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Presence of PD-1 similarity genes in monocytes may promote the development of type 1 diabetes mellitus and poor prognosis of pancreatic cancer

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ABSTRACT

Introduction To identify proteins and corresponding genes that share sequential and structural similarity with programmed cell death protein-1 (PD-1) in patients with type 1 diabetes mellitus (T1DM) via bioinformatics analysis.

Research design and methods All proteins with immunoglobulin V-set domain were screened in the human protein sequence database, and the corresponding genes were obtained in the gene sequence database. GSE154609 was downloaded from the GEO database, which contained peripheral blood CD14+ monocyte samples from patients with T1DM and healthy controls. The difference result and the similar genes were intersected. Analysis of gene ontology and Kyoto encyclopedia of genes and genomes pathways was used to predict potential functions using the R package 'cluster profiler'. The expression differences of intersected genes were analyzed in The Cancer Genome Atlas pancreatic cancer dataset and GTEx database using t-test. The correlation between the overall survival and disease-free progression of patients with pancreatic cancer was analyzed using Kaplan-Meier survival analysis.

Results 2068 proteins with immunoglobulin V-set domain similar to PD-1 and 307 corresponding genes were found. 1705 upregulated differentially expressed genes (DEGs) and 1335 downregulated DEGs in patients with T1DM compared with healthy controls were identified. A total of 21 genes were overlapped with the 307 PD-1 similarity genes, including 7 upregulated and 14 downregulated. Of these, mRNA levels of 13 genes were significantly increased in patients with pancreatic cancer. High expression of *MYOM3* and *HHLA2* was significantly correlated with shorter overall survival of patients with pancreatic cancer, while high expression of *FGFRL1*, *CD274*, and *SPEG* was significantly correlated with shorter disease-free survival of patients with pancreatic cancer.

Conclusions Genes encoding immunoglobulin V-set domain similar to PD-1 may contribute to the occurrence of T1DM. Of these genes, *MYOM3* and *SPEG* may serve as potential biomarkers for the prognosis of pancreatic cancer.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ It is already known that programmed cell death protein-1 plays an important role in the development of type 1 diabetes mellitus (T1DM) and pancreatic cancer.

WHAT THIS STUDY ADDS

⇒ This study identifies 63 genes corresponding to 483 proteins with immunoglobulin V-set domain and subcellular localization in patients with T1DM, which may contribute to the occurrence of T1DM. In addition, this study identifies potential prognostic biomarkers for pancreatic cancer, including *MYOM3*, *HHLA2*, *FGFRL1*, *CD274*, and *SPEG*, which were found to be significantly correlated with overall survival or disease-free progression of patients with pancreatic cancer.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides new insights into the potential mechanisms underlying T1DM and identifies potential biomarkers for the prognosis of pancreatic cancer. These findings may have implications for future research on the development of novel treatments for T1DM and the identification of prognostic biomarkers for pancreatic cancer. The results of this study could ultimately impact clinical practice and policy by improving patient outcomes through earlier detection and targeted treatment strategies.

INTRODUCTION

Programmed cell death protein-1 (PD-1) belongs to the CD28/CTLA-4 co-receptor family containing a single extracellular immunoglobulin variable (V) domain.[1] PD-L1 is a ligand for PD-1 and is a member of the CD28/B7 family.[2] PD-1 is a critical immune checkpoint protein in human immune cells, which plays an important role in regulating immune responses and maintaining immune homeostasis by interacting with PD-L1.[3] PD-1 deficiency may lead to various autoimmune diseases.[4] Multiple studies have shown that the incidence of type 1 diabetes mellitus (T1DM) is significantly increased in the presence of PD-1 deficiency in pre-diabetic NOD mice.[5] In addition, PD-1/PD-L1 signaling pathway

is also involved in malignant tumorigenesis and immune escape.[6] It has been reported that the occurrence and immune escape of pancreatic cancer are related to the PD-1/PD-L1 pathway.[7] Previous studies have reported upregulation of PD-L1 in human pancreatic cancer samples.[8] It has also been shown that PD-L1 blockers can effectively inhibit pancreatic cancer in mouse models.[9] These results suggest that the PD-1/PD-L1 pathway plays an important role in pancreatic cancer.

Monocytes, the largest type of white blood cells and part of the innate immune system's phagocytic cells, have been shown to play a crucial role in the progression of cancer and autoimmune disorders. They are capable of inducing tumor cell killing via cytokines or phagocytosis induction and involved in the progression and regression of inflammation.[10] Notably, PD-1 expression was found to be elevated in the monocytes of patients with hepatocellular carcinoma and contributed to the suppression of CD8 T cell.[11] Individuals diagnosed with T1DM have been shown to exhibit elevated levels of pro-inflammatory monocytes and circulating inflammatory mediators.[12] The aforementioned evidence indicates that monocytes and PD-1/PD-L1 pathway have become crucial regulators in the progression of cancer and autoimmune diseases.

Given the significance of PD-1 pathway in T1DM and pancreatic cancer and the crucial role of monocytes in the progression of cancer and autoimmune disorders, this study aims to use bioinformatics analysis to identify proteins and their corresponding genes that share structural and sequential similarities with PD-1 in patients with T1DM. These identified proteins and genes could serve as potential targets for further investigation in future studies.

MATERIALS AND METHODS

Screening for proteins with similar structures to PD-1 protein

Human (GRCh38.p13) genome sequence database, protein sequence database and gene annotation file were downloaded from the National Center for Biotechnology Information (https://www.ncbi.nlm.nih.gov/genome/?term=txid9606(orgn)); (protein sequence: https://ftp.ncbi.nlm.nih.gov/genomes/all/GCF/000/001/405/GCF_000001405.39_GRCh38.p13/GCF_000001405.39_GRCh38.p13_protein.faa.gz; gene annotation file: https://ftp.ncbi.nlm.nih.gov/genomes/all/GCF/000/001/405/GCF_000001405.39_GRCh38.p13/GCF_000001405.39_GRCh38.p13_genomic.gff.gz; genome sequence file: https://ftp.ncbi.nlm.nih.gov/genomes/all/GCF/000/001/405/GCF_000001405.39_GRCh38.p13/GCF_000001405.39_GRCh38.p13_genomic.fna.gz;

HMMER software: https://www.ebi.ac.uk/Tools/hmmer/; Pfam database: http://Pfam.xfam.org/; software parameters: –noali -E 1e-5 Pfam-A.hmm).

To identify the immunoglobulin V-set domain of PD-1, we used the Hmmscan program for Pfam annotation and applied a filtering criterion based on an E-value threshold of less than 1e-5.[13] All proteins with immunoglobulin V-set domain similar to the PD-1 were then screened in human protein sequence database, and the corresponding genes were obtained in gene sequence database.

Protein subcellular localization analysis

The subcellular distribution and functions of the obtained similar proteins were predicted using the Hum-mPLoc 3.0 database (http://www.csbio.sjtu.edu.cn/bioinf/hum-mPLoc3/).[14]

Identification of differentially expressed genes in patients with T1DM

The GSE154609 dataset[15] containing 12 T1DM samples and 12 healthy controls was downloaded from the GEO database (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE154609) to identify differentially expressed genes (DEGs) in patients with T1DM using wilcox-test (R language, wilcox.test; R V.4.1.2 (https://www.r-project.org/)). Data were visualized using box plots. During comparison, filter according to the upper and lower limit algorithm of the box plot, that is, the upper limit of each group of data was Q3+1.5 IQR, the lower limit was Q1–1.5 IQR (IQR=Q3–Q1). After the difference result ($p<0.05$) was obtained, the similar genes obtained in the first step were intersected. P value less than 0.05 was considered statistically significant.

Gene ontology and Kyoto encyclopedia of genes and genomes

DEGs were subjected to gene ontology (GO) functional annotation (http://www.geneontology.org/) and Kyoto encyclopedia of genes and genomes (KEGG) pathway analysis (http://www.kegg.jp/). Statistical analysis of GO and KEGG enrichment data was carried out using the R package 'cluster profiler'. A p value less than 0.05 was considered statistically significant.

Prognosis and differential expression analysis in pancreatic cancer

To compare the mRNA levels of the genes related to both T1DM and PD-1 similarity, 179 pancreatic cancer samples and 4 normal pancreatic samples were downloaded from The Cancer Genome Atlas (TCGA) database. To increase the normal control sample size, 167 normal pancreatic samples were downloaded from the GTEx database. Expression differences of intersected genes were analyzed by t-test. Kaplan-Meier survival analysis was performed to assess the correlations of the genes related to both T1DM and PD-1 similarly with the prognosis (overall survival and disease-free progression) of patients with pancreatic cancer. A p value less than 0.05 was considered statistically significant.

RESULTS

Identification of proteins sharing sequential and structural similarity with PD-1

According to the structural similarity, the proteins with immunoglobulin V-set domain similar to PD-1 and their corresponding genes were screened in the Pfam

database. We found that 2068 proteins encoded by 307 genes may share structural and functional similarities with PD-1 (online supplemental tables 1–3). However, using the Hum-mPLoc bioinformatics tool, we found that only 483 of these proteins have subcellular localization information, which correspond to 63 genes. Eighty-two were located in the cytoplasm, 348 were located in the cell membrane, 14 were located in the nucleus, and 39 were located in the extracellular region (figure 1A and online supplemental table 4).

Identification of DEGs in patients with T1DM and enrichment analysis

To identify the genes that might contribute to T1DM occurrence due to analogous pathway of PD-1 in T cells, we sought to find out the genes in the intersection between T1DM-related genes and the 307 genes encoding potential analogs (immunoglobulin V-set domain) of PD-1. In the GSE154609 dataset containing 12 peripheral blood CD14+ monocyte samples of patients with T1DM and 12 healthy controls, we identified 1705 upregulated DEGs and 1335 downregulated DEGs in patients with T1DM compared with healthy controls (online supplemental table 5). Among these DEGs, a total of 21 genes (figure 1B) were overlapped with the 307 PD-1 homologies, including 7 upregulated (figure 1C) and 14 downregulated (figure 1D) genes (online supplemental tables 6 and 7). The 1705 upregulated and 1335 downregulated DEGs were further subjected to GO annotation and KEGG pathway analysis. These genes were mainly annotated as receptor complex, external side of plasma membrane, and M band (figure 2A and online supplemental table 8). KEGG pathway analysis revealed that these genes were mostly enriched in the prostate cancer, central carbon metabolism in cancer, and EGFR tyrosine kinase inhibitor resistance pathways (figure 2B and online supplemental table 9).

T1DM-related genes are highly expressed in pancreatic cancer and associated with the prognosis of pancreatic cancer

To investigate the clinical significance of the 21 common genes related to both both T1DM and PD-1 similarity, we compared their mRNA levels between pancreatic cancer tissue samples (n=179) from the TCGA database and normal tissue samples from TCGA database (n=4) and GTEx database (n=167). As shown in figure 3A, compared with those in normal controls, the mRNA levels of *SIGLEC10, SPEG, BTN3A1, CD300LF, CEACAM1, FCER1A, HHLA2, IL1R2, MCAM, MYOM3, PDGFRB, PIGR*, and *PILRA* were significantly increased in patients with pancreatic cancer. Furthermore, high expression of *MYOM3* and *HHLA2* was significantly correlated with shorter overall survival of patients with pancreatic cancer (figure 3B) and that high expression of *FGFRL1*, *CD274*, and *SPEG* was significantly correlated with shorter disease-free survival of patients with pancreatic cancer (figure 3C). These results suggest that these genes may serve as risk factors for T1DM onset and prognostic factors in patients with pancreatic cancer.

DISCUSSION

PD-1 is a member of the CD28/CTLA-4 co-receptor family, sharing 25% sequence identity. It is recognized as a type I membrane protein possessing a singular extracellular immunoglobulin V domain.[16] PD-1 and PD-L1 interact using their V domains A'GFCC' β-sheets to form a pair of V domains in an Fv-like structure, similar to the V domains of antibodies, T cell receptors, or Fv paired (TCR) and CD8 to function.[17] Due to its significant involvement in the regulation of peripheral tolerance, a lack of PD-1 may contribute to the development of multiple autoimmune diseases.[18] Multiple studies have shown the presence of PD-1 deficiency in pre-diabetic NOD mice significantly increases the incidence of T1DM.[19 20] Antibodies specific for PD-1 or PD-L1 but not PD-L2 accelerate insulitis in NOD mice, and also induce T1DM within 10 days.[21 22] Not only do T cells act through the PD-1 pathway, but our study found that through gene encoding, a functionally similar protein was also present in peripheral blood mononuclear cells of T1DM.

The study found that islet macrophages (derived from monocytes) are located near blood vessels, and they communicate with cellular and acellular components of the blood through filopodia that extend into the vascular lumen. They also interact with β-cells to capture insulin and deliver it to self-reactive T cells, which are essential for immune responses.[23] This led us to wonder if monocytes could play the same role. On the one hand, multiple studies have shown that diabetes, through high blood glucose levels, alters monocyte/macrophage metabolism, leading to failure of innate immune and inflammatory processes, and dysregulation of macrophage-specific signal transduction.[24–26 24] On the other hand, Ying *et al* found that macrophages can protect and aggravate T1DM by increasing islet inflammation and affecting β-cell proliferation.[25] However, whether monocytes/macrophages affect T1DM through the PD-1 pathway has not been studied. Therefore, this aspect of research may be a direction in the future. Although the mechanisms of immune checkpoint inhibitor (ICI)-induced T1DM remain unclear, studies have linked the onset of T1DM with autoimmune responses.[26] Because the pathogenesis of ICI-induced T1DM is the same as that of T1DM, the PD-1 pathway may be blocked. In addition, epidemiological studies have suggested a close relationship between diabetes mellitus and pancreatic cancer.[27] Some researchers even suggest that new-onset diabetes may be an early manifestation of pancreatic cancer, which provides important clues for the early diagnosis of pancreatic cancer.[28] Meanwhile, several studies have reported that diabetes mellitus affects the prognosis of patients with pancreatic cancer.[29] However, the underlying molecular mechanism is still unclear. It is worth mentioning that pancreatic cancer evades the immune response by

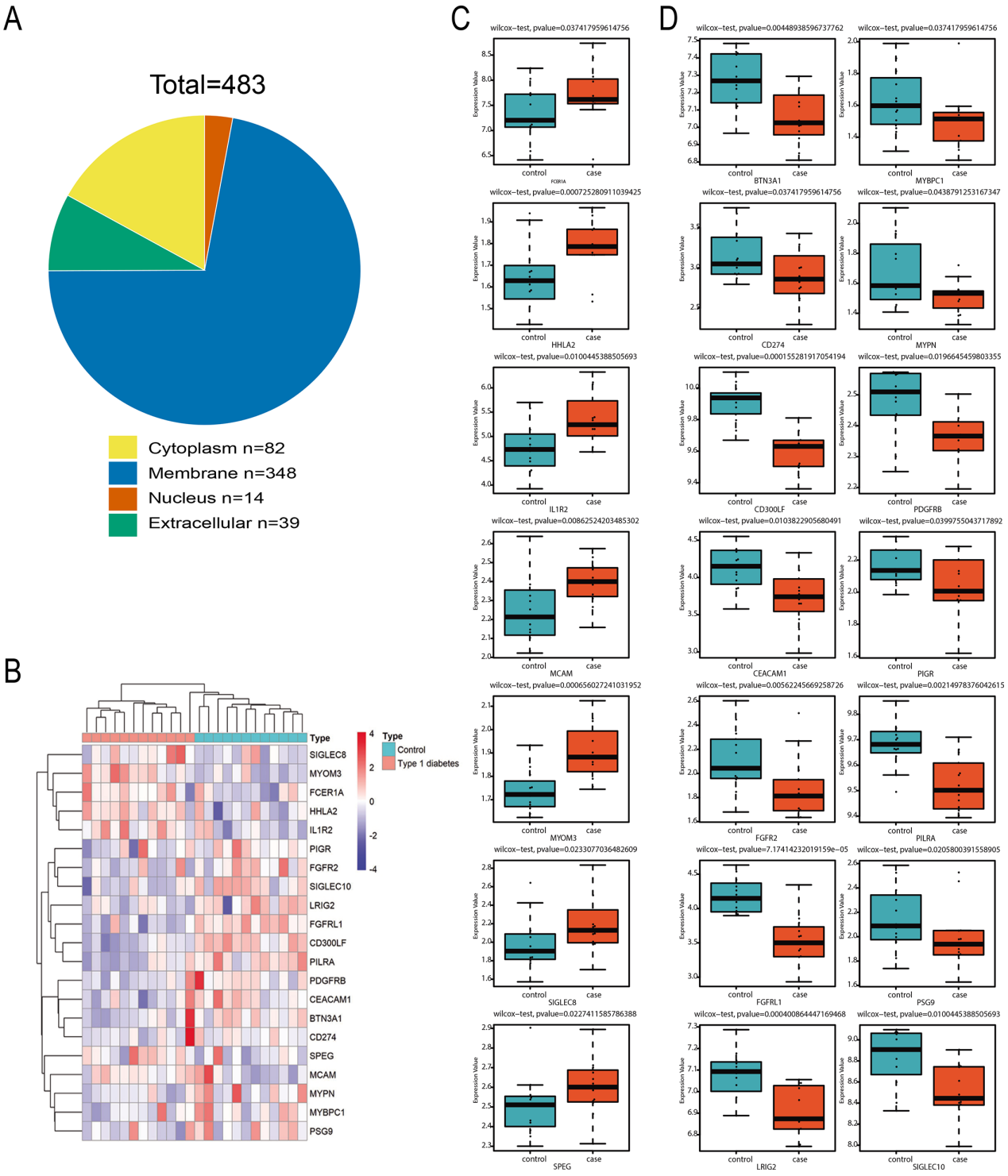

Figure 1 Identification of differentially expressed genes (DEGs) in patients with type 1 diabetes mellitus (T1DM) compared with healthy controls. (A) Hum-mPLoc bioinformatics analysis was performed to predict the localization of proteins sharing sequential and structural similarity with programmed cell death protein-1. (B) The GSE154609 dataset containing 12 T1DM samples and 12 healthy controls was obtained from the GEO database (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE154609). The heat map shows 21 DEGs in patients with T1DM compared with healthy controls. (C) Box plots of seven significantly upregulated genes in diabetic samples. (D) Box plots of 14 significantly downregulated genes in diabetic samples.

inducing the development of immunosuppressive T cells, thereby blocking the PD-1 pathway.[8] Based on the role of PD-1/PD-L1 pathway in T1DM and pancreatic cancer, in this article, we discuss these two diseases together.

In this study, we aimed to identify proteins and the corresponding genes sharing sequential and structural similarity with PD-1 in T1DM. We found 21 genes associated with both T1DM and PD-1 similarity which were

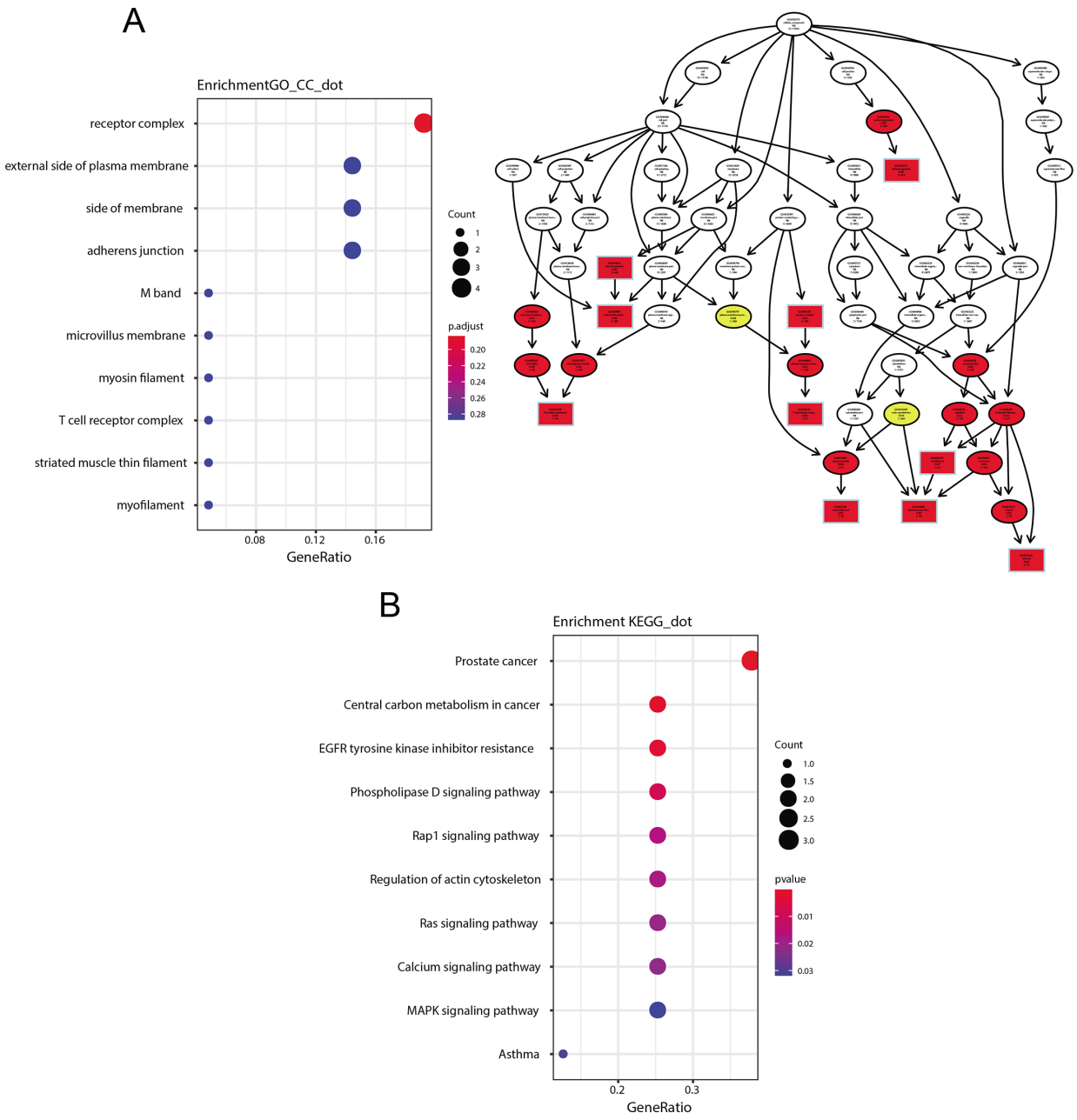

Figure 2 Functional enrichment analysis of DEGs in patients with T1DM. A total of 985 upregulated genes and 1253 downregulated genes in patients with T1DM were subjected to gene ontology (GO) functional annotation (http://www.geneontology.org/) and Kyoto encyclopedia of genes and genomes (KEGG) pathway analysis (http://www.kegg.jp/). (A) Scatter plot (left) and directed acyclic graph (right) for GO term enrichment analysis. Rectangular nodes represent GO terms; oval nodes represent biological processes; yellow indicates p<0.05; red indicates p<0.01. (B) A dot plot for KEGG enrichment analysis. Gene ratio=the numbers of DEGs annotated in a specific pathway/the numbers of all genes annotated. Top 10 pathway terms enriched are displayed in the figure. DEGs, differentially expressed genes; T1DM, type 1 diabetes mellitus.

screened from peripheral blood CD14+ monocyte samples of patients with T1DM. We identified 7 upregulated and 14 downregulated genes, out of which 13 genes, including *BTN3A1* and *CEACAM1*, were significantly upregulated in pancreatic cancer. High expression of *MYOM3*, *HHLA2*, *FGFRL1* and *CD274* and low expression of *SPEG* were significantly associated with poor prognosis of patients with pancreatic cancer. These genes may also be potential risk factors for T1DM and prognostic factors for pancreatic cancer, and may serve as potential biomarkers for PD-1 inhibitor-induced T1DM.

Consistent with our results, previous researches have linked several genes to cancer, diabetes, and immune checkpoint pathways. For instance, *SIGLEC10*, a member of the Siglec family, is involved in the modulation of immune tolerance and is associated with the pathogenesis of autoimmune diseases, inflammatory reactions, and tumors.[30 31] Therapeutic drugs targeting Siglec antibodies

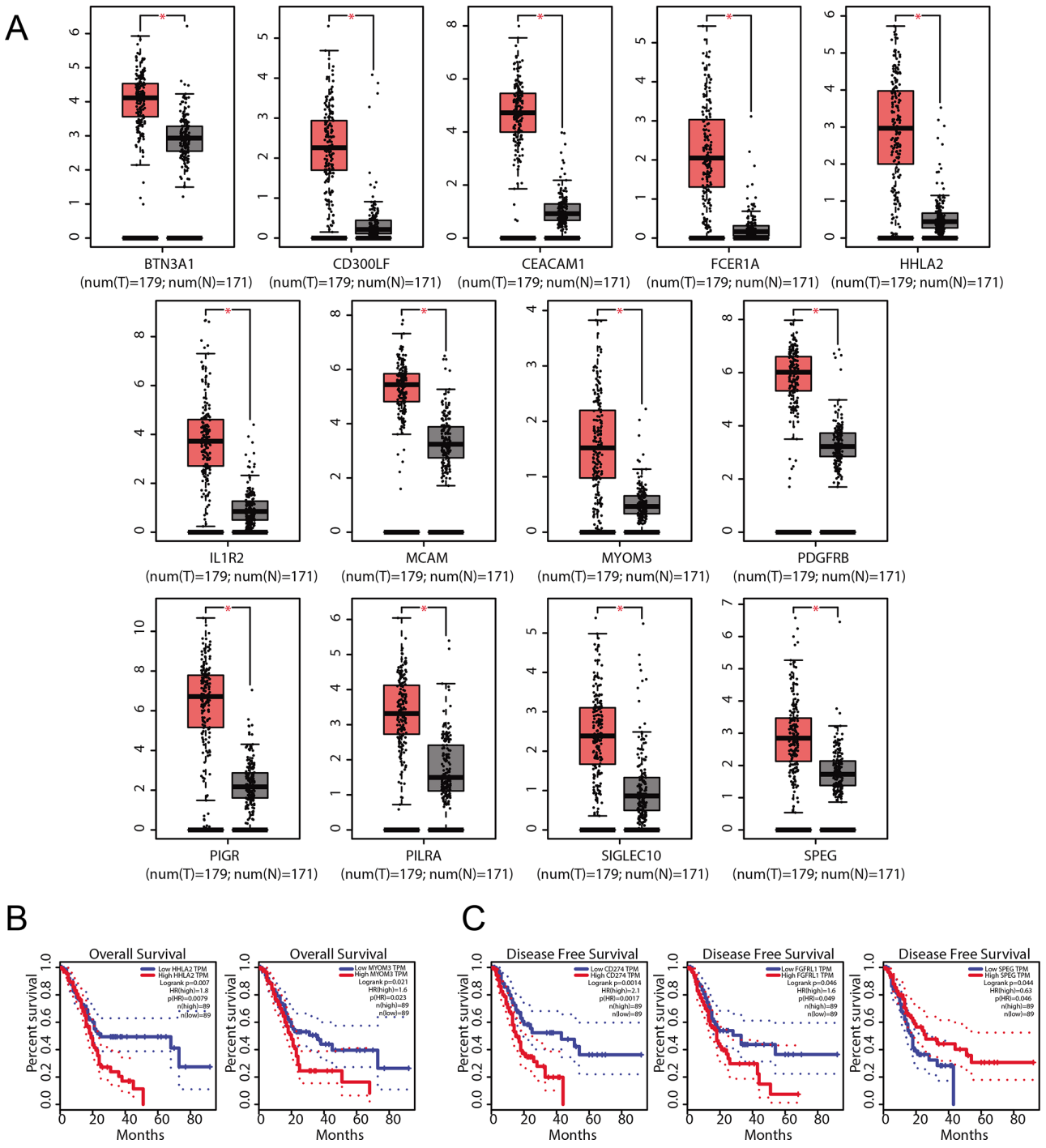

Figure 3 The expression of T1DM-related genes in pancreatic cancer and the association with the prognosis of patients. The clinical characteristics and mRNA levels of the 21 T1DM-related genes of 179 patients with pancreatic cancer were collected from the TCGA database. The same information of healthy controls was collected from the TCGA database (n=4) and GTEx database (n=167). (A) The mRNA levels of *SIGLEC10, SPEG, BTN3A1, CD300LF, CEACAM1, FCER1A, HHLA2, IL1R2, MCAM, MYOM3, PDGFRB, PIGR*, and *PILRA* were compared between patients with pancreatic cancer and healthy controls. (B,C) Patients with pancreatic cancer were classified into low-expression and high-expression groups according to the mRNA levels of each DEG. Kaplan-Meier survival analysis was performed to assess the association of each DEG with the overall survival (B) and disease-free survival (C) of patients with pancreatic cancer. DEG, differentially expressed gene; T1DM, type 1 diabetes mellitus; TCGA, The Cancer Genome Atlas.

or glycosylation ligands have been developed and used in the treatment of various Siglec-associated diseases.[32] Additionally, butyrophilin (BTN) and butyrophilin-like (BTNL) families have been found to participate in the progression of inflammatory diseases and tumors by modulating antigen-specific responses of αβT and γδ-T cells.[33] This suggests that targeting *SIGLEC10* through immunotherapy may hold promise for treating certain

diseases. Additionally, the extracellular domains of BTN and BTNL molecules share a structural similarity with the B7 family of co-stimulatory ligands, which includes PD-L1, B7-H3, and B7-H4. Consequently, BTN and BTNL are classified as members of this family.[34] Studies have shown that these families can play a role in the progression of inflammatory diseases and tumors by modulating the antigen-specific responses of αβT and γδ-T cells.[35 36] For example, anti-BTN3A antibodies have shown efficacy in acute myeloid leukemia and pancreatic cancer both in vitro and in vivo.[37] *BTN3A1* homolog *BTN3A2* is related to gastric cancer and T1DM.[38] Carcinoembryonic antigen-related cell adhesion molecule 1 (*CEACAM1*), a glycoprotein belonging to the carcinoembryonic antigen cell family, plays a crucial role in tumor progression, immune regulation, and inflammation.[39 40] Additionally, *CEACAM1* is a crucial molecule in insulin signaling and metabolism.[41] Given its diverse functions, *CEACAM1* has the potential to emerge as a significant therapeutic target for both autoimmune disorders and cancer treatment in the future. *HHLA2* is a newly identified immune checkpoint protein that is rarely expressed in normal pancreatic tissue but widely expressed in pancreatic cancer lesions.[42] Several studies have highlighted a strong correlation between *HHLA2* expression and poor clinical outcomes in various types of cancer, including pancreatic cancer.[42 43] Furthermore, the inhibitory effects of *HHLA2* on CD4 and CD8 T cell activity suggest that targeting *HHLA2* could be a promising approach for the treatment of cancer and autoimmune disorders.[44] *IL1R2*, an interleukin-1 receptor family member, acts as a decoy receptor that competitively binds to IL1β, inhibiting its interaction with *IL1R1* and thereby impeding IL1β signaling in inflammatory conditions.[45] Overexpression of *IL1R2* has been associated with various cancers, as well as conditions such as arthritis, Alzheimer's disease, and diabetes.[46] *CD146*, also known as melanoma cell adhesion molecule (*MCAM*), shares homology with multiple cell adhesion molecules.[47] It is involved in critical biological processes such as signal transduction, cell migration, angiogenesis, and immune response.[48] Several investigations have reported a marked increase in $CD146^+$ T cells at sites of inflammation in patients with autoimmune disorders.[49] In addition, our study identified potential new candidate genes, such as *MYOM3* and *SPEG*, that have not been associated with cancer and diabetes, and may serve as new potential candidates for future studies.

However, it is important to note the limitations of our study. First, whether monocytes can play a role in the PD-1 pathway of T cells, there is no relevant research, and further experiments are needed to verify our findings. Second, our samples were obtained from databases and may not fully represent the population characteristics in other regions.

Monocytes are known to interact with T cells to perform functions, such as in tuberculosis disease.[50] However, there is limited research on whether monocytes are also involved in the development of T1DM, pancreatic cancer and ICI-induced fulminant T1DM through the PD-1 pathway. Here, we investigated whether monocytes would play a similar role to T cells and sought to identify the genes involved.

CONCLUSIONS

In this study, we find the presence of PD-1 similarity genes in monocytes in patients with T1DM. These 21 similarity genes encode immunoglobulin V-set domain similar to PD-1. Our results suggest that these genes can promote the development of T1DM and contribute to the poor prognosis of pancreatic cancer.

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