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Comprehensive expression analysis reveals several miRNAs against acute pancreatitis via modulating autophagy

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ABSTRACT

Acute pancreatitis (AP) had been one of the main reasons for hospitalization worldwide. However, the mechanisms related to AP remained to be unclear. This study identified 37 miRNAs and 189 mRNAs were differentially expressed in pancreatitis and normal samples. Bioinformatics analysis showed DEGs were significantly related to PI3K-Akt signaling, FoxO signaling, Oocyte meiosis, Focal adhesion, and Protein digestion and absorption. By constructing a signaling-DEGs regulation network, we found COL12A1, DPP4, COL5A1, COL5A2, and SLC1A5 were related to regulating Protein digestion and absorption, THBS2, BCL2, NGPT1, EREG, COL1A1 were related to regulating PI3K signaling, CCNB1, CDKN2B, IRS2, PLK2 were related to modulating FOXO signaling. Next, we constructed a miRNA-mRNA regulation network in AP, consisting of 34 miRNAs and 96 mRNAs. The protein-protein interaction networks and the miRNA-targets networks analysis show that hsa−miR−199a−5p, hsa−miR−150, hsa−miR−194, COL6A3 and CNN1 acted as hub regulators in AOf note, through comprehensive expression analysis, we found several miRNAs and mRNAs were significantly related to modulating autophagy signaling in AP, including hsa−miR−181c, hsa−miR−181d, hsa−miR−181b, hsa−miR−379 and hsa−miR−199a−5Overall, this study screening differently expressed miRNAs in AP and revealed miRNA- autophagy regulation may serve as a potential prognosis and Therapeutic marker for AP.

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Introduction

Acute pancreatitis (AP) is an autoimmune digestive system disease caused by trypsin abnormal activation for many reasons (1). About 20% of AP would develop into severe acute pancreatitis (SAP) (2). SAP usually affects extrapancreatic organs such as the lung, liver and kidney due to local or systemic complications, which contributed to multiple organ failure and even death (3). The mortality rate of SAP is as high as 30% (3). Numerous studies reported pathological calcium signals in acinar cells, premature activation of trypsinogen, and dysregulation of autophagy had a key role in the progression of sap (4). Of note, about 18% of AP patients would relapse further and develop into chronic pancreatitis (5). However, the mechanisms related to the pathogenesis of AP are not clear. Therefore, finding new biomarkers is of great significance to improve the diagnostic rate of AP and establish relevant mechanisms.

Studies have indicated miRNAs had an important role in post-transcriptional regulation (6). Notably, previous reports have confirmed miRNAs are also related to regulating the bioactivity of acute pancreatitis and have become a potential biomarker for this disease (7-10). For example, MiR-9 regulates FGF10 and NF-κB signaling pathway and reduce the inflammatory response and apoptosis in the acute pancreatitis model (7). In the Rankine-induced acute pancreatitis model, mir-146b-3p protects AR42J cells from injury by targeting anxa2 (8). Mir-339-3p regulates TNF-induced AR42J cell acute pancreatitis by targeting AR42J receptor-related factor 3 (9). Hypertriglyceridemia leads to abnormal srebp1c/mir-153 signal transduction to aggravate acute pancreatitis and delay tissue repair (10). In addition, some miRNAs have been revealed as potential prognostic biomarkers of AP (11). For example, circulating microRNA-146a and microRNA-146 b show potential as markers for the management and prognosis of acute pancreatitis (12). Liu et al reported 205 miRNAs differentially expressed in AP patient serum and control serum (11). Understanding the expression profile and potential role of miRNAs in AP can provide new targets for the prognosis and treatment of AP.

The role of miRNAs in AP remained largely unclear. Therefore, it is necessary to comprehensively analyze miRNA and mRNA dysregulation in the pathogenesis of AIn the present study, the expression profiles of miRNA and mRNA were analyzed by using the public database, and their related functions of them were predicted using the bioinformatic tool. Furthermore, we established a miRNA-mRNA network to reveal the hub genes in our results may provide new treatment choices for AP.

Materials and Methods

Data resource

Non-coding RNA profiling by an array of 22 normal controls and 27 pancreatitis samples was downloaded

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from the GEO database (GSE24279) (13). Also, gene expression profiling by the array for chronic pancreatitis (CP) and normal tissue was downloaded from the GEO database (GSE123375) (14). There are 5 CP patients and 5 normal samples.

Data analysis

The gene expression profile and the metadata were downloaded from the GEO database. The differential expression analysis for mRNA or miRNA expression profile data was performed by the "limma" package (15) in R. P<0.05 and log(FC)>1 were considered significant differences. Enrichment analysis was performed in the R package "clusterProfiler" (16), separately. A hypergeometric test is used to calculate the significance of enrichment, and p<0.05 is considered significant enrichment. Gene The Gene Set Enrichment Analysis (GSEA) for all the mRNA was performed by GSEA software power by UC San Diego and Broad Institute (17). The protein-protein interaction background networks (PPI) were downloaded for the "STRING" database. We use the "miRBase" (18) database for miRNA target prediction. The heatmap for differentially expressed genes was drawn by the pheatmap package. The Principal Component Analysis (PCA) was performed by the R package "ggbiplot".

Statistical analysis

All the statistical analyses were performed in R (version 3.6.1). P<0.05 was considered a significant difference.

Results

Identification of differentially expressed mRNA and miRNA in pancreatitis group compared with normal group

The analysis flow chart is shown in Figure 1. Through the limma package, 37 miRNAs were identified to be differentially expressed between pancreatitis and normal samples by the cutoff for FDR< 0.05 and log (FC)>1 (Figure 2C). These 23 miRNAs were enhanced, and 14 miRNAs were suppressed in the pancreatitis group. The UMAP plot shows that the pancreatitis group and normal group have different expression patterns in miRNA level (Figure 2B). Also, we highlight the top 12 most significant differences in miRNA in a boxplot (Figure 2A). Among them, hsa-miR-215, hsa-miR-182, hsa-miR-148a, hsa-miR-29c, hsa-miR-194, hsa-miR-192, hsa-miR-200a, hsa-miR-335 were suppressed in AP compared to control samples, however, hsa−miR−150 and hsa−miR−214 were up-regulated in AP compared to control samples.

There are 189 mRNAs to be found to have differentially expressed in pancreatitis and normal grouThe heatmap for these genes shows that they can classify all the samples in two groups well separately (Figure 3A). By normalization, the genes expressed in all samples were basically at the same level (Figure 3B). The PCA analysis results revealed significant differences in the expression patterns between patients with pancreatitis and normal samples (Figure 3C).

Functional enrichment analysis for DEGs in AP

A total of 208 Gene Ontology (GO) terms were enriched for these differentially expressed mRNAs which included 177 Biological Processes, 29 Cellular Components and 2 Molecular Functions (Figure 4A). Among them, the most

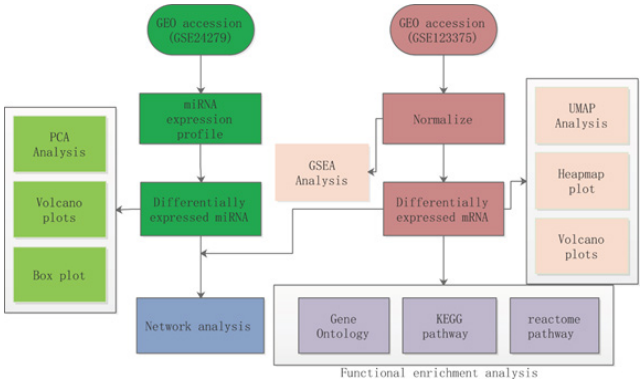

Figure 1. The workflow in data analysis.

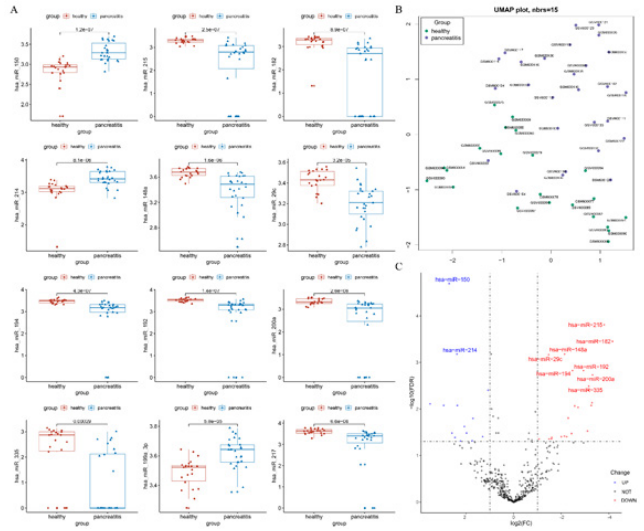

Figure 2. Differentially expressed miRNAs pancreatitis and normal group (A) Boxplot for the top 12 miRNAs. (B) UMAP plot for all the miRNAs. (C) Volcano plot for differentially expressed miRNAs, the red dots represent the up-regulated in the pancreatitis group, and black dots mean there is no significant difference between the two groups.

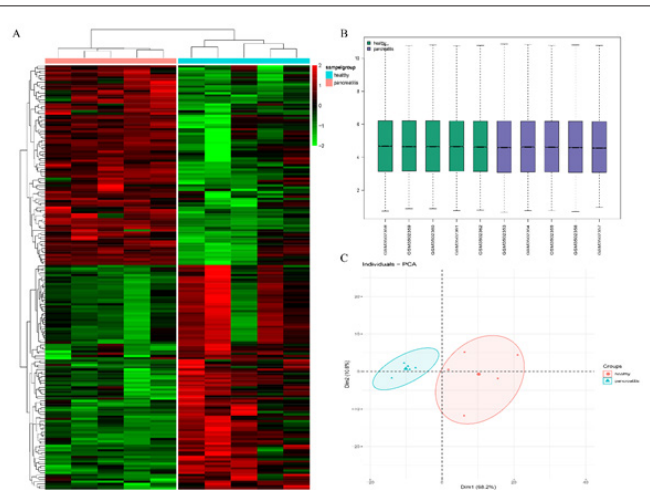

Figure 3. Differentially expressed mRNAs between pancreatitis and normal group (A) Heatmap for all the Differentially expressed mRNAs. (B) Boxplot for all the sample expressions after normalization. (C) PCA analysis for all the genes.

significantly enriched terms in BP spindle organization, extracellular matrix organization, mitotic nuclear division, extracellular structure organization and regulation of nuclear division (Figure 4B), the most enriched CC terms are collagen-containing extracellular matrix, extracellular matrix and spindle. GSEA analysis shows that the most

significantly enriched term in BP is the secretion by cell (Figure 4C).

The GSEA analysis in pathways identified that 19 KEGG pathways (Figure 5A) and 131 Reactome pathways were enriched for all genes in profiling (Figure 5B), including Hedgehog signaling, Protein digestion and absorption, and Wnt signaling, Metabolic pathways, Neutrophil extracellular trap formation, Cell cycle, Sphingolipid metabolism, Pre-NOTCH Transcription and Translation, Asparagine N-linked glycosylation. Furthermore, 9 hub signalings were enriched for all these genes, including PI3K-Akt signaling, FoxO pathway, Oocyte meiosis, Focal adhesion, Protein digestion and absorption and ECM-receptor interaction, and Progesterone-mediated oocyte maturation.

By constructing signaling-DEGs regulation network, we found COL12A1, DPP4, COL5A1, COL5A2, SLC1A5 were related to regulate Protein digestion and absorption, THBS2, BCL2, NGPT1, EREG, COL1A1 were related to regulate PI3K signaling, CCNB1, CDKN2B, IRS2, PLK2 were related to modulate FOXO signaling (Figure 5D).

Construction of miRNA-mRNA regulation network in AP.

Next, we constructed 1 miRNA-mRNA regulation network in AAs presented in Figure 6, 34 miRNAs and 96 mRNAs were included in this network. The protein-protein interaction networks and the miRNA-targets networks analysis show that hsa−miR−199a−5p, hsa−miR−150, hsa−miR−194, COL6A3 and CNN1 have the highest connectivity and are hub nodes in the network (Figure 6A). Interestingly, the previous studies had revealed hsa−miR−199a−5p, hsa−miR−150, hsa−miR−194 were highly associated with autophagy.

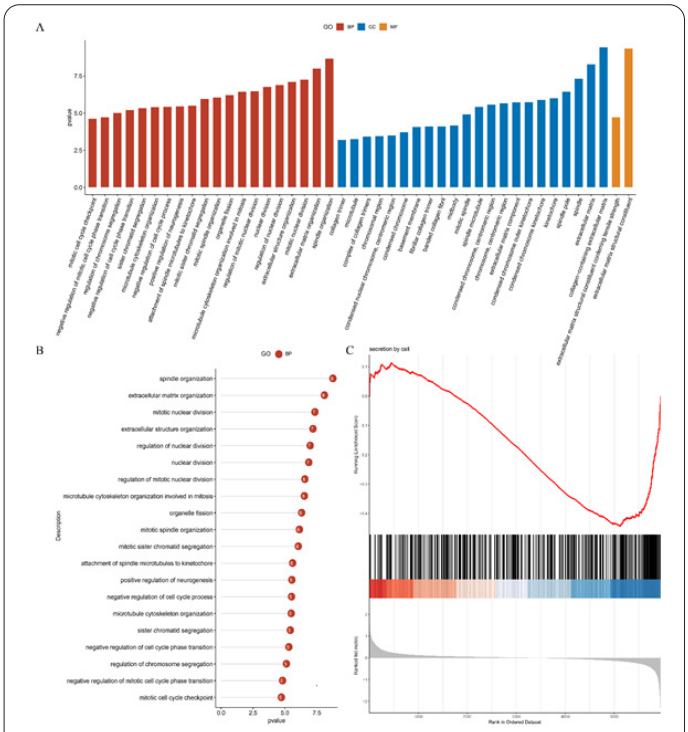

Figure 4. Gene Ontology enrichment analysis for differentially expressed genes. (A) Significantly enriched in Gene Ontology (GO), red is Biological Process (BP) terms, blue represents Cellular Component (CC) terms and yellow is the Molecular Function (MF) terms (B) All significantly enriched in B (C) The most significantly enriched term in Biological Process for GSEA.

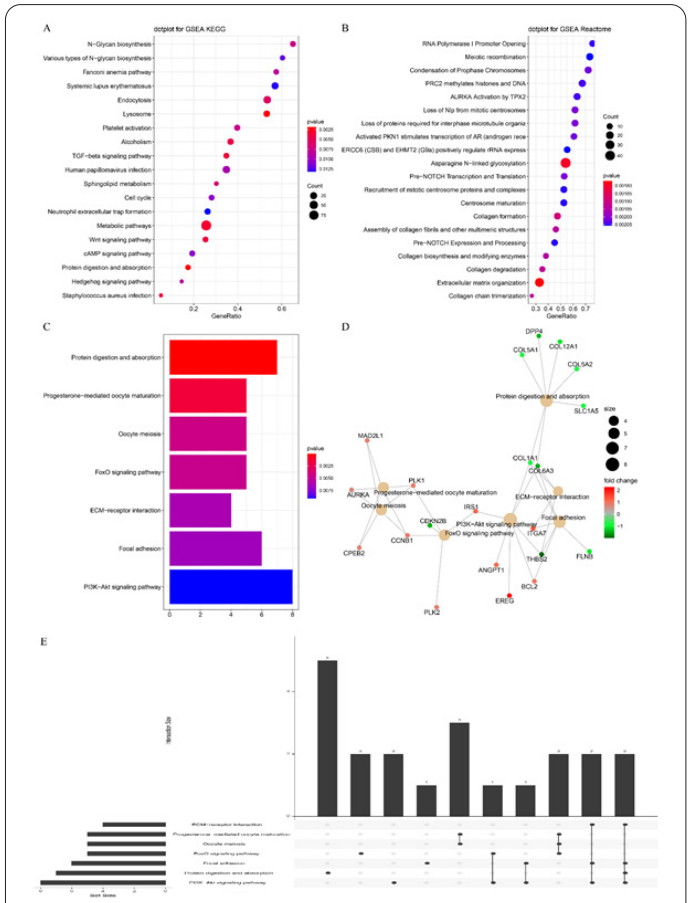

Figure 5. Pathway enrichment analysis for differentially expressed RNAs. (A) Significantly enriched terms in KEGG for GSEA. (B) Significantly enriched terms in Reactome for GSEA. (C) Enriched pathway in KEGG. (D) Network for the enriched pathway in KEGG and related genes. (E) Differentially expressed genes in KEGG pathways.

The gene co-expression network analysis indicated that some of the DEGs have similar expression patterns. Among them, TENM3, SH3BGRL2, SAP30 and RBP1 co-expression with multiple genes (Figure 6B). Consistent with that, we found the hub co-expression gene *TENM3* also interacted with *ATG3, ATG4B, ATG7*, which were autophagy-related genes.

Of note, through comprehensive expression analysis, we found several miRNAs and mRNAs were significantly related to modulating autophagy signaling in AFor example, the network showed hsa−miR−181b/c/d was revealed to modulate ATG3/ATG4B/ATG7 though SAP30/RBP1/TENM3 axis, hsa−miR−379 was revealed to regulate Autophagy through RBP1, and hsa−miR−199a−5p could modulate CCNB, thus affecting autophagy.

Discussion

Acute pancreatitis is characterized by inflammatory diseases of the pancreas (19). This is the second leading cause of total hospitalization, the largest contributor to total cost and the fifth leading cause of death in hospitals, and the global incidence rate is increasing (1). Therefore, it is urgent to understand the regulatory mechanism of AP and determine the biomarkers of disease. In this study, a total of 37 miRNAs were identified for differential expression in pancreatitis and normal samples. Notably, some of these miRNAs have been reported to be associated with pancreatitis. For example, it has been reported

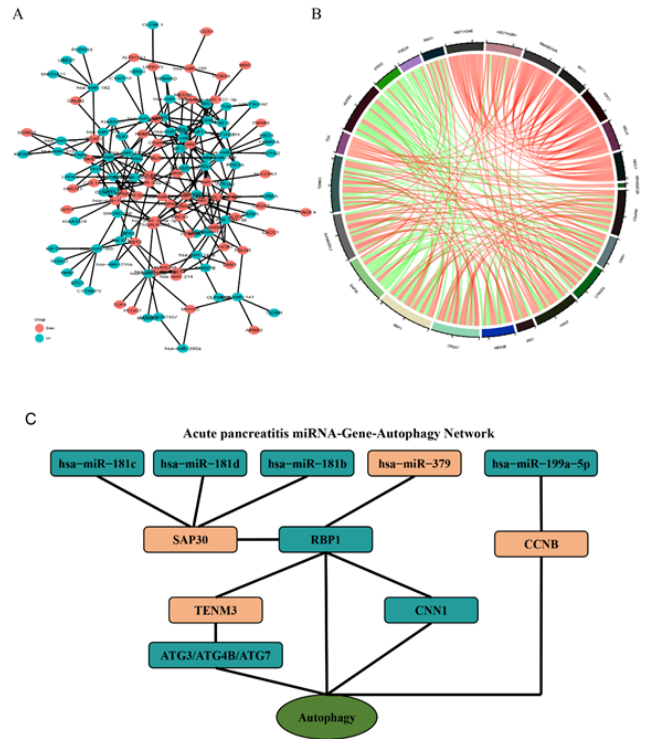

Figure 6. Network analysis for differentially expressed mRNAs and miRNAs. (A) PPI for DEGs from the STRING database and the miRNA-target network from miRBase. (B) Co-expression for the most related genes. The connection line represents the co-expression of two genes, the red represents positive correlation and green represents negative correlation and the color shade represents the size of the correlation coefficient. (C) Identification of hub network related to autophagy regulation.

that hsa-mir-150 is downregulated during pancreatic stellate cell activation. Mir-214-3p aggravates renal damage and inflammatory response in hyperlipidemic pancreatitis complicated with acute renal injury (20). Circulating small RNA-182 in plasma and its potential value in the diagnosis and prognosis of pancreatic cancer (21). miR-148a inhibition of autophagy downregulates the IL-6/STAT3 signaling pathway of Frostinin-induced acute pancreatitis (22) and participates in regulating the activation of pancreatic stellate cells through competitive endogenous RNA (23). Malat1-microrna-194-yap1 bidirectional feedback loop regulates the progression of TGF in acute pancreatitis (24). mir-200a-pten induces epithelial cell apoptosis, pancreatic stellate cell mesenchymal transformation and fibrosis (25).

At the same time, through the analysis of an independent database, we also found AP-related mRNA. A total of 189 mRNA were differentially expressed in pancreatitis and normal pancreas. Bioinformatics analysis showed that PI3K/Akt and FOXO signaling pathways were related to API3K/Akt pathway and was found to have a crucial role in inflammation. PI3K / Akt inhibitor decreased the level of inflammatory cytokines in SAP rats and alleviated thyroid injury in rats with severe AP (26). During the course of pancreatitis, the expression of PI3K / Akt increased significantly. At the same time, we note that some hub genes are related to the regulation of these genes, such as Plk1 and plk2. Plk1 and plk2, members of the polo-like kinase (PLK) family, are checkpoints for controlling cell division, which is an indispensable process in complete mitosis (27). Many studies have shown that the up-regulation of PLK1 is a common early event in pancreatic cancer (28). This study first reported the important role of these genes in the pathogenesis of AP.

Autophagy is a highly conserved dynamic equilibrium evolutionary process, which widely exists in cells (29). With autophagy, cells could re-use degradation products from Damaged organelles and misfolded proteins. Numerous reports have shown that autophagy plays an important role in maintaining cell homeostasis under starvation (29). The reported autophagy may be closely related to heart injury associated with severe acute pancreatitis (30). In addition, targeted autophagy can provide therapeutic targets for AP (30). For example, spautin-a41 reduces cerulein-induced acute pancreatitis by inhibiting dysregulated autophagy (31). β1 syntrophin protects cerulein-induced acute pancreatitis via modulating autophagy initiation. Recently, increasing evidence showed that miRNAs play multiple functional roles in modulating the autophagy of Understanding the role of miRNA in autophagy regulation in the pathogenesis of AP is helpful to formulate targeted treatment plans and improve clinical efficacy. MiR-141 inhibits autophagy during the formation of AP autophagy bodies through the HMGB1/beclin-1 pathway. mir-181b expression level was decreased in AP rats (32). Inhibiting the expression of miR-155 can reduce the pathological injury of the pancreas in the AP model (33). On the contrary, the upregulation of miR-155 promotes autophagy and eventually aggravates the pathology of AMir-375 is significantly related to AP and served as a potential biomarker for AMir-375 was found to suppress autophagy by inhibiting Atg7, thus promoting inflammatory response and acinar cell apoptosis in the SAP model (34). In this study, we constructed the miRNA-mRNA interaction network in AP and further demonstrated the functional importance of miRNAs in AP.

Through comprehensive expression analysis, we found several miRNAs and mRNAs were significantly related to modulating autophagy signaling in AP, including hsa−miR−181c, hsa−miR−181d, hsa−miR−181b, hsa−miR−379 and hsa−miR−199a−5In previous studies, MiR-181 suppressed autophagy via PTEN/PI3K/Akt signaling, thereby regulating cisplatin resistance in NSCLC (35). In addition, mir-181-5p from Exosomes prevents liver fibrosis by autophagy activation. MiR-199a was reported to regulate autophagy by regulating mTOR expression in the cerebral infarction model. In Parkinson's disease model, miR-199a modulates autophagy via GSK3β. Moreover, Mir199a-5p was also reported to modulate autophagy to inhibit hepatic insulin sensitivity by inhibiting atg14 (36), inhibit cardiomyocyte autophagy by targeting HSPA and destroy autophagy by activating mTOR. Our studies for the first time comprehensively analyzed the potential miRNAs related to autophagy regulation in AP.

Conclusions

A total of 37 miRNAs and 189 mRNAs were identified to be differentially expressed in pancreatitis and normal samples. Bioinformatics analysis showed DEGs were significantly related to PI3K-Akt signaling, FoxO pathway, Oocyte meiosis, Progesterone-mediated oocyte maturation, Protein digestion and absorption and Focal adhesion. Next, we constructed a miRNA-mRNA regulation network in AP, consisting of 34 miRNAs and 96 mRNAs. The protein-protein interaction networks and the miRNA-

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Data Availability Statement

Publicly available datasets were analyzed in this study. This data can be found in GEO database (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE24279 and https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE123375).

Ethics Statement

According to our local legal and institutional requirements, research on human participants from public datasets does not require ethical review and approval. According to national legislation and institutional requirements, this study does not require written informed consent for participation.

Author Contributions

Conceptualization and writing, Xiaoju Su; methodology, Fanyang Kong; software, Qichen Zhang; data validation, Mengni Jiang; investigation and formal analysis, Xiangyu Kong; funding acquisition, Lei Wang, Xiangyu Kong and Yiqi Du. All authors have read and approved the manuscript.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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