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Identification of key genes and pathways associated with diabetes of the exocrine pancreas

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Abstract

This study aimed to identify potential essential genes and pathways in diabetes of the exocrine pancreas (DEP) and explore possible molecular mechanisms. The array dataset GSE76895 was downloaded from the Gene Expression Omnibus database. Pancreatic tissue samples from 20 Diabetes of the exocrine pancreas and 32 nondiabetic individuals were selected for analysis. GEO2R analyzed differentially expressed genes (DEGs) in the 2 groups. Gene ontology annotation, Kyoto Encyclopedia of Genes Genomes and Reactome pathway enrichment analyses and Gene Set Enrichment Analysis were performed in this study. Protein-protein interaction (PPI) networks were constructed using Cytoscape software, and core networks were identified using MCODE plugins. A total of 62 genes, including 59 up-regulated and 3 down-regulated genes, were differentially expressed in DEP samples compared with nondiabetic patients. PPI network with 53 nodes and 138 edges was established. HLA-DRA is identified as the central gene of the PPI network and maybe a marker gene for DEP. Furthermore, up-regulated DEGs are mainly enriched in pathways related to the immune system and infection. The results of this study suggest that HLA-DRA and immune system pathways may play essential roles in DEP.

Abbreviations: BP = biological process, CAMs = cell adhesion molecules, CC = cell component, DEGs = differentially expressed genes, DEP = diabetes of the exocrine pancreas, ES = enrichment score, GSEA = Gene Set Enrichment Analysis, GEO = Gene Expression Omnibus, GO = gene ontology, MCODE = Molecular Complex Detection, MF = molecular function, PPI = protein-protein interaction, KEGG = Kyoto Encyclopedia of Genes and Genomes, T2DM = type 2 diabetes mellitus.

Keywords: diabetes of the exocrine pancreas, enrichment analysis, PPI network

1. Introduction

Diabetes is a severe chronic disease and a significant worldwide public health problem. The number and prevalence of diabetes have steadily increased over the past decades. Diabetes is a metabolic disease characterized by hyperglycemia.[1] Hyperglycemia occurs due to defects or the destruction of insulin secretion. Long-term hyperglycemia can cause chronic damage and dysfunction of various tissues, especially the eyes, kidneys, heart, blood vessels, and nerves.[2]

Diabetes of the exocrine pancreas (DEP), also known as type 3c diabetes, is a type of diabetes that occurs when the pancreas is damaged or destroyed.[3] DEP patients showed varying degrees of exocrine and endocrine dysfunction. Studies have shown that most DEP patients are misdiagnosed as type 2 diabetes mellitus (T2DM) patients, and about 1.8% of adults with diabetes should be classified as DEP.[4] Acute and chronic pancreatitis are the most common causes of DEP. In addition, it is also related to pancreatic tumors, pancreatic insufficiency, and a family history of T2DM.[5,6] Impaired pancreatic β cell function and insulin resistance appear to have different contributions to hyperglycemia in patients with DEP.

Although increasing information in medical literature is related to diabetes in exocrine pancreas, some fundamental molecular mechanisms have yet to be determined. Therefore, the crucial genes or pathways related to DEP need to be determined.

2. Methods

2.1. Microarray data

We obtained the GSE76895 dataset through the NCBI Gene Expression Omnibus (GEO) public database (http://www.ncbi.nlm.nih.gov/geo/), uploaded by Mark et al.[7] The dataset contained pancreatic tissue samples from 20 DEP patients and 32 nondiabetic patients, and 36 T2DM patients. Microarray data

YZ and SL contributed equally to this work.

The datasets generated during and/or analyzed during the current study are publicly available.

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were based on GPL570 Platforms ([HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array). Additional approval by an ethics committee was not necessary because the datasets included in the current study were downloaded from public databases, and data acquisition and application were performed according to GEO publication guidelines and data access policies.

2.2. Obtain differential expression genes (DEGs)

DEGs between DEP and nondiabetic groups were determined by GEO2R online tools.[8] |log2FC| ≥1 and *P*-value < 0.05 were set as cutoff criteria. The DEGs with log2FC > 0 were considered up-regulated genes. The down-regulated genes were filtered according to log2FC <0. We also used DEG data to draw a volcano plot.

2.3. Genes related to T2DM

We identified the DEGs between the pancreatic tissue samples of T2DM patients and nondiabetic patients in the GSE76895 dataset and then intersected them with the DEGs of DEP patients to draw a Venn diagram. We also identified related genes that coincided with T2DM.

2.3. Gene ontology, Kyoto Encyclopedia of Genes Genomes (KEGG), and reactome pathway enrichment analyses

Gene ontology (GO) (http://geneontology.org/) expresses the scientific knowledge of gene function (protein and noncoding RNA molecules produced by genes) of many different organisms, from humans to bacteria, in a computational way. GO describes the understanding of the field of biology from 3 aspects: molecular function, cellular composition and biological process.[9] KEGG (https://www.kegg.jp) is a database that integrates information on genome, chemistry and system functions.[10] Reactome (reactome.org/PathwayBrowser) is a database of human biological responses and signaling pathways, which provides intuitive bioinformatics tools for the visualization, interpretation, and analysis of pathway knowledge.[11] Up and down-regulated genes were subjected to GO annotation, KEGG and Reactome pathway enrichment analyses. $P < 0.05$ was used as the threshold value, and the number of genes enriched in each pathway was ≥2. The up-regulated and down-regulated DEGs were subjected to GO annotation, KEGG, and Reactome pathway enrichment analysis.

2.4. Gene set enrichment analyses

Gene Set Enrichment Analysis (GSEA) is a computational method that can determine whether a defined set of genes shows statistically significant, concordant differences between 2 biological states.[12] First, the RNA-sequencing data from GEO were divided into 2 groups (DEP vs nondiabetic patients). Then we used GSEA to identify the potential molecular mechanisms of DEP, choosing the annotated gene sets of (c2.cp.KEGG.v7.0.symbols.gmt) as the reference gene sets. Differences at nominal $P < 0.05$, False Discovery Rate (FDR) <0.05 and enrichment score (ES) >0.6 were defined as the cutoff criteria.

2.5. PPI network and module analysis

Online functional protein association network analysis website STRING(https://string-db.org/) evaluates the PPI network.[13] Then, construct PPI networks using Cytoscape software to examine the potential correlations between these DEGs.[14] Subsequently, the Molecular Complex Detection (MCODE) app from Cytoscape was used to identify the modules of the PPI network. Parameters were set as Node Score Cutoff = 0.2, Degree Cutoff = 2, K-Core = 4 and Max. Depth = 100.

2.6. Statistics

For the visualization of the correlation of gene expression with fasting glucose, the relationship between 2 variables was plotted with GraphPad Prism (GraphPad Software Inc, La Jolla, CA). The student *t*-test was performed for statistical significance comparison between the 2 groups. Correlations were evaluated using Pearson correlation analyses. $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Identification of DEGs in DEP

There were 20 DEP pancreatic tissues and 32 nondiabetic pancreatic tissues in our present study. By comparison, we identified 62 DEGs (59 up-regulated and 3 down-regulated), with $P < 0.05$ and |log2FC|≥1. (Fig 1A). The miRNA (mir8071) was found in up-regulated genes. LncRNA (XIST) was significantly down-regulated in DEP pancreatic tissues (Table 1, Supplemental Digital Content, http://links.lww.com/MD/G813).

3.2. Genes related to T2DM

We identified 40 DEGs in the pancreatic tissue samples from T2DM and nondiabetic patients and used Venn diagram software to identify the common DEGs between T2DM and DEP (Table 2, Supplemental Digital Content, http://links.lww.com/MD/G813). We found 4 common genes ALDOB, LY96, IRF8, and ELFN1 (Fig 1B).

3.3. GO and pathway enrichment analyses

GO, KEGG pathway and Reactome pathway analyses were respectively performed for 62 DEGs (59 up-regulated and 3 down-regulated DEGs). The GO biological process (BP) analysis showed that the up-regulated DEGs were mainly enriched in the aspects of the immune response, regulation of the immune response, complement activation, classical pathway, complement, activation, phagocytosis, engulfment. The GO cellular composition analysis displayed that the up-regulated DEGs were significantly enriched in the aspects of extracellular space, extracellular region, extracellular exosome, blood microparticle, extracellular matrix, ER to Golgi transport vesicle membrane. The GO molecular function (MF) analysis demonstrated that the up-regulated DEGs were enriched in the aspects of immunoglobulin receptor binding, antigen binding, platelet-derived growth factor binding, serine-type endopeptidase activity, MHC class II receptor activity, extracellular matrix structural constituent (Table 1).

Significantly enriched KEGG pathways of up-regulated genes included Staphylococcus aureus infection, Leishmaniasis, Pertussis, Asthma, Cell adhesion molecules (CAMs), and Tuberculosis (Table 2).

The significantly enriched Reactome pathways by up-regulated DEGs were Immunoregulatory interactions between a Lymphoid and a nonLymphoid cell, Phosphorylation of CD3 and TCR zeta chains, Scavenging of heme from plasma, Generation of second messenger molecules, Assembly of collagen fibrils and other multimeric structures, Cell surface interactions at the vascular wall (Table 3). However, the down-regulated DEGs had no significant pathway enrichment.

3.4. Gene set enrichment analyses

In order to explore the underlying mechanism of DEP, GSEA was used to obtain the DEP-related gene collection based on

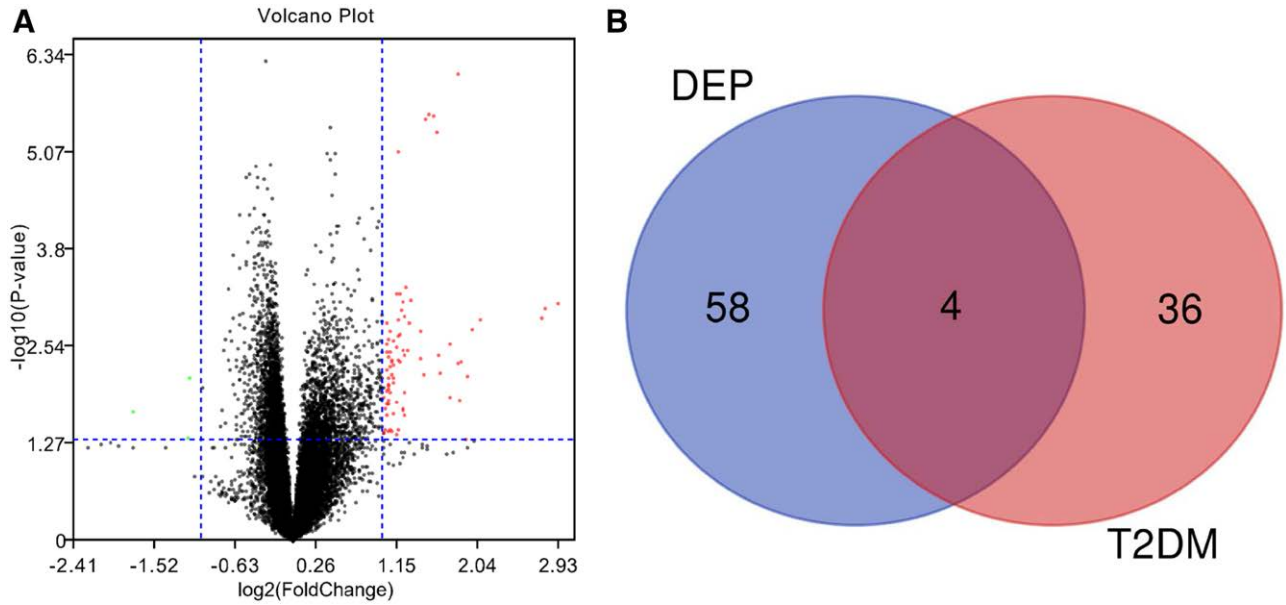

Figure 1. DEGs from the GSE76895 dataset. A, Volcano plot of DEGs between DEP and nondiabetic patients pancreatic tissues in the GSE76895 dataset. Red dots: significantly up-regulated genes; Green dots: significantly down-regulated genes; black dots: nondifferentially expressed genes. $P < 0.05$ and $\log_2$FC > 1 were considered statistically significant. B, Venn diagram of overlapping DEGs from T2DM and DEP.

Table 1

GO analysis of DEGs in DEP

Expression	Category	Term	Count	%	*P*-value	FDR
Up-regulated	GOTERM_BP_DIRECT	Immune response	14	0.2	2.00E-10	8.50E-08
	GOTERM_BP_DIRECT	Regulation of immune response	10	0.2	2.40E-09	5.10E-07
	GOTERM_BP_DIRECT	Complement activation, classical pathway	6	0.1	1.10E-05	1.60E-03
	GOTERM_BP_DIRECT	Complement activation	5	0.1	1.30E-04	1.40E-02
	GOTERM_BP_DIRECT	Phagocytosis, engulfment	4	0.1	1.50E-04	1.30E-02
	GOTERM_BP_DIRECT	Collagen fibril organization	4	0.1	2.10E-04	1.50E-02
	GOTERM_CC_DIRECT	Extracellular space	19	0.3	2.90E-08	2.40E-06
	GOTERM_CC_DIRECT	Extracellular region	20	0.3	7.70E-08	3.20E-06
	GOTERM_CC_DIRECT	Extracellular exosome	21	0.3	8.60E-05	2.40E-03
	GOTERM_CC_DIRECT	Blood microparticle	6	0.1	8.60E-05	1.80E-03
	GOTERM_CC_DIRECT	Extracellular matrix	7	0.1	2.30E-04	3.90E-03
	GOTERM_CC_DIRECT	ER to Golgi transport vesicle membrane	4	0.1	4.90E-04	6.80E-03
	GOTERM_MF_DIRECT	Immunoglobulin receptor binding	4	0.1	5.00E-05	6.00E-03
	GOTERM_MF_DIRECT	Antigen binding	5	0.1	1.90E-04	1.10E-02
	GOTERM_MF_DIRECT	Platelet-derived growth factor binding	3	0	4.10E-04	1.60E-02
	GOTERM_MF_DIRECT	Serine-type endopeptidase activity	6	0.1	6.90E-04	2.00E-02
	GOTERM_MF_DIRECT	MHC class II receptor activity	3	0	7.80E-04	1.80E-02
	GOTERM_MF_DIRECT	Extracellular matrix structural constituent	4	0.1	8.60E-04	1.70E-02

Table 2

KEGG analysis of DEGs in DEP

Expression	Category	Term	Count	%	*P*-value	FDR
	KEGG_PATHWAY	*Staphylococcus aureus* infection	6	0.1	2.10E-06	1.60E-04
	KEGG_PATHWAY	Leishmaniasis	5	0.1	1.80E-04	6.90E-03
	KEGG_PATHWAY	Pertussis	5	0.1	2.20E-04	5.70E-03
	KEGG_PATHWAY	Asthma	4	0.1	2.30E-04	4.40E-03
	KEGG_PATHWAY	Cell adhesion molecules (CAMs)	6	0.1	2.30E-04	3.60E-03
	KEGG_PATHWAY	Tuberculosis	6	0.1	6.50E-04	8.40E-03

the actual overall trend analysis and compare enrichment analysis such as KEGG. The pathways closely related to the DEP were "Autoimmune thyroid disease", "Leishmania infection", "Tryptophan metabolism", "Hematopoietic cell lineage", "Intestinal immune network for IgA production", "Toll like receptor signaling pathway", "Antigen processing and presentation", "Pathogenic escherichia coli infection", "Natural killer cell mediated cytotoxicity", "Cell adhesion molecules cams", "Allograft rejection", "Type 1 diabetes mellitus", "Thyroid cancer", "Apoptosis", "P53 signaling pathway". (Fig. 2)

Table 3

Reactome Pathways analysis of DEGs in DEP

Expression	Category	Term	Count	%	*P*-value	FDR	Genes
Up-regulated	Reactome Pathways	Immunoregulatory interactions between a Lymphoid and a nonLymphoid cell	10	16.94915254	1.77E-08	1.19E-06	COL1A1, C3, COL3A1, COL1A2, IGKC, CD300A, IGLV1-44, ITGB2, SLAMF7, IGLC1
	Reactome Pathways	Phosphorylation of CD3 and TCR zeta chains	4	6.779661017	1.04E-04	0.002669234	PTPRC, HLA-DRA, HLA-DQA1, HLA-DQB1
	Reactome Pathways	Scavenging of heme from plasma	5	8.474576271	1.20E-04	0.002669234	IGKC, IGLV1-44, IGLC1, IGHA2, JCHAIN
	Reactome Pathways	Generation of second messenger molecules	4	6.779661017	3.15E-04	0.0052812	HLA-DRA, FYB, HLA-DQA1, HLA-DQB1
	Reactome Pathways	Assembly of collagen fibrils and other multimeric structures	4	6.779661017	6.53E-04	0.008755635	COL1A1, COL3A1, MMP7, COL1A2
	Reactome Pathways	Cell surface interactions at the vascular wall	4	6.779661017	0.001046052	0.0104324	COL1A1, COL1A2, FCER1G, ITGB2

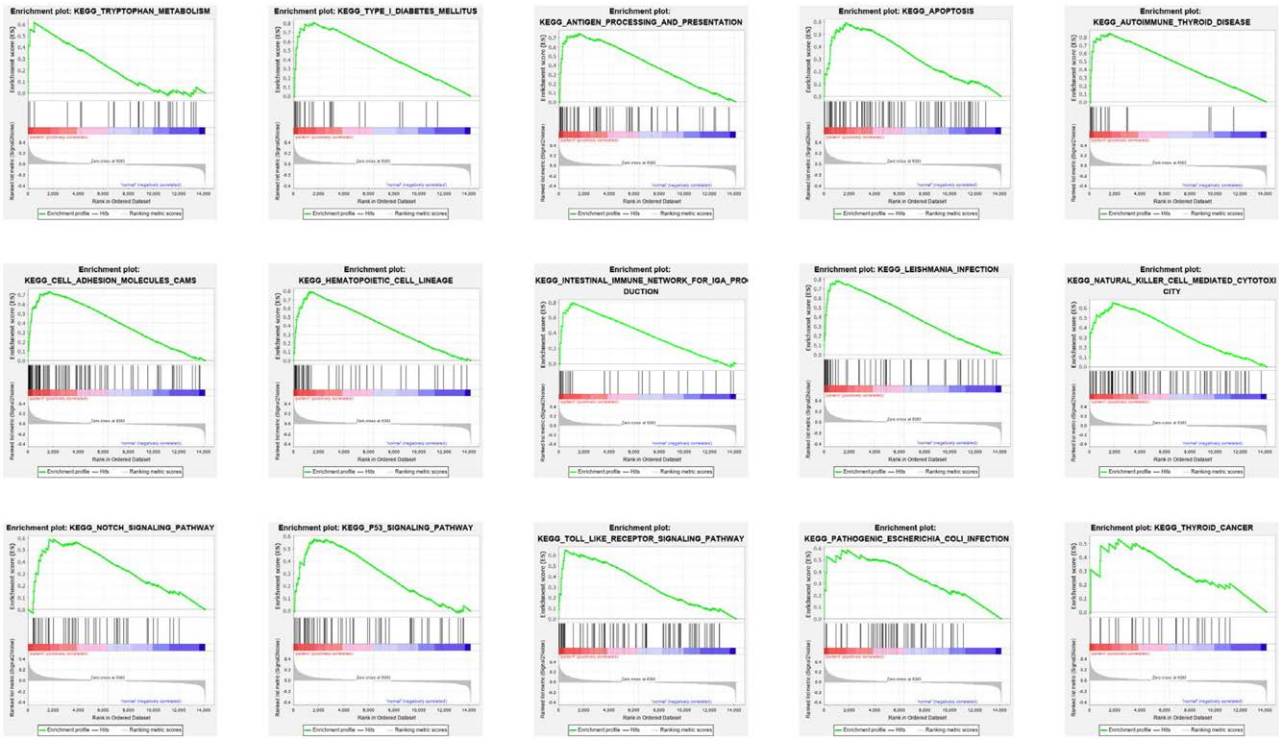

Figure 2. List of the 15 most common functional gene sets enriched in DEP samples.

3.5. Protein–protein interaction network (PPI) and modular analysis

Due to the elimination of pseudogenes, noncoding genes and unrecognized genes, we obtained a 53-nodes, 138 edges PPI network (average node degree:5.15, PPI enrichment *P*-value:<1.0e-16). After removing the individual nodes, a total of 43 DEGs (42 up-regulated genes and 1 down-regulated gene) from DEP were screened into the DEGs PPI network. Then we applied MCODE for further analysis and found a core network of 12 genes (CD52, RNASE6, LY86, ITGB2, CD53, FCER1G, HLA-DRA, PTPRC, IRF8, FYB, LAPTM5, C1QC). The hub gene of the network was HLA-DRA. (Fig. 3)

3.6. HLA-DRA, ALDOB, LY96, IRF8, ELFN1 genes expression associated with fasting glucose

In the GSE76895 data set, HLA-DRA, ALDOB, LY96, IRF8, and ELFN1 in DEP were significantly increased compared with non-diabetic. The expression of these genes was positively correlated with fasting glucose (Fig. 4). Fasting glucose data were obtained from dataset GS76895.

4. Discussion

Diabetes of the exocrine pancreas is a specific disease that distinguishes it from type 1 diabetes mellitus (T1DM) and T2DM. The cause is primarily due to damage or destruction of the pancreas. However, the pathogenesis of DEP has not been fully elucidated, and the key genes and pathways of DEP need to be further discovered. Therefore, it is of great significance to explore the potential biomarkers of DEP. This study identified 62 DEGs, including 59 up-regulated and 3 down-regulated DEGs, based on the GEO dataset via bioinformatics methods. In the PPI network, we have identified a major network (including CD52, RNASE6, LY86, ITGB2, CD53, FCER1G, HLA-DRA, PTPRC, IRF8, FYB, LAPTM5, C1QC) with HLA-DRA as the core gene. The function and pathway enrichment analysis of DEGs shows that the DEGs are mainly enriched in pathways and processes related to immunity, metabolism, infection,

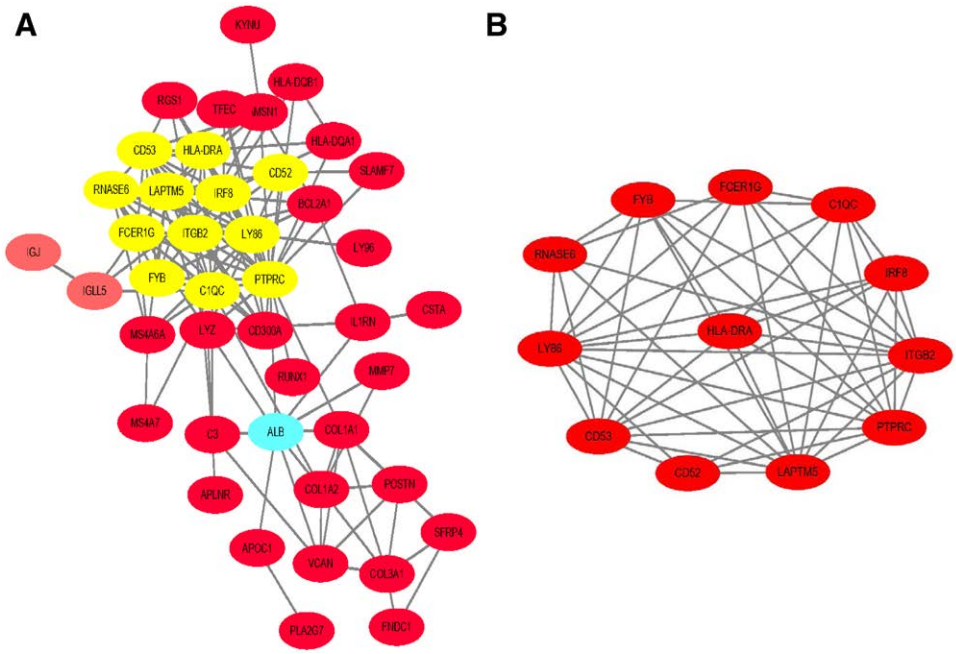

Figure 3. Common DEGs PPI network constructed by Cytoscape software. A, A total of 43 DEGs in the DEGs Protein-protein interaction network complex. Red nodes represent up-regulated and cyan nodes represent down-regulated genes. Yellow nodes represent the core network genes. B, Module analysis via Cytoscape software (degree cutoff = 2, node score cutoff = 0.2, k-core = 2, and max. Depth = 100).

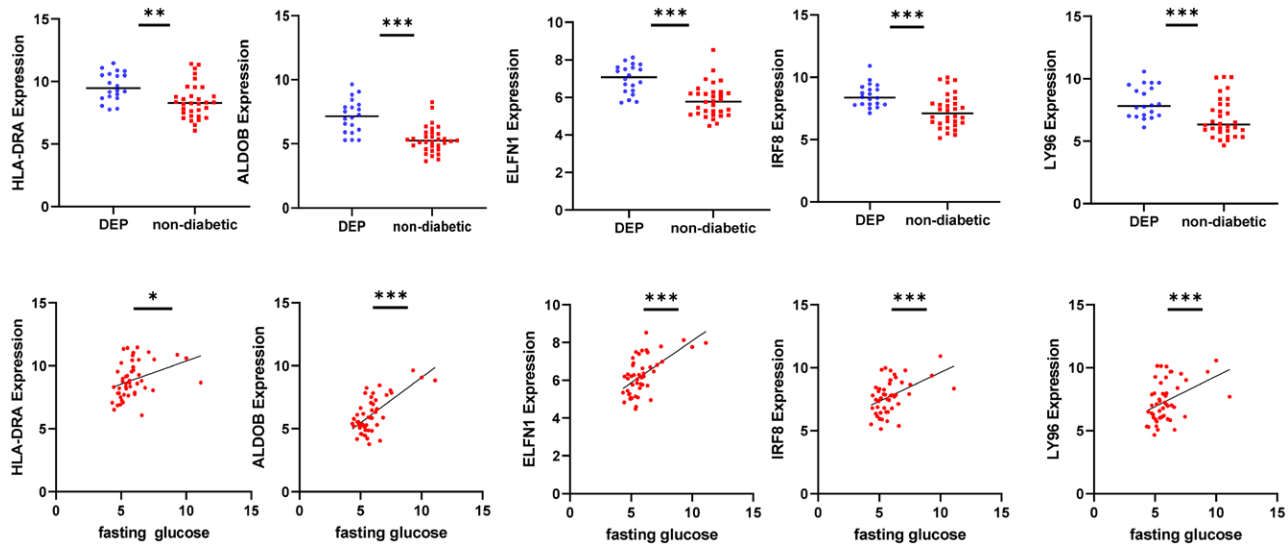

Figure 4. A HLA-DRA, ALDOB, LY96, IRF8, ELFN1 expression were increased in DEP compared with nondiabetes. B HLA-DRA, ALDOB, LY96, IRF8, ELFN1 expression were positively correlated with fasting glucose.

and tumors. Therefore, these core genes and pathways have a positive effect on the diagnosis and treatment strategies of DEP.

We found 4 common genes, ALDOB, LY96, IRF8, and ELFN1, between T2DM and DEP. The change in ALDOB gene expression may be related to the change in insulin secretion. Gerst et al[15] reported that high expression of ALDOB mRNA in the pancreas could lead to decreased insulin secretion levels. IRF8 is considered to be the primary regulator of autophagy and macrophage polarization. Guo et al[16] demonstrated that IRF8 is involved in advanced glycation end products induced macrophage autophagy and M1 polarization. The role of LY96 and ELFN1 in diabetes remains to be further studied.

Acute and chronic pancreatitis are the leading causes of DEP, while other less common reasons are pancreatic etiologies, including surgical pancreatic resection, pancreatic cancer, hemochromatosis, and congenital agenesis of the pancreas.[6]

The results of the KEGG pathway analysis verified that DEP is associated with infection-related pathways. Studies have shown that inflammation can lead to decreasing expression of peripheral tissue antigens in pancreatic lymph nodes and, at the same time, produce new islet antigens that are intolerant to T cells. During the progression of T1DM, inflammation causes self-reactive T cells to escape and become active and may contribute to the pathogenesis of T1DM.[17]

Enrichment analysis of GO and Reactome found that DEP is closely related to the immune response-related pathways. Thus, we believe that DEP is associated with islet infection or Immune-related factors. The cause of type 1 diabetes is due to

the infiltration of CD4(+) and CD8(+) T lymphocytes, B lymphocytes, natural killer cells, dendritic cells and other immune cells, which are involved in the damage of pancreatic beta cells.[18] Among them, macrophages and CD4(+) T cells are the main participants, and CD8(+) T cells are the most important initiators of the immune process leading to the death of β cells.[19] In addition, Andersson et al[20] found that cytokines (including interleukin 1 beta, tumor necrosis factor-alpha, and interferon-gamma) inhibit glucose-stimulated insulin release. Therefore, the pathway of the immune system may be significantly related to DEP.

The relationship between pancreatitis, pancreatic cancer and DEP may be interrelated. Through GSEA analysis, we found that DEP is related to tumor-related pathways such as P53, in addition to autoimmunity and infection pathways. Since diabetes and chronic pancreatitis are both risk factors for pancreatic cancer,[21] DEP may significantly increase the risk of pancreatic cancer.

We found that the protein network with HLA-DRA as the core hub played a vital role in DEP by analyzing protein interaction networks. Aydemir et al[22] found that genetic variation in the HLA-DRA1 gene can regulate the susceptibility of HLA-DR3 homozygotes to type 1 diabetes. The single nucleotide polymorphism in HLA-DRA1 intron 1 can alter the risk of T1DM in HLA-DR3 haplotype homozygous individuals. Therefore, our results are consistent with previous results, indicating that HLA-DRA may be the key gene related to DEP.

In summary, HLA-DRA and immune system pathways may play an essential role in diabetes of the exocrine pancreas. However, the prediction of this crucial gene and pathway should be verified through a series of experiments. Besides, the molecular mechanism of DEP needs to be compared with other types of diabetes for in-depth research.

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