Original Article

Cadherin dysregulation in gastric cancer: insights into gene expression, pathways, and prognosis

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Background: The Cadherin gene family holds immense significance in maintaining the integrity and functionality of stomach tissues, playing crucial roles in cell-cell adhesion, cell migration and differentiation. Dysregulation of cadherin expression and function has been closely associated with various gastric diseases, particularly gastric cancer (GC). Understanding the regulation and clinical implications of cadherin genes in GC is essential to improve our knowledge and to identify new potential prognostic markers and therapeutic targets.

Methods: In this study, we provide an overview on the role of cadherin family genes in GC using bioinformatics analysis. We analyzed the expression, mutational status, and prognostic value of these genes based on available public datasets. Our methodology involved data mining, differential expression analysis, functional enrichment analysis, and survival analysis to explore the association between cadherin gene expression and clinical outcomes in GC patients. Additionally, we investigated the relationship between cadherin expression and immune cell infiltration to gain insights into the tumor microenvironment's role in GC progression.

Results: Our bioinformatics analysis revealed significant differential expression of 16 cadherin genes in GC samples compared to normal tissues. Approximately up to 52% of the analyzed cancer samples exhibited genomic alterations in these cadherins, indicating their potential relevance in GC development. Functional enrichment analysis demonstrated that these differentially expressed cadherins were closely associated with critical cellular processes, including cell adhesion and immune-modulation. Remarkably, lower expression levels of most cadherin genes were linked to improved prognosis in GC patients, suggesting their potential importance as valuable prognostic biomarkers.

Conclusions: The findings deriving from our comprehensive study provide important insights into the dysregulation of cadherin genes in GC and their impact on gene expression, molecular pathways, and prognosis. The associations with clinical outcomes and immune cell infiltration highlight the potential role of cadherin genes as prognostic biomarkers and therapeutic targets in GC.

Keywords: Cadherin genes; gastric cancer (GC); gene expression; biomarkers; prognosis

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Introduction

Stomach adenocarcinoma (STAD) is the fifth most common cancer globally and the third leading cause of cancer-related deaths (1). The incidence of STAD varies geographically, with the highest rates seen in Eastern Asia and Latin America (2). Risk factors for STAD include infection with the bacterium *Helicobacter pylori*, a diet high in salt and processed foods, smoking, and a family history of the disease (3-7). Clinical symptoms of STAD may include abdominal pain, nausea, vomiting, weight loss, and anemia (8,9). The current treatment options for STAD include surgery, chemotherapy, targeted therapy, immunotherapy and radiation therapy (10-12). However, the effectiveness of these treatments depends on the stage of the disease at diagnosis, and the prognosis for patients with advanced stage disease remains poor.

Cadherin family genes are a group of transmembrane proteins that play crucial roles in cell-cell adhesion, tissue morphogenesis, and embryonic development (13-15). Cadherins are expressed in a wide variety of tissues, including the stomach, and are known to mediate cell-cell interactions that are essential for the maintenance of tissue architecture (16). Dysregulation of cadherin gene expression and function has been implicated in the development and progression of many cancers, including STAD (17-22). Aberrant expression or loss of function of cadherins can result in altered cell adhesion, migration, and invasion, leading to increased tumor cell dissemination and metastasis. Cadherins are known to promote as well as inhibit cancer growth and can function both as oncogenes and tumor suppressors (14,23,24). For example, E-cadherin, a major cell-cell-adhesion molecule, functions as a tumor suppressor and its downregulation results in metastasis of tumor cells (24). Further, expression of wild-type E-cadherin was shown to significantly inhibit the growth of colorectal tumor cell line (25). In contrast, proteolysis of E-cadherin generates fragments that promote tumor growth, survival, and motility, indicating cleavage of E-cadherin transforms this tumor suppressor into an oncogenic factor in certain cancer types (23). Such dual roles for other cadherins in cancer have been reviewed in detail elsewhere (14). Additionally, cadherin family genes are attractive targets for cancer therapy, as they are important in tumor progression and are often differentially expressed in cancer cells compared to normal cells (26). Thus, studying the expression, mutational status, and prognostic potential role of cadherin family genes in STAD is critical for identifying new biomarkers and therapeutic targets that may improve patient outcomes.

Several studies investigated the relationship between dysregulation of cadherin gene expression and STAD (27-30). For example, Long *et al.* reported that high *CDH17* expression was associated with more advanced stages (III–IV *vs.* I–II), higher histologic grades (3–4 *vs.* 1–2), increased invasion grades (T3–4 *vs.* T1–2), and lymph node metastasis (positive *vs.* negative) in GC (27). In other studies, Hansford *et al.* evaluated the risks of GC in individuals with germline mutations in the E-cadherin (*CDH1*) gene. They identified 31 different pathogenic *CDH1* mutations among 34 patients with GC. Based on their findings, the cumulative lifetime incidence of GC in individuals with germline *CDH1* mutations at the age of 80 was estimated to be 70% for males and 56% for females (28). Donner *et al.* reported that mutations in the *CDH1* gene are found in 30% of hereditary diffuse gastric cancer (HDGC) families and a germline truncating mutation in the gene encoding α-E-catenin (*CTNNA1*) was discovered in some families with HDGC (29). Lobo *et al.* also found that germline variants in the *CTNNA1* gene are significantly associated with HDGC (30). In addition, several studies have explored the relationship between cadherin gene expression and patient survival, with different results. Although some studies have reported that decreased expression of cadherin genes is associated with poor outcomes (31,32), others have found poorer outcomes

Highlight box

Key findings

- Cadherin dysregulation plays a significant role in gastric cancer (GC) development and progression, with potential as biomarkers and therapeutic targets.

What is known and what is new?

- Dysregulation of cadherin expression and function has been associated with various gastric diseases, particularly GC. However, the specific mechanisms and prognostic significance of cadherin dysregulation in GC remain unclear.
- In this study, the expression, mutational status, and prognostic potential of cadherin family genes in stomach adenocarcinoma through bioinformatics analysis were investigated.

What is the implication, and what should change now?

- This study provides comprehensive insights into the dysregulation of cadherin genes in GC and their impact on gene expression, pathways, and prognosis. These findings highlight the potential role of cadherin genes as prognostic markers and therapeutic targets in GC.

in case of increased expression of cadherin genes (27). Overall, the existing literature suggests that cadherin family genes are key players in the development and progression of STAD, and further investigation is warranted to fully understand their clinical significance.

Despite the existing literature on cadherin family genes in STAD, there are still several gaps in our knowledge that need to be addressed. For instance, it is not clear how many cadherin family members are associated with the pathogenesis of STAD, which cadherin family member has the greatest effect on development of STAD, and what is the molecular mechanism through which cadherin genes are involved in STAD progression. To fill these gaps, our study aimed to investigate the expression, mutational status, and prognostic role of cadherin family genes in STAD using bioinformatics analysis. Specifically, we analyzed differential expression, mutations and copy number variations (CNVs), survival rate, microRNA (miRNA) targeting cadherin, and immune cell infiltration in STAD tissue samples to identify potential biomarkers and therapeutic targets for this disease, as well as contribute to a better understanding of the function of cadherin family genes in this disease. We present this article in accordance with the STREGA reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-700/rc).

Methods

Cadherin family genes and estimating their differential expression

The cadherin family of genes were collected using the HGNC portal (https://www.genenames.org/data/genegroup/#!/group/16). This superfamily consists of three subfamilies, including major cadherins, protocadherins, and cadherin-related. The first 2 subfamilies are further subdivided into specific groups. The differential expression of cadherins between STAD and normal tissues were obtained from Gene Expression Profiling Interactive Analysis 2 (GEPIA2; http://gepia2.cancer-pku.cn/) (33), which applies two different methods [analysis of variance (ANOVA) and limma] for the differential expression calculation of genes, through the use of The Cancer Genome Atlas (TCGA) (34) and Genotype Tissue Expression (GTEx) (35) RNA-seq data. We selected cadherins that were significantly differentially expressed between STAD and normal samples with a $|\log_2$ fold change (FC) $\geq 1|$ and Benjamini and Hochberg (B&H) corrected P value <0.05. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Cadherin-correlated genes and functional analysis

To understand the functions of the selected cadherins, we identified cadherin-coexpressed genes using GEPIA2, which considers tumor RNA sequencing expression data from the TCGA project (34) and analyzes them using standard processing pipelines. The 'Similar Genes Detection' program (http://gepia2.cancer-pku.cn/#similar) was used to obtain the correlated genes. This tool provided the top 1,000 genes with a similar expression pattern to the cadherin genes along with their correlation coefficient values calculated by Pearson correlation method. The correlated genes were used for performing functional analysis including Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway and Gene Ontology biological process (GO-BP) enrichment through WebGestalt (http://www.webgestalt.org/) (36). The annotations with B&H corrected P<0.1 were considered statistically significant. Hiplot (https://hiplot.cn/) (37) was used to visualize the pathway and GO-BP results.

Analysis of mutations and CNVs

Genomic aberrations, including single nucleotide variants, CNVs, and structural variants for differentially expressed cadherin genes were analyzed using cBioPortal (https://www.cbioportal.org/) (38). This portal provides a web resource for exploring, visualizing, and analyzing multidimensional cancer genomics data and uses TCGA as one of the sources for cancer omics data analysis. We used all TCGA GC samples (n=440) for the analysis of genomic aberrations. Of these, 436 samples have mutation and structural variant data, whereas 438 samples have copy number alteration data. Furthermore, muTarget (https://www.mutarget.com/) (39) was used to identify genes that are differentially expressed between cadherin-mutated and cadherin-wildtype GC samples. muTarget combines RNA-sequencing and mutation data to identify gene expression changes related to a gene mutation. For GC, there were 372 samples that had both messenger RNA (mRNA) expression and mutation data in muTarget. The tool was queried with each selected cadherin with the following filters: 'Tumor type(s): Gastric cancer' 'Mutation type: All somatic mutations', 'P value cutoff: 0.01', 'Fold change cutoff: 2', 'FDR cutoff: 5%', and 'Exclude genes with a mean expression below 100' to identify genes that are

differentially expressed between cadherin-mutated and cadherin-wildtype GC samples. The cadherins mutated in less than 10 patient samples were not considered for the analysis.

Survival analysis

We used the Kaplan-Meier Plotter (https://kmplot.com/) (40,41) and the University of Alabama at Birmingham Cancer data analysis Portal (UALCAN; http://ualcan.path.uab.edu/index.html) (42) databases to assess the association between differentially expressed cadherins and overall survival (OS) of GC patients. Both resources integrate survival and mRNA expression data from TCGA. Additionally, UALCAN calculates effect of mRNA expression and race or gender of patients on their survival. The associations with a P<0.05 were considered statistically significant.

miRNA analysis

We used the miRDB database (https://mirdb.org/) (43) to predict miRNAs targeting the differentially expressed cadherins. In miRDB, the targets have been predicted by MirTarget tool, which was developed by analyzing thousands of miRNA-target interactions from high-throughput sequencing experiments. The experimentally verified interactions between miRNA-cadherin were obtained from the miRTarBase (https://mirtarbase.cuhk.edu.cn) (44). Furthermore, differentially expressed miRNAs between GC and normal samples were identified based on TCGA-miRNA seq data using dbDEMC database v3.0 (https://www.biosino.org/dbDEMC/) (45). This database uses the limma method (46) to identify differential expression of miRNAs between cancer and normal samples. The miRNAs with an adjusted P<0.05 (B&H correction) and an absolute FC of 1.5 were considered significant. A network between the selected cadherins and corresponding miRNAs was constructed using Cytoscape 3.9.1 (47). Only differentially expressed miRNAs were considered for network construction. Furthermore, the correlation between miRNA expression and their corresponding cadherin targets was assessed by Pearson correlation method.

Immune cell infiltration analysis

We performed immune cell infiltration analysis using ImmuCellAI portal (http://bioinfo.life.hust.edu.cn/ImmuCellAI) (48). TCGA RNA-seq data (TPM values) for stomach cancer and normal patients were uploaded onto ImmuCellAI and abundance of 24 different immune cell types were estimated in each group using the single-sample gene set enrichment analysis (ssGSEA) algorithm. Then, the significance of differential immune cells infiltration between cancer and normal tissues were calculated using unpaired *t*-test, and values with P<0.05 were considered significant. Further, correlation between the expression of cadherin genes and abundance of immune cell types were derived using Pearson correlation method. The correlation analysis was performed using corrplot R package (https://github.com/taiyun/corrplot) and the correlation R values with P<0.05 were considered significant.

Results

Cadherin genes are differentially expressed between STAD and normal samples

We used the HGNC portal to collect a total of 125 cadherin family of genes. These belonged to seven different groups, namely 7D cadherins (n=2), cadherin-related (n=17), CELSR cadherins (n=3), clustered protocadherins (n=64), desmosomal cadherins (n=7), major cadherins (n=2), non-clustered protocadherins (n=12), type I classical (n=5), and type II classical cadherins (n=13). Further, we used RNA-seq data to identify cadherins that showed significant differential expression between stomach cancer (TCGA data, n=408) and normal (TCGA + GTEx data, n=211) samples. Of 125 cadherins, 16 genes were identified to be significantly different in their expression with $|\log_2 FC > 1|$ and false discovery rate (FDR)-P<0.05 (*Table 1*). Among these, 4 belonged to the cadherin-related group, 3 each belonged to type I classical cadherins and non-clustered protocadherins, 2 belonged to desmosomal cadherins, and 1 each belonged to the type II classical, major, 7D cadherin, and clustered protocadherin groups. It is noteworthy that all the cadherins except *CDH2* were upregulated in GC compared to normal controls (*Table 1*). Furthermore, although *PCDHGA10*, *PCDH17*, and *CDH2* were significantly different between cancer and normal samples, their relative expression was low [median transcripts per million (TPM) <5] in both these sample groups (*Figure 1A*). *CDH17* was highly upregulated in STAD, with a nearly 5-fold difference ($\log_2$ scale) between the tumor and normal samples (*Figure 1B*). The other cadherins that were highly upregulated with a $\log_2 FC$

Table 1 Cadherins differentially expressed between stomach adenocarcinoma and normal tissue samples

Gene symbol	Gene name	Cadherin group	Log_2 fold change (limma)	Adjusted P value (limma)
CDH1	Cadherin 1	Type I classical	1.598	1.12E–48
CDH11	Cadherin 11	Type II classical	2.281	2.44E–57
CDH13	Cadherin 13	Major cadherin	1.719	1.95E–46
CDH17	Cadherin 17	7D cadherin	4.908	3.79E–74
CDH2	Cadherin 2	Type I classical	–1.225	3.84E–32
CDH3	Cadherin 3	Type I classical	3.137	2.19E–97
CDHR2	Cadherin related family member 2	Cadherin related	1.614	7.73E–14
CDHR5	Cadherin related family member 5	Cadherin related	3.544	4.82E–67
CLSTN1	Calsyntenin 1	Cadherin related	1.437	2.91E–66
DSC2	Desmocollin 2	Desmosomal	2.008	2.96E–34
DSG2	Desmoglein 2	Desmosomal	2.645	1.5E–100
FAT1	FAT atypical cadherin 1	Cadherin related	1.953	3.6E–98
PCDH1	Protocadherin 1	Non-clustered protocadherin	1.518	4.43E–46
PCDH17	Protocadherin 17	Non-clustered protocadherin	1.192	7.76E–60
PCDH18	Protocadherin 18	Non-clustered protocadherin	1.01	7.88E–30
PCDHGA10	Protocadherin gamma subfamily A, 10	Clustered protocadherin	1.079	3.39E–34

>2 included *CDHR5*, *DSC2*, *DSG2*, *CDH3*, and *CDH11*. The only downregulated cadherin, *CDH2* was found to be 1.2-fold lower in cancer patients compared to normal controls (*Table 1* and *Figure 1B*).

Cadherin-correlated genes in GC are associated with adhesion and cancer-related pathways

Genes with similar expression pattern are commonly used to infer the functional roles of their partners. Hence, we first identified genes that are correlated (*Pearson* correlation coefficient ≥0.25) with the differentially expressed cadherins identified by us in GC compared to normal samples, and then used those correlated genes for functional enrichment analysis. As expected, the correlated genes corresponding to most of the cadherins were involved in cancer, adhesion, extracellular matrix (ECM)-receptor interaction, or junction related pathways (all pathways were significant with *FDR* P<0.1). *Figure 2* shows selected pathways enriched by the genes correlated with differential cadherins. A complete list of pathways can be found in Supplementary file available at https://cdn.amegroups.cn/static/public/jgo-23-700-1.xlsx. *CDH13*- followed by *PCDH1*-correlated genes were enriched in most KEGG pathways (n=66 and 65, respectively). Focal adhesion and ECM-receptor interaction were the top 10 pathways for *CDH11*-, *CDH13*-, *PCDH17*-, *PCDH18*-, and *PCDHGA10*-correlated genes, indicating that these genes are directly involved in adhesion or junction related functions. *CDH1*-correlated genes were mainly involved in endocytosis, and autophagy/mitophagy related pathways. *CDH17*- and *CDHR2*-correlated genes were involved in metabolic pathways, such as tricarboxylic acid cycle (TCA) cycle, fructose and mannose metabolism, and propanoate metabolism. *CDHR5*-correlated genes were primarily enriched in fat digestion and glucose metabolism pathways. *FAT1*-correlated genes were involved in apoptosis, RNA transport, and splicing pathways. The GO-BP analysis results were in similar lines to that of pathway enrichment (all annotations were significant with FDR P<0.1). For instance, *CDH1*-correlated genes were enriched for transport and vesicular organization related BPs. Similarly, *CDH11*- and *CDH13*-correlated genes were involved in adhesion and tissue migration-related processes. Supplementary file available at https://cdn.amegroups.cn/

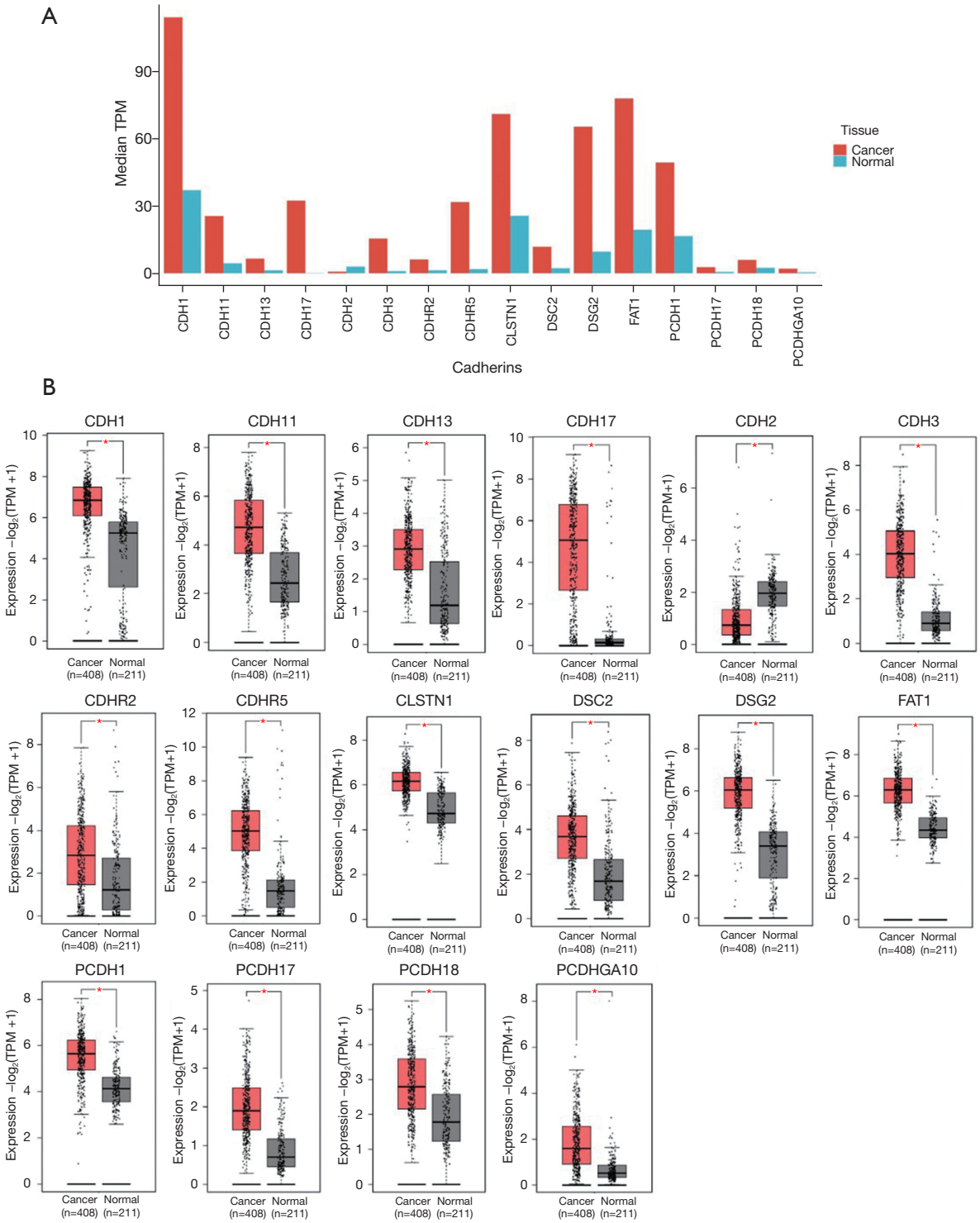

Figure 1 Differentially expressed cadherins between stomach adenocarcinoma and normal samples. The cadherin genes are differentially expressed with a $|\log_2 FC| > 1$ and adjusted $P<0.05$. (A) Barplot indicating the differences in median TPM of differentially expressed cadherins in cancer and normal samples. (B) Boxplots indicating the distribution of expression values of cadherins in stomach adenocarcinoma and normal samples. The boxplots were generated by querying GEPIA2 database with individual cadherin genes and by selecting "STAD" as the dataset (http://gepia2.cancer-pku.cn/#analysis). *, significant difference. TPM, transcripts per million; FC, fold change; STAD, stomach adenocarcinoma; n, number of samples.

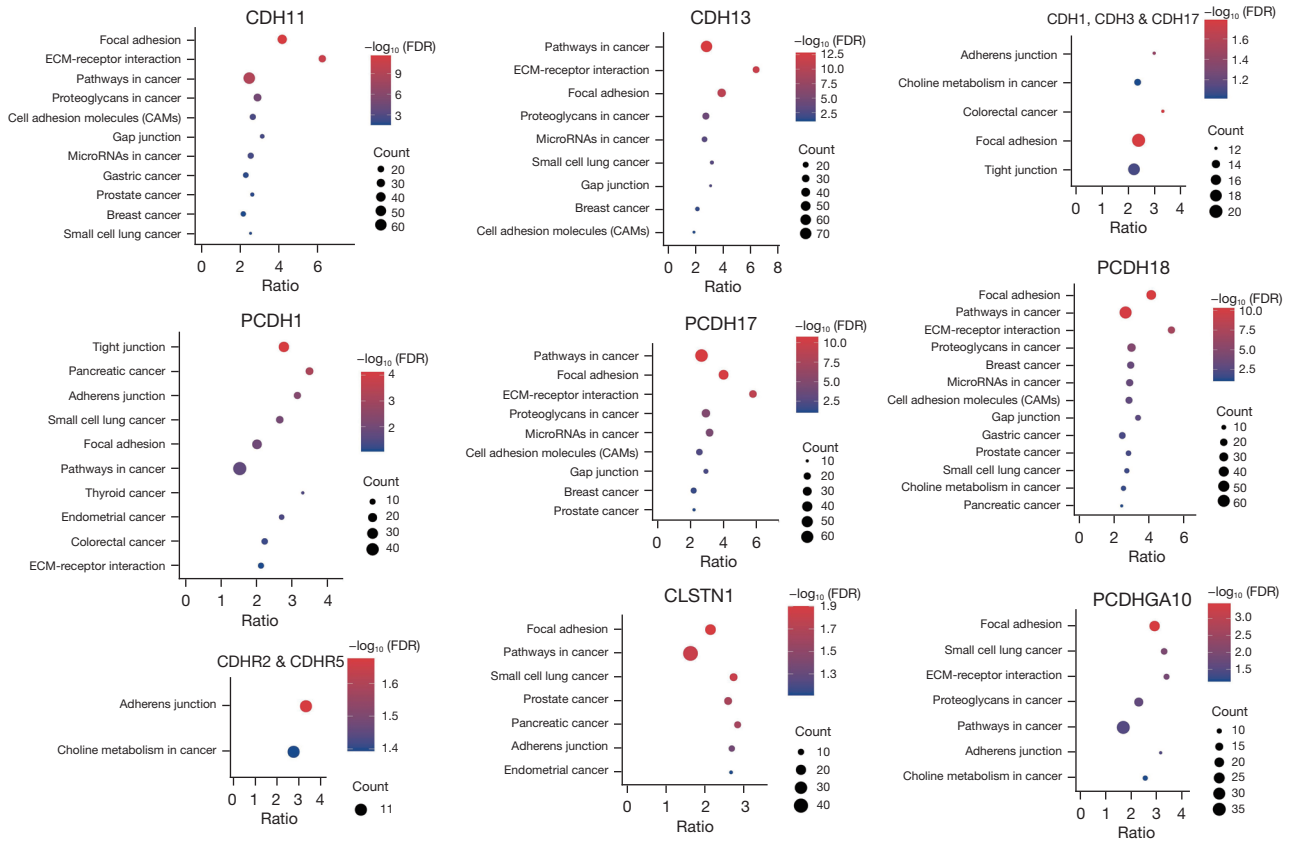

Figure 2 KEGG pathways significantly enriched by cadherin-correlated genes in gastric cancer. The genes correlated with differentially expressed cadherins between gastric cancer and normal tissues were obtained from GEPIA2 based on TCGA RNA-seq expression data. Pathway analysis of the correlated genes was performed using WebGestalt. Only pathways known to be well-annotated in the context of cadherin function (i.e., related to cancer, adherens junction, adhesion, and ECM-receptor interaction) are shown in the bubble charts. For genes *CDH1*, *CDH3*, and *CDH17*, and *CDHR2* and *CDHR5*, the pathways are shown in the same plot due to the lesser number for each of these genes. No such well-annotated pathways were found for *CDH2*-, *DSC2*-, *DSG2*-, and *FAT1*-correlated genes with the considered threshold (FDR P<0.1), hence these genes are not shown in the figure. A complete list of significant pathways for all 16 genes has been provided in Supplementary file available at https://cdn.amegroups.cn/static/public/jgo-23-700-1.xlsx. ECM, extracellular matrix; FDR, false discovery rate; KEGG, Kyoto Encyclopedia of Genes and Genomes, TCGA, The Cancer Genome Atlas.

static/public/jgo-23-700-2.xlsx represents the list of GO-BPs significantly enriched by cadherin-correlated genes.

Cadherins are altered in GC patients and affect the expression of other genes

In TCGA, a total of 440 GC patients have data on genomic aberrations. Of these, 436 patients have mutation data, 438 patients have CNV data, and 436 patients have SV data. We investigated the genomic aberrations in cadherins that are significantly differentially expressed between STAD and normal samples. Our results demonstrated that the 16 selected cadherins were altered across 227 (~52% of the profiled) GC patients. *Figure 3A* shows the patients with mutations or CNVs/SVs in at least 1 of the 16 cadherins considered for analysis. Protocadherin 17 (*PCDH17*) was found to be the most commonly altered cadherin gene in GC (54 of 440 samples =12.3%) followed by Fat atypical cadherin 1 (*FAT1*) (53 of 440 samples =12%), whereas *PCDHGA10* was the least commonly altered cadherin in GC patients (12 of 440 =2.7%). Furthermore, we analyzed the rate of single nucleotide variations (SNVs) and CNVs/structural variations (SVs) independently and found that SNVs are more common across all the cadherins analyzed

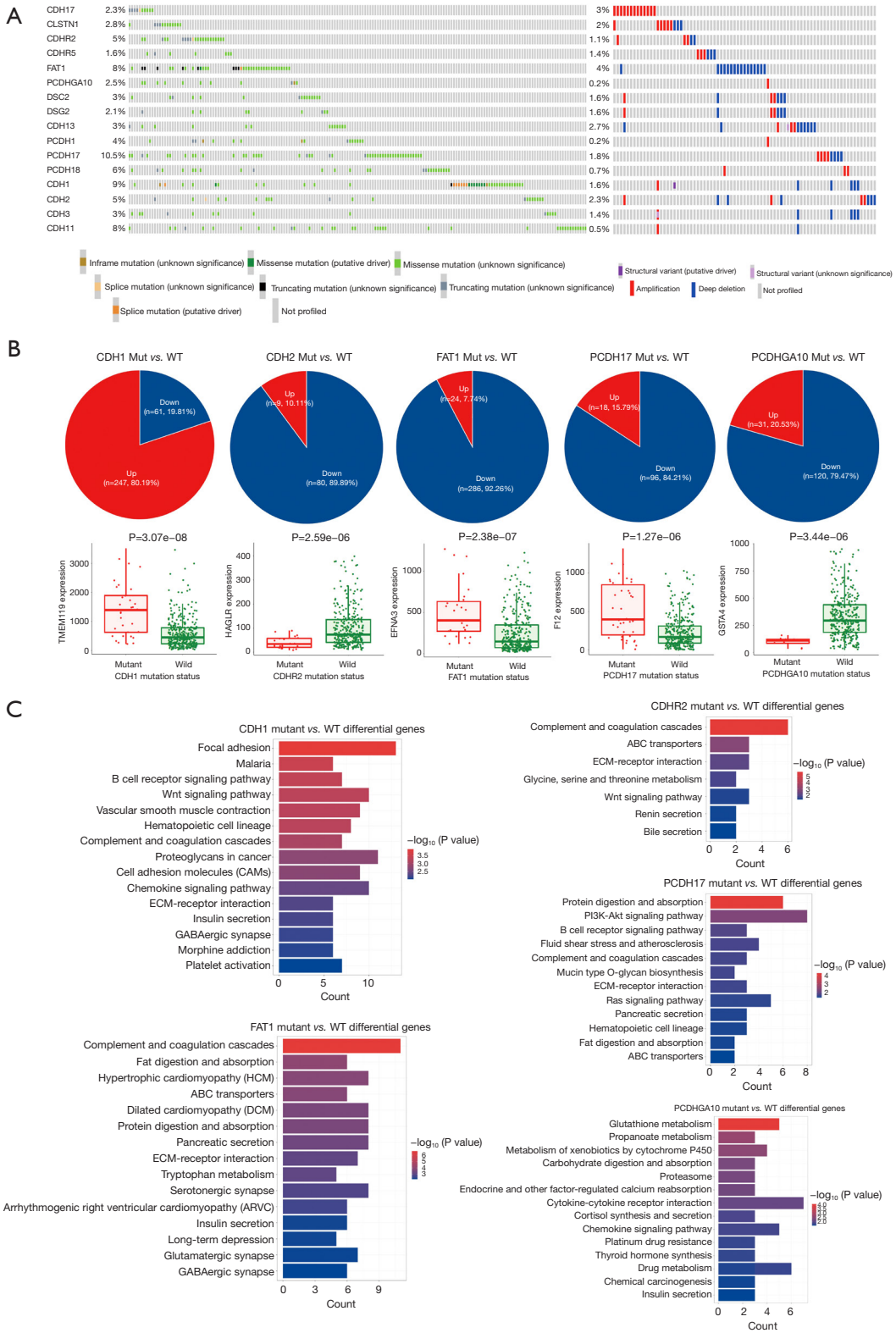

Figure 3 Analysis of mutations and copy number variations in cadherin genes differentially expressed between GC and normal samples. (A) Single nucleotide mutations (left) and CNVs/SVs (right) in 16 cadherin genes across gastric cancer patients were analyzed using TCGA genomic data through cBioPortal. A total of 440 GC patient samples were used for profiling genomic aberrations. Among these, mutation

data was available for 436 patients, CNV data was available for 438 patients and SVs were identified in 436 GC patients. The left hand-side figure shows patients with mutations in at least 1 of the 16 cadherins studied (total n=181, which accounts for ~41% of all patients with mutation data). The right hand-side figure shows patients with CNVs/SVs in at least 1 of the 16 cadherins studied (total n=79, which accounts for ~18% of all patients with CNV/SV data). The figures were generated by querying cBioPortal (https://www.cbioportal.org/) with all 16 cadherin genes and by selecting "Stomach Adenocarcionoma (TCGA, PanCancer Atlas)" as the dataset, and "Mutations", "Structural Variant" and "Putative copy-number alterations from GISTIC" as the genomic profiles. (B) Pie charts (top) indicating the number of genes up- or down-regulated between cadherin-mutant and wildtype cancer samples. Boxplots (bottom, obtained from muTarget tool) indicating the most significant differential gene in cadherin-mutant versus -wildtype gastric cancer samples. The analysis was performed using muTarget tool (https://www.mutarget.com/) and is based on TCGA RNA-seq and genomic data of gastric cancer patients. Of the 16 differentially expressed cadherins, mutations in five genes significantly affected the expression of other genes. Cadherins mutated in less than 10 samples were not considered for the above analysis. (C) Top 15 KEGG pathways affected by cadherin-mutants in gastric cancer. Pathway analysis was performed using the genes differentially expressed (log_2FC >1 and FDR P<0.05) between cadherin-mutant and cadherin-wildtype gastric cancer samples. Mut, mutant; WT, wildtype; ECM, extracellular matrix; GC, gastric cancer; CNVs, copy number variations; SVs, structural variants; TCGA, The Cancer Genome Atlas; KEGG, Kyoto Encyclopedia of Genes and Genomes; GISTIC, genomic identification of significant targets in cancer; FC, fold change; FDR, false discovery rate; Up, upregulated; Down, downregulated; n, number of samples.

except for *CDH17* (*Figure 3A*). Interestingly, 10.5% of GC patients had SNVs, while 1.8% patients had CNVs/SVs in *PCDH17*. Similarly, 8% patients had SNPs in *FAT1*, whereas 4% had CNVs/SVs. Moreover, 3% GC patients had CNVs/SVs and 2.3% patients had SNPs in *CDH17*. As expected, missense mutations were more common across the GC patients for all genes. In addition to missense mutations, *CDH1* harbored splice site mutations in a higher number of patients than the other cadherins. Furthermore, although 14 cadherins harbored both amplifications and deletions, *CDH17* harbored only amplifications, and *FAT1* harbored only deletions in GC patients.

Next, we intended to explore whether mutations in these cadherins affect the expression of other genes. We used muTarget tool to assess the effect of mutant cadherins on the expression of other genes in GC. Our results revealed that mutations in 5 (*CDH1*, *CDHR2*, *FAT1*, *PCDH17*, and *PCDHGA10*) of the 16 genes affected the expression of other genes significantly (with log_2FC >1 and *FDR* P<0.05) in GC (*Figure 3B*). The *FAT1*-mutant gene significantly affected the expression of most genes (n=310) followed by *CDH1*-mutant gene (n=308). Except in *CDH1*, mutation in all cadherins decreased the expression of the affected genes. Some 80% of the dysregulated genes in *CDH1*-mutant GC samples were upregulated, whereas less than 25% genes were upregulated in the other 4 cadherin-mutant samples. *Figure 3B* shows the most significantly dysregulated gene for each cadherin-mutant. The top 5 differentially expressed genes (DEGs) between cadherin-mutant and wildtype samples are shown in *Table 2* (complete list of DEGs is provided in Supplementary file available at https://cdn.amegroups.cn/static/public/jgo-23-700-3.xlsx). To understand the effect of cadherin mutations at the molecular level, we performed pathway enrichment analysis of the downstream affected genes in cadherin-mutant versus cadherin-wildtype GC samples. The pathways that were significant with *FDR* P<0.1 were considered significant. Our results revealed that mutation of all five cadherins except *PCDHGA10* mainly affected the ECM-receptor interaction pathway. Furthermore, mutation of all cadherins affected immune system-related pathways including 'Complement and coagulation cascades' being amongst the top 10 pathways (*Figure 3C*). Interestingly, mutation in *FAT1* affected cardiac disease related pathways, such as cardiomyopathy. Adhesion- and inflammation-related genes are known to be involved in these cardiac pathways. Additionally, *PCDHGA10*-mutants were shown to mainly affect the metabolic pathways, including glutathione and propanoate metabolism. Thus, our analysis showed that mutations in cadherin genes commonly affect adhesion-related pathways by regulating the corresponding genes products. However, a few mutant cadherins were found to affect the cardiac and metabolic pathways and their significance in GC needs to be experimentally verified.

Expression of cadherin genes is associated with survival of stomach cancer patients

Further, we investigated whether these differentially expressed cadherins affect the OS of GC patients. Our

Table 2 Top 5 differentially expressed genes between cadherin-mutant and wildtype gastric cancer samples

Gene	Log_2 fold change (mutant/wildtype)	P value	P value (false discovery rate)
CDH1 mutant *vs.* wildtype			
TMEM119	1.3	3.07E−08	4.11E−04
OMD	1.8	1.65E−07	6.29E−04
PCOLCE	1.0	3.06E−07	6.29E−04
CYP1B1	1.7	3.34E−07	6.29E−04
GAS1	1.2	4.87E−07	6.29E−04
CDHR2 mutant *vs.* wildtype			
HAGLR	−2.4	2.59E−06	5.22E−03
DIPK1B	−1.1	7.94E−06	9.26E−03
SYT8	1.5	8.30E−06	9.26E−03
NR5A2	−2.0	1.40E−05	1.11E−02
ONECUT2	−1.9	3.84E−05	1.41E−02
FAT1 mutant *vs.* wildtype			
EFNA3	1.3	2.38E−07	9.66E−04
VTN	−3.0	4.30E−07	9.66E−04
SERPINF2	−2.7	4.38E−07	9.66E−04
CREB3L3	−2.1	5.78E−07	9.66E−04
MMP24	−1.5	6.49E−07	9.66E−04
PCDHGA10 mutant *vs.* wildtype			
GSTA4	−2.0	3.44E−06	1.90E−02
CAPN12	−2.8	7.71E−06	1.90E−02
IFITM1	1.5	8.03E−06	1.90E−02
TNFSF9	2.4	8.92E−06	1.90E−02
EIF5AL1	1.9	9.98E−06	1.90E−02
PCDH17 mutant *vs.* wildtype			
F12	1.1	1.27E−06	1.83E−03
CARD11	−1.5	1.79E−06	2.15E−03
RGS5	−1.0	3.60E−06	2.32E−03
WASF3	−1.1	5.08E−06	2.84E−03
SLC7A2	−2.5	8.98E−06	3.99E−03

results revealed that 7 (*CDH2*, *CDH11*, *CDH13*, *FAT1*, *PCDH17*, *PCDH18*, and *PCDHGA10*) of the 16 cadherins were significantly (P<0.05) associated with OS of STAD patients (*Figure 4*). Low expression at the mRNA level of all the cadherins except *FAT1* correlated with higher survival rate. For instance, the median survival rate was 70 months when *CDH2* expression is lower compared to 25 months when its expression is higher in GC patient cohorts (P=0.007). Similarly, patients with lower expression of *PCDHGA10* survived 73 months compared to those with higher expression (median survival, 23 months; P=0.002). However, patients with lower expression of *FAT1* survived 26 months as compared to those with higher expression, who survived 56 months (P=0.012). Thus, our analysis revealed that lower expression of most cadherins, yet higher expression of *FAT1*, is associated with better prognosis of GC patients. Additionally, expression levels of *CDH11*, *FAT1*, and *PCDH17* were significantly associated with the survival rate of stomach cancer patients of different race or gender (Figures S1-S4).

Abundances of major immune cells are correlated with cadherin genes in stomach cancer

We aimed to estimate the immune cells infiltration in gastric cancer (GC) samples and then explore whether their abundance is correlated with the expression of selected cadherin genes in stomach cancer. Our analysis revealed that 11 of the 24 immune cells had significant differences (P<0.05) in their abundance between GC patients and normal controls (*Figure 5A*). Among these, B cells, dendritic cells (DCs), natural killer (NK) cells, CD4 T cells, and natural killer T (NKT) cells were considerably more abundant (median abundance >0.01) in both cancer and normal samples, whereas the remaining 6 cell types were less abundant in both conditions (median abundance <0.01). The abundance of B cells, DC, and NKT cells was higher in cancer samples, whereas that of NK cells and CD4-T cells was lower in cancer samples than in normal samples (Supplementary file available at https://cdn.amegroups.cn/static/public/jgo-23-700-4.xlsx).

Further, we correlated the expression of 16 cadherin

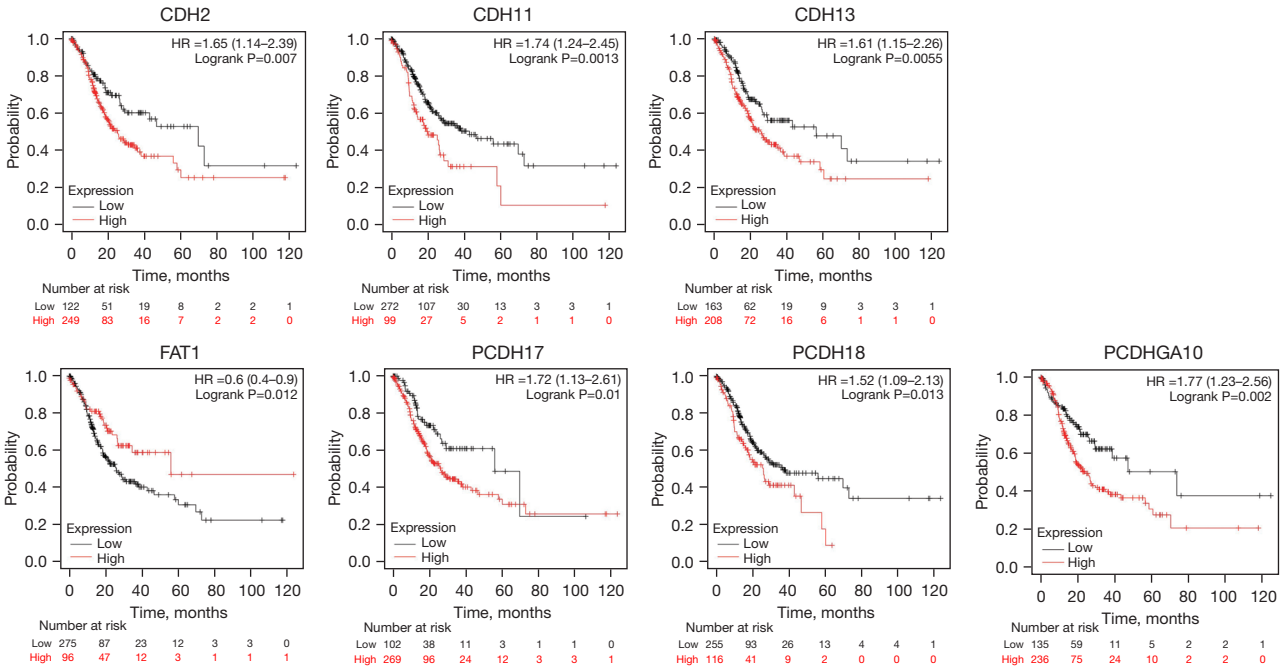

Figure 4 Prognostic significance of cadherin genes in stomach adenocarcinoma. RNA sequencing based expression of the cadherin genes was correlated with survival time of the patients. Of the 16 selected cadherin genes, the ones with significant relationship with patient survival are shown here. For the above analysis, gastric cancer samples having both expression and survival data were used. The survival plots for gastric cancer were generated by querying KM plotter with each cadherin gene (https://kmplot.com/analysis/index.php?p=service&cancer=gastric). The data in parenthesis are shown as lower and upper HR values, respectively. HR, hazard ratio; KM, Kaplan-Meier.

genes with the abundance of immune cell types that were significantly different (P<0.05) between cancer and normal stomach samples (*Figure 5B*). B cell abundance significantly correlated with 9 cadherin genes (all negative correlations), DC abundance correlated with 7 cadherin genes (6 positive and 1 negative), NKT cells correlated with 9 cadherin genes (8 positive and 1 negative), NK cells correlated with 9 genes (4 positive and 5 negative), and CD4 T cells correlated with 10 cadherins (4 positive and 6 negative). *CDH1* and *CDH17*, each correlated significantly with all 5 highly abundant cell types (B cell, DC, NK, NKT, and CD4 T cell). Most of these were negative correlations. Interestingly, both *CDH1* and *CDH17* correlated positively with NKT cells. *Figure 5C* shows the correlation details for *CDH1* with five highly abundant immune cell types (B cell, DC, NK cell, CD4 T cell, and NKT cell).

miRNA analysis revealed novel miRNA-cadherin interactions

We first identified miRNAs that are differentially expressed between GC and normal stomach samples based on TCGA miRNA-seq data. A total of 361 miRNAs (upregulated: 187; downregulated: 174) were significantly different between these two groups with absolute FC 1.5 ($\log_2$FC >0.58) and adjusted P<0.05 (*Figure 6A*). We then explored which of these upregulated miRNAs targeted the downregulated cadherins and vice versa in GC. Our results revealed that 9 upregulated miRNAs targeted the only downregulated cadherin, *CDH2*, whereas 79 downregulated miRNAs targeted the remaining 14 upregulated cadherins (*CDHR2* was not targeted by any miRNA), resulting in a total of 135 miRNA-gene interactions. Further, using these interactions, we constructed a network to identify miRNAs that are targeting multiple cadherins. The network contained a total of 103 nodes and 135 edges. *PCDH17* was targeted by the highest number of miRNAs (n=37) followed by *CDH11* with 19 miRNAs (*Figure 6B*). Furthermore, 2 miRNAs (hsa-miR-23b-3p and hsa-miR-495-3p) targeted 4 cadherins each, whereas 5 miRNAs (has-miR-9-3p, has-let-7a-2-3p, has-miR-4775, has-miR-9-5p, has-miR-548ba) targeted 3 cadherins each (*Table 3* and Supplementary file available at

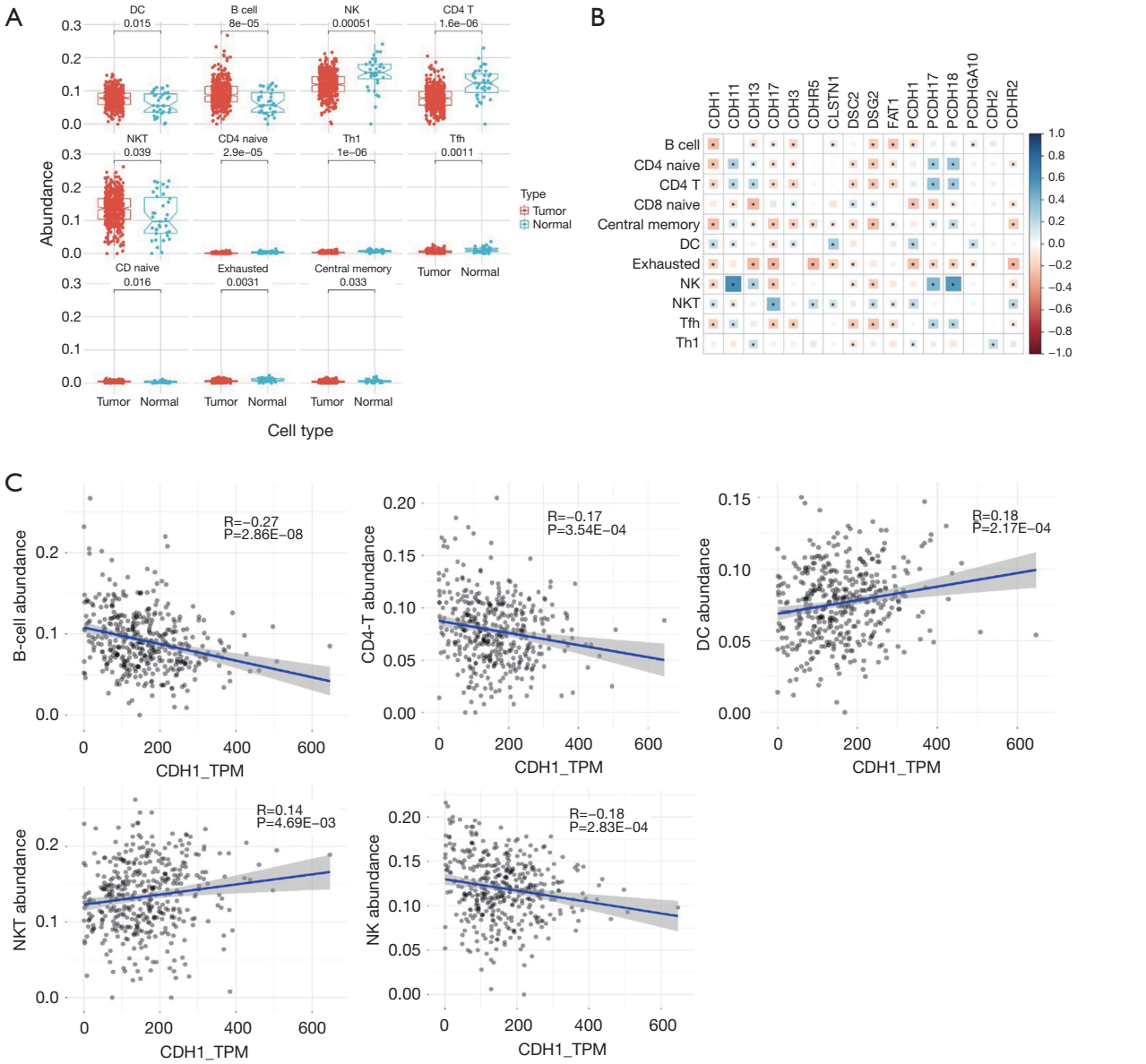

Figure 5 Immune infiltration analysis and correlation with cadherin genes. (A) Differential abundance of immune cells between STAD patients and normal controls. Only significantly different immune cells are shown. (B) Correlation between the significantly different immune cells and cadherin genes in STAD patients. Significant correlations are indicated by an asterisk. (C) Scatter plots showing correlation between *CDH1* expression and abundance of 5 immune cell types (B cell, CD4-T cell, DC, NKT, and NK cell), in STAD patients. These immune cell types had a considerable abundance in both cancer and normal patients. DC, dendritic cell; NK, natural killer; NKT, natural killer T cell; Tfh, T follicular helper; Th1, T helper 1; TPM, transcripts per million; STAD, stomach adenocarcinoma.

https://cdn.amegroups.cn/static/public/jgo-23-700-5.xlsx). The miRNA hsa-miR-23b-3p targeted *CDH1*, *DSC2*, *PCDH17*, and *PCDH18*, whereas hsa-miR-495-3p targeted *CDH1*, *DSG2*, *CDH13*, and *PCDH18*. Surprisingly, except for 1 miRNA-gene interaction (hsa-miR-548ba-*PCDH17*), none of the interactions have been experimentally verified according to the data obtained from miRTarBase, a database of experimentally verified miRNA-target interactions.

To further strengthen the regulatory role of the miRNAs by targeting the cadherin genes, we performed

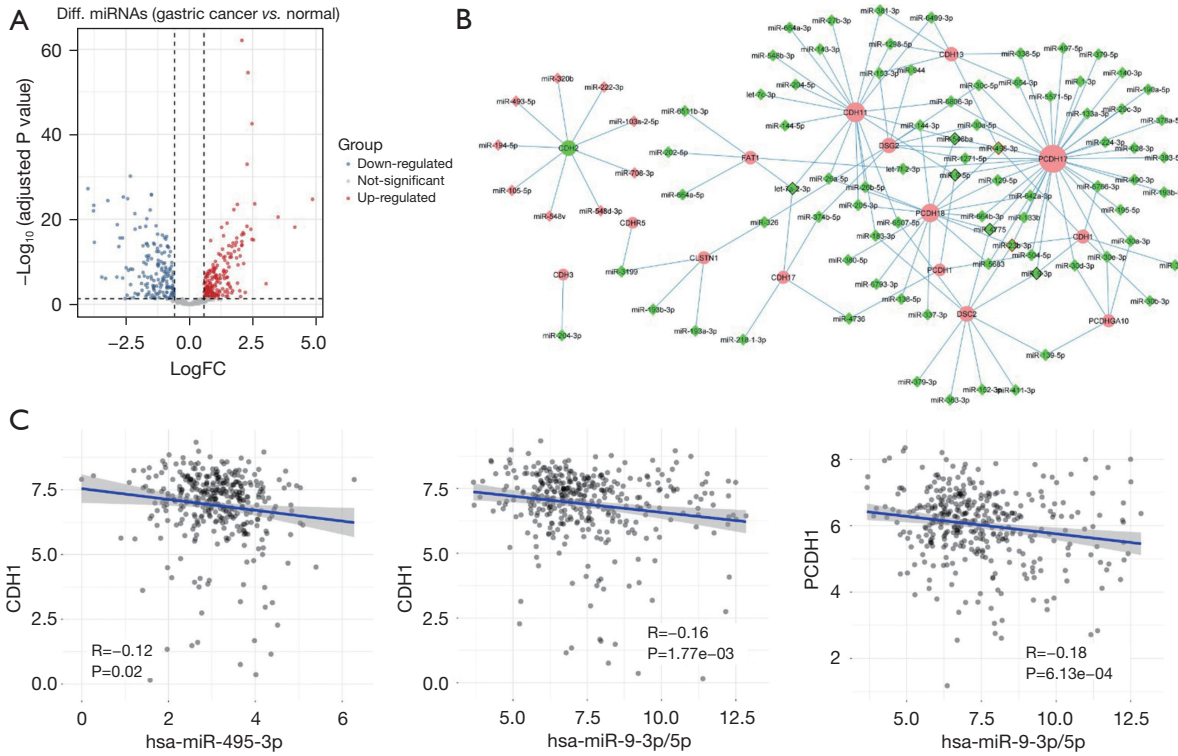

Figure 6 miRNA analysis of selected cadherin genes. (A) Volcano plot showing up- and down-regulated miRNAs in gastric cancer versus normal tissues based on TCGA data. A log_2FC of 0.58 (absolute fold-change 1.5) and FDR corrected P<0.05 was used as a significance threshold. (B) Network of miRNAs and cadherin genes. Interactions for upregulated miRNAs and their downregulated targets and vice versa are shown in the network. Node size refers to degree (number of interacting molecules). Circular node: Cadherin gene; Diamond node: miRNAs; Red and Green nodes: upregulated and downregulated in gastric cancer compared to normal tissues; Red border diamond node: miRNA targeting four cadherins; Black border diamond node: miRNA targeting 3 cadherins. The network was constructed using Cytoscape 3.9.1 (https://cytoscape.org/). (C) Correlation between miRNA and mRNA expression in gastric cancer. TCGA normalized data was used as input for Pearson correlation analysis. The correlation R and P values are indicated above each plot. Only significant negative correlations are shown here. Diff., differential; FC, fold change; miRNA, microRNA; TCGA, The Cancer Genome Atlas; FDR, false discovery rate.

co-expression analysis between top miRNAs and cadherin-mRNA expression in GC by using normalized expression values. Of the 23 cadherin-miRNA pairs tested (*Table 3*), the correlation for many pairs was insignificant, but a few pairs positively correlated. We observed significant negative correlations for hsa-miR-495-3p-*CDH1* (P=0.02), hsa-miR-9-3p-*CDH1* (P=1.77E−03), and hsa-miR-9-5p-*PCDH1* (P=6.13E−04) pairs (*Figure 6C*). The negative correlation was also observed for hsa-let-7a-2-3p-*CDH11*, hsa-let-7a-2-3p-*CDH17*, hsa-miR-23b-3p-*CDH1*, and hsa-miR-495-3p-*DSG2* pairs, however the correlation values were statistically insignificant. Thus, our miRNA-cadherin interaction analysis indicated that cadherins are actively regulated by many miRNAs in GC and *PCDH17* is the most commonly miRNA-regulated cadherin in GC. However, experimental validation of the miRNA-cadherin interactions is required to understand their functional significance.

Discussion

The cadherin family of genes are essential in maintaining the integrity and function of stomach tissues, including cell-cell adhesion, cell migration, and differentiation (16). Dysregulation of cadherin expression and function has been linked to various gastric diseases, including GC (22). Therefore, understanding the regulation of cadherin expression and function in the stomach is crucial for the development of targeted therapeutic strategies for gastric diseases. In this study, we investigated the expression, mutational status, functional importance, and prognostic

Table 3 List of microRNAs targeting at least three cadherin genes in gastric cancer

microRNA name	Log_2 fold change		Cadherin symbol	Interaction in miRTarbase
	microRNA	Cadherin		
hsa-miR-23b-3p	−0.98	1.60	*CDH1*	–
hsa-miR-9-3p	−2.23	1.60	*CDH1*	–
hsa-miR-495-3p	−0.65	1.60	*CDH1*	–
hsa-let-7a-2-3p	−0.89	4.91	*CDH17*	–
hsa-let-7a-2-3p	−0.89	1.95	*FAT1*	–
hsa-miR-4775	−1.51	2.01	*DSC2*	–
hsa-miR-9-3p	−2.23	2.01	*DSC2*	–
hsa-miR-23b-3p	−0.98	2.01	*DSC2*	–
hsa-miR-495-3p	−0.65	2.65	*DSG2*	–
hsa-miR-495-3p	−0.65	1.72	*CDH13*	–
hsa-miR-9-5p	−1.49	1.52	*PCDH1*	–
hsa-miR-4775	−1.51	1.19	*PCDH17*	–
hsa-miR-9-5p	−1.49	1.19	*PCDH17*	–
hsa-miR-23b-3p	−0.98	1.19	*PCDH17*	–
hsa-miR-548ba	−2.46	1.19	*PCDH17*	Yes
hsa-miR-9-3p	−2.23	1.19	*PCDH17*	–
hsa-miR-495-3p	−0.65	1.01	*PCDH18*	–
hsa-miR-23b-3p	−0.98	1.01	*PCDH18*	–
hsa-miR-548ba	−2.46	1.01	*PCDH18*	–
hsa-miR-4775	−1.51	1.01	*PCDH18*	–
hsa-let-7a-2-3p	−0.89	2.28	*CDH11*	–
hsa-miR-9-5p	−1.49	2.28	*CDH11*	–
hsa-miR-548ba	−2.46	2.28	*CDH11*	–

Log_2 fold change correspond to difference in gastric cancer *vs.* normal. Negative fold change values indicate down-regulation, whereas positive values indicate up-regulation.

potential of cadherin family genes in STAD.

In this study, we identified 16 cadherin genes that showed significant differential expression between GC and normal samples. *CDH1* is an important player in epithelial-mesenchymal transition, a root cause of invasive and metastatic cancer cell spreading (49). The differential expression of *CDH1* has been reported to vary depending upon the histological subtypes of GC (50). For instance, *CDH1* is upregulated in intestinal type GC, whereas it is downregulated in the diffuse type of adenocarcinoma owing to mutation and epigenetic modifications (50). In the current study, we used TCGA samples for the differential expression analysis of cadherins. A total of 450 STAD tumor samples in TCGA had the histological classification available. Among these, 41% (186 samples) belong to intestinal type, whereas only 16% (71 samples) belong to diffuse type. A higher percentage of intestinal subtype in the TCGA-STAD sample pool could explain the upregulation of *CDH1* in our study. Furthermore, we found that *CDH17* was highly upregulated in STAD between tumor and normal samples. These findings are consistent with a previous study that has reported the upregulation of *CDH17* in GC (27), and suggest that *CDH17* may be a potential diagnostic or therapeutic target for this disease.

In addition, we identified several other cadherin genes that were highly upregulated in GC, including *CDHR5*, *DSC2*, *DSG2*, *CDH3*, and *CDH11*. These genes have been previously implicated in cancer cell invasion, migration, and metastasis. For example, up-regulation of *CDHR5* expression promotes malignant phenotype of pancreatic ductal adenocarcinoma (51); *DSC2* expression was significantly increased in prostate cancer cells (52); *DSG2* has been identified as a biomarker that promotes tumor proliferation and metastasis and is positively correlated with poor prognosis in early-stage cervical cancer (53); *CDH3* expression is upregulated in thyroid cancer tissues compared to the adjacent normal tissues, and siRNA-mediated downregulation of *CDH3* has been shown to inhibit the growth, migration, and invasion of thyroid cancer cells (54). The upregulation of these genes could be indicative of increased tumor aggressiveness and poor patient outcomes. Future studies should explore the potential clinical utility of these genes as prognostic biomarkers or therapeutic targets in GC.

Interestingly, we found that *CDH2*, a classical cadherin gene that has been previously implicated in cancer cell invasion and metastasis (55,56) to be downregulated in GC patients compared to normal controls. This finding is somewhat unexpected given the established role of *CDH2* in promoting cancer cell invasion and metastasis. It is possible that downregulation of *CDH2* may be a compensatory mechanism to counteract the effects of other upregulated cadherin genes in GC. Alternatively, it may indicate a different role for *CDH2* in the pathogenesis of GC, which could be clarified using siRNA-based gene silencing strategies.

The identification of genes that are correlated with differentially expressed cadherins and genes that are

affected by mutated cadherins in GC allowed us to perform functional enrichment analysis and gain insights into the functional importance of these cadherins in GC. Our analysis revealed that the correlated genes for most of the cadherins were involved in focal adhesion, ECM-receptor interaction, or junction-related pathways, all of which are related to cell adhesion. The focal adhesion and ECM-receptor interaction pathways play an important role in cell migration, proliferation, survival, and differentiation of cancer cells (57,58), and their dysregulation has been implicated in many pathological conditions, including cancer (59,60). The junction-related pathways are important for coordinating cell behavior, maintaining tissue integrity, and regulating the transport of ions and small molecules across epithelial and endothelial cell layers (61-64). Dysfunction of these junctions can have significant impacts on tissue and organ function and may contribute to the development of various diseases, including inflammation, cancer progression, and tumor metastasis (65-67).

Additionally, our functional enrichment analysis showed that the downstream genes for all mutated cadherins in GC were involved in the complement and coagulation cascades pathway. The complement system is a group of proteins that act to defend against invading pathogens by marking them for destruction and recruiting other immune cells to the site of infection (68-70). The coagulation system, on the other hand, is responsible for forming blood clots to stop bleeding after injury (71-74). Both systems are tightly regulated to prevent excessive immune activation or clot formation, which can lead to harmful effects. Furthermore, complement proteins can bind to ECM components such as laminin, fibronectin, and collagen, playing a role in immune surveillance and defense against invading pathogens (75,76). Coagulation factors, such as fibrinogen also interact with ECM and promote clotting (77,78). Dysregulation of these pathways can have serious consequences, and result in autoimmune diseases or thrombosis (79-83). Therefore, understanding the regulation of these pathways is key to the study of molecular mechanisms of cadherins during development of GC.

Finally, our immune cell infiltration analysis showed that 11 immune cell types have significantly different abundance between GC patients and normal controls, with B cells, DCs, and NKT cells being more abundant in cancer samples, whereas NK cells and CD4 T cells were less abundant. Correlating the expression of 16 cadherin genes with the abundance of immune cell types revealed that B cell abundance was negatively correlated with all 9 cadherin genes, whereas DC and NKT cell abundance was positively correlated with a majority of the cadherin genes. These findings further support interaction between immune cell types and the expression of cadherin genes in GC.

We found that about 45% of DEGs were significantly associated with the survival of STAD patients. Lower mRNA levels of most cadherins were correlated with higher survival rates. Reduced cadherin expression can contribute to weakened cell-cell adhesion, leading to decreased tumor cell migration, invasion, and metastasis. This could result in better containment of the tumor and slower disease progression.

Moreover, low cadherin expression may also reflect a less dedifferentiated state of cancer cells. High levels of cadherins are associated with epithelial-to-mesenchymal transition (EMT), a process whereby epithelial cells acquire more migratory and invasive properties (26,84). In contrast, low cadherin expression suggests a more epithelial phenotype, which is typically associated with a better prognosis in GC.

It is important to note that the relationship between cadherin expression and survival rates in GC is complex and can vary depending on the specific cadherin and the molecular context of the tumor. Further experimental validations are needed to fully understand the underlying mechanisms and potential therapeutic implications of cadherin expression in GC patients.

Abnormal expression of miRNAs has been observed in GC tissues compared to normal stomach tissues. These dysregulated miRNAs can act as oncogenes or tumor suppressors, influencing various cellular processes involved in cancer development, progression, and metastasis (85-89). Part of cadherin gene expression change in GC could result through miRNAs. We found that a total of 361 miRNAs exhibited significant differences between GC and normal samples. The miRNA-mRNA network analysis revealed that 9 upregulated miRNAs targeted *CDH2*, whereas 79 downregulated miRNAs targeted the upregulated cadherins (excluding *CDHR2*). These findings suggest that multiple miRNAs actively regulate cadherins in GC. However, further validations are warranted to clarify the functional significance of these miRNA-cadherin interactions in GC.

Conclusions

In conclusion, our study provides valuable insights into the alterations of cadherin genes in GC and their downstream effects on gene expression and pathways. However, further

experimental validations are needed to elucidate the exact mechanisms by which these cadherins contribute to the development and progression of GC and their potential clinical implications.

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Footnote

Reporting Checklist: The authors have completed the STREGA reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-700/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-700/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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