensive framework for integrated network analysis by using R and allows the scoring of the network by a modular scoring function based on signal-noise decomposition of the p value [19,20]. In the present study, a sub-network was screened out based on the PPI network by using BioNet and β uniformly mixed numerical model with FDR<0.001. As a logically visible subdivision of one PPI network, the sub-network may be the core of the PPI network, which could represent the function of network. Then the nodes with Connectivity Degree not less than 2 were selected. Moreover, GO and KEGG pathway enrichments were conducted to the sub-network. GO terms are significantly overrepresented in a set of genes from three aspects, including cellular component (CC), molecular function (MF) and biological process (BP) [21]. In our work, the significant GO BP terms were selected with p<0.05 and enrichment score>3.0. Further, remarkable KEGG pathways (p<0.05) were identified.

Results

DEGs indentifying

By using a series of bioinformatics approaches, the DEGs between 9 small intestinal and 23 gastric

GIST samples were screened out. Compared with small intestinal samples, a total 354 and 376 genes were up-regulated and down-regulated in gastric samples, respectively.

KEGG pathway analysis for DEGs

After the DEGs were identified, their functions were predicted by using KEGG pathway analysis. Based on the criteria of p<0.05 and Classification Stringency = Medium, the up-regulated genes, including LAMA2, TNN, ADCY5 and PDGFRA, were mainly enriched in ECM-receptor interaction (p=0.00481) and Gap junction (p=0.025787), while the down-regulated genes, such as MYC, FZD3, CYCS and PIK3CG, significantly disturbed colorectal cancer (p=0.039443) (Table 1).

PPI network

By using STRING and Cytoscape, a PPI network was constructed, including 378 nodes and 780 PPIs. Hub nodes with connectivity degree not less than 10 were selected and listed in Table 2. FGF2, MYC, TGFBI, CD34, HDAC1 and SDC2 were remarkable nodes with connectivity degree not less than 20. These genes may play important roles in determining tissue specificity of GIST.

Table 1. The significant pathways enriched by DEGs with p <0.05

DEGs	*Category*	*Term*	*Description*	*Count*	*p value*	*Genes*
Up	KEGG	hsa04512	ECM-receptor interaction	7	0.00481	LAMA2, TNN, AGFN, THBS1, COL4A6, SDC2, SDC3
Up	KEGG	hsa04540	Gap junction	6	0.025787	ADCY5, PDGFRA, TUBA4A, GUCY1A3, GUCY1B3, PLCB1
Down	KEGG	hsa05210	Colorectal cancer	6	0.039443	PIK3CG, FZD10, CYCS, FZD3, FZD5, MYC

DEGs and KEGG represent different expressed genes and Kyoto encyclopedia of genes and genomes, respectively

Table 2. Hub nodes with Connectivity Degree not less than 10 in protein-protein interaction network

Gene	*Degree*	*Gene*	*Degree*	*Gene*	*Degree*	*Gene*	*Degree*
FGF2	29	AR	17	KITLG	13	TIPIN	11
MYC	26	SDC3	16	VEGFC	12	GPC4	10
TGFBI	22	PLCB1	16	BUB1B	12	EDN3	10
CD34	22	PIK3CG	16	KIAA0101	12	INTU	10
HDAC1	20	COL18A1	15	THBS1	12	TK1	10
SDC2	20	MSH2	15	COL4A4	11	VCAM1	10
VIM	19	NPY	14	TYMS	11	MC4R	10
ADCY5	19	ELN	13	PDGFRA	11	CYCS	10
MMP2	17	ZWILCH	13	ATAD2	11	ADM	10

Table 3. The significant nodes in sub-network with Connectivity Degree not less than 2

Gene	*Degree*	*Gene*	*Degree*	*Gene*	*Degree*
TGFBI	11	COL4A5	4	PPA1	2
HDAC1	10	MYB	4	PDGFA	2
CD34	8	COL22A1	4	CHGA	2
VIM	7	NPY	4	ANTXR2	2
COL4A4	6	TWIST1	3	PGF	2
PDGFRA	5	BMPR1A	3	NKX3-2	2
MMP2	5	HDAC9	3		
RBBP4	5	EPS15	3		
SKI	5	VEGFC	3		
COL4A6	4	PLAT	2		
COL16A1	4	EMILIN1	2		

Sub-network analysis

As there were so many interactions in the PPI network, it was hard for us to extract the most useful information. Therefore, we further mined the core of the PPI network. A sub-network was constructed and visualized by BioNet package and Cytoscape with FDR<0.001, respectively. In the sub-network, compared to small intestinal GIST, a total 25 up- and 18 down-regulated genes in gastric GIST samples were identified (Figure 1). Additionally, the nodes with connectivity degree not less than 2 were selected which included TGFBI, HDAC and CD34 (Table 3).

GO analysis of sub-network

With p<0.05 and enrichment score>3.0, a total of three clusters were selected (Table 4). In cluster 1 (Enrichment Score = 3.71), the most significant BP term was blood vessel development (p=4.58E-06) and 8 DEGs, including PLAT, VEGFC and PGF, were discovered enriched in it. In cluster 2 (Enrichment Score=3.61), appendage development was the most remarkable BP term (p=9.54E-06) with CHD7, SKI and NR2F2 disturbed this term. Additionally, in cluster 3 (Enrichment Score=3.34), 7 DEGs, such as CHD7, TWIST1 and NKX3-2, were enriched in the most significant BP term, skeletal system development (p=2.40E-04).

KEGG pathway analysis of sub-network

The nodes in the sub-network were found mainly disturbed in 4 KEGG pathways, including pathways in cancer, focal adhesion, bladder cancer and cytokine-cytokine receptor interaction (Table 5). DEGs, such as COL4A4, VEGFC, PGF and MMP2, were the genes enriched in these 4 pathways.

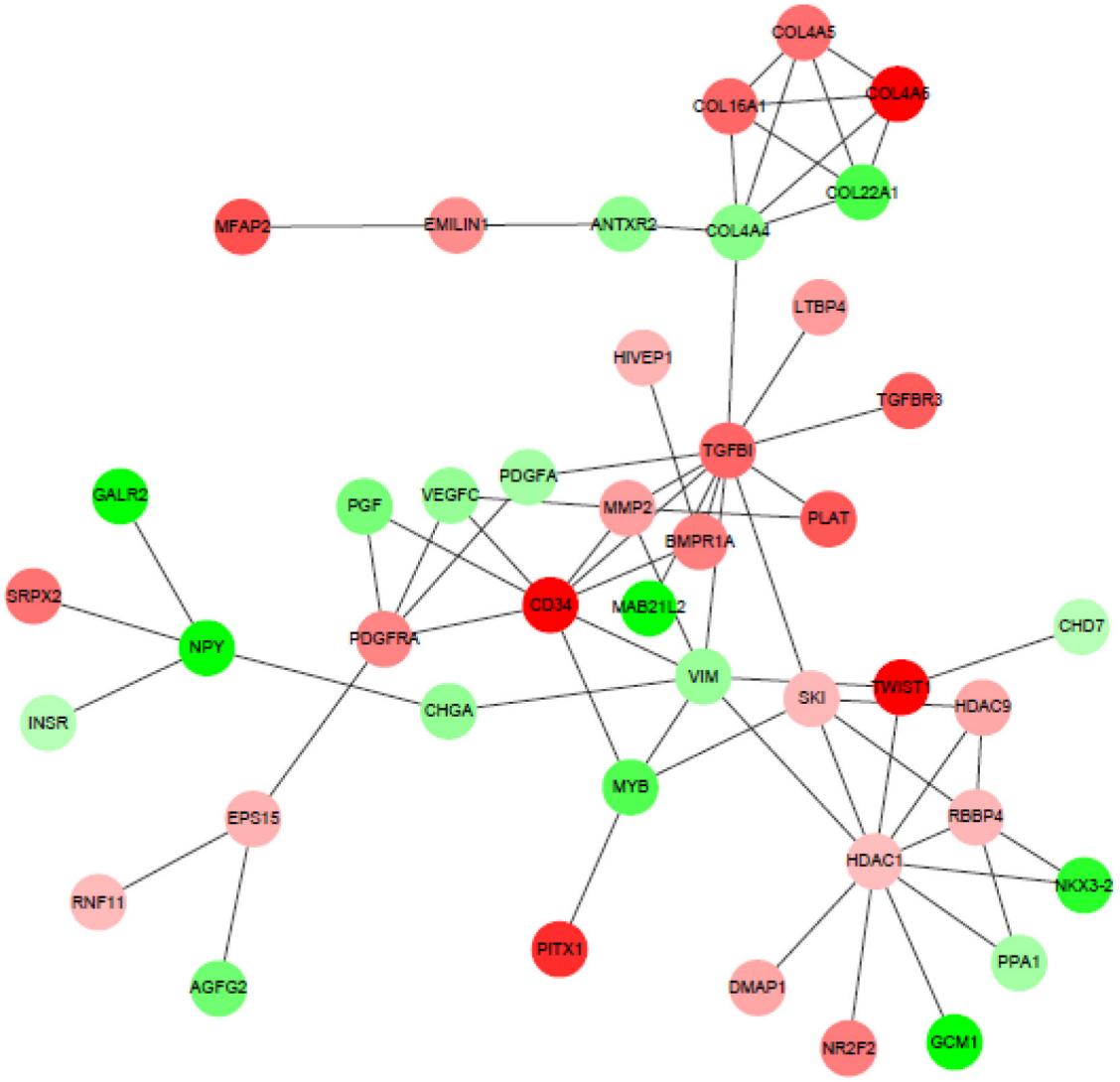

Figure 1. The sub-network in protein-protein network. Red and green circles are up- and down-regulated genes, respectively. The nodes with darker color represent the more significant differential expression.

Table 4. The significant biological process terms enriched by nodes in sub-network (p < 0.05)

Category	*Term*	Description	*Count*	*p value*	Genes
Cluster1	*Enrichment Score:3.7128781254738166*				
BP	GO:0001568	blood vessel development	8	4.58E-06	PLAT, VEGFC, PGF, et al.
BP	GO:0001944	vasculature development	8	5.38E-06	PLAT, VEGFC, PGF, et al.
BP	GO:0070482	response to oxygen levels	5	6.34E-04	PLAT, PGF, PDGFA, MMP2, PDGFRA
BP	GO:0048514	blood vessel morphogenesis	5	0.002803	PLAT, VEGFC, PGF, PDGFA, NP2F2
BP	GO:0001666	response to hypoxia	4	0.006224	PLAT, PGF, PDGFA, MMP2
Cluster 2	*Enrichment Score:3.6051435205357927*				
BP	GO:0048736	appendage development	6	9.54E-06	CHD7, SKI, NR2F2, et al.
BP	GO:0060173	limb development	6	9.54E-06	CHD7, SKI, NR2F2, et al.
BP	GO:0035137	hindlimb morphogenesis	4	5.08E-05	CHD7, PITX1, BMPR1A, et al.
BP	GO:0035108	limb morphogenesis	5	1.65E-04	CHD7, SKI, PITX1, et al.
BP	GO:0035107	appendage morphogenesis	5	1.65E-04	CHD7, SKI, PITX1, et al.
BP	GO:0048598	embryonic morphogenesis	7	1.95E-04	CHD7, SKI, TWIST1, et al.
BP	GO:0001501	skeletal system development	7	2.40E-04	CHD7, NKX3-2, TWIST1, et al.
BP	GO:0030326	embryonic limb morphogenesis	3	0.024743	CHD7, SKI, TWIST1
BP	GO:0035113	embryonic appendage morphogenesis	3	0.024743	CHD7, SKI, TWIST1
Cluster 3	*Enrichment Score:3.3887502359292947*				
BP	GO:0001501	skeletal system development	7	2.40E-04	CHD7, NKX3-2, TWIST1, et al.
BP	GO:0060324	face development	3	4.16E-04	CHD7, PDGFRA, MMP2
BP	GO:0060322	head development	3	6.84E-04	CHD7, PDGFRA, MMP2

GO: gene ontology, BP: biological process

Table 5. The significant pathways disturbed by nodes in sub-network (p < 0.05)

Category	*Term*	*Description*	*Count*	*p value*	*Genes*
KEGG	hsa05200	Pathways in cancer	8	1.79E-05	COL4A4, VEGFC, HDAC1, et al.
KEGG	hsa04510	Focal adhesion	6	1.99E-04	COL4A4, VEGFC, PGF, et al.
KEGG	hsa05219	Bladder cancer	3	0.006533	VEGFC, PGF, MMP2
KEGG	hsa04060	Cytokine-cytokine receptor interaction	4	0.038827	VEGFC, PDGFA, PDGFRA, EMPR1A

KEGG represent Kyoto encyclopedia of genes and genomes

Discussion

GISTs are the most common mesenchymal tumors of the gastrointestinal tract, which rarely occur outside the digestive tract. In our study, the underlying mechanism of GIST tissue specificity was explored with bioinformatics methods. Firstly, a total 730 DEGs were identified between 9 small intestinal and 23 gastric GIST samples, and then these genes were discovered mainly enriched in ECM-receptor interaction, gap junction and colorectal cancer pathways. Moreover, FGF2, MYC, TGFB1 and CD34 were hot nodes in the PPI network. Interestingly, TGFB1 and CD34 were also hub genes in the sub-network. Finally, the genes in the sub-network significantly disturbed blood vessel development, appendage development and skeletal system development, as well as 4 KEGG pathways. Our study focused on the potential pathogenesis of GISTs in different tissues based on a series of molecular results.

Firstly, between 9 small intestinal and 23 gastric GIST samples, a total 354 and 376 genes were up- and down-regulated in gastric GIST samples, respectively. Then the up-regulated genes, such as LAMA2, TNN and ADCY5, were discovered significantly enriched in ECM-receptor interaction and gap junction. The interactions between extracellular matrix (ECM) and cells have the ability to regulate cellular activities, such as apoptosis, migration, proliferation, adhesion and differentiation [22]. A gap junction directly connects the cytoplasm of two cells, allowing various molecules and ions to pass freely between cells [23]. The genes enriched

in these two pathways were up-regulated, suggesting that the functions of these pathways were highlighted in gastric GIST samples, which may prompt GIST initiation and progression in different tissues. Additionally, down-regulated genes, including Myc, FZD5 and CYCS remarkably disturbed the colorectal cancer pathway. This result indicates that the colorectal pathway was suppressed in gastric GIST samples.

Then, the hub nodes in the PPI and sub-network were selected. In detail, fibroblast growth factor 2 (FGF2), Myc, TGFB1 (transforming growth factor beta 1) and CD34 with higher degrees than others in the PPI network were selected, suggesting these genes play important roles in GIST differentiation. Otherwise, TGFB1, histone deacetylase 1 (HDAC1) and CD34, were hub nodes in the sub-network. These genes, especially TGFB1 and CD34, may play important roles in gastric GIST differentiation and progression. Serum TGFB1 level was found elevated in breast cancer patients and had a favorable prognostic value [24]. As a cell surface glycoprotein, CD34 functions as a cell-cell adhesion factor, mediating the attachment of stem cells to bone marrow or to stromal cells [25]. The aforementioned findings have explored the roles of TGFB1 and CD34 in several diseases [24,25], however, few reported their roles in GISTs. Therefore, our findings provide a new insight in the functions of these genes in GIST differentiation and progression.

Furthermore, the DEGs in the sub-network were found remarkably enriched in blood vessel development, appendage development and skeletal system development. In detail, DEGs, such as plasminogen activator (PLAT), vascular endothelial growth factor C (VEGFC) and placental growth factor (PGF) mainly disturbed blood vessel development. Many researchers have discovered that (PLAT) inhibitor-1 is a therapeutic target which could inhibit angiogenesis, malignancy and tumor growth in humans [26]. VEGFC is found abnormally expressed in prostate cancer [27]. PGF could inhibit tumor growth and angiogenesis, which also has a significant vascular remolding effect [28]. These genes have roles in tumor growth which is consistent with our results. Meanwhile, CHD7, SKI and NR2F2 mainly disturbed appendage development. Chromodomain-helicase-DNA-binding protein 7 (CHD7) was also discovered enriched in the skeletal system development. As an ATP-dependent chromatin remodeler, CHD7 mutation could induce the CHARGE syndrome [29]. The up- or down-regulation of these genes may disturb the GO BP terms, inducing the tissue specificity of GISTs.

Finally, genes in the sub-network were found enriched in 4 KEGG pathways, including pathways in cancer, focal adhesion, and bladder cancer and cytokine-cytokine receptor interaction. Several genes, such as PDGFA, VEGFC and PGF were discovered abnormally expressed in these pathways. Focal adhesion, which is a specific type of large macromolecular assemblies, could mediate the regulatory effects of ECM adhesion on cell behavior [30]. Cytokine-cytokine receptor interaction has been reported to participate in the assembly of the dodecamer complex, which could link cytokine binding to receptor activation [31]. These results suggest that the abnormal expression of genes may disturb the pathways, prompting GIST differentiation.

Our present study predicted the potential mechanism of GIST tissue specificity by using a series of bioinformatics methods. Our findings suggest that the molecular mechanisms of these GISTs from different tumor sites might be different. Genes involved in ECM-receptor interaction and gap junction were differently expressed, which might be critical in the tissue specificity of GISTs. However, there is a need to conduct further research to verify these results.

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Conflict of interests

The authors declare no conflict of interests.

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