Original Article

Identification of autophagy-related genes as potential biomarkers for type 1 diabetes mellitus

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Background: Type 1 diabetes mellitus (T1DM) is a metabolic disease in which the autoimmune destruction of pancreatic islet β-cells occurs. This study sought to investigate the role of autophagy-related genes and immune cells in the development of T1DM.

Methods: We acquired the raw gene expression profiles of 302 T1DM and 422 normal control peripheral blood samples from the Gene Expression Omnibus (GEO) database. The differentially expressed genes (DEGs) were identified using the Limma package, and Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were performed. The Search Tool for the Retrieval of Interacting Genes/Proteins (https://string-db.org/) and Cytoscape autophagy genes were intersected with the DEGs for the immune cell analysis and the correlation analysis.

Results: A total of 568 DEGs were identified in the T1DM and normal samples, of which 301 were upregulated and 267 were downregulated. The results of the functional and pathway enrichment analyses showed that the DEGs were closely associated with autophagy and immunity. Member RAS oncogene family (*RAB11A*), protein tyrosine phosphatase non-receptor type 11, lamin A/C, heat shock protein70, heat shock protein family A member 4, cluster of differentiation 8A, caspase 3 (*CASP3*), exportin 1, proto-oncogene, non-receptor tyrosine kinase, SMAD family member 4, and sirtuin 1 (*SIRT1*) were located at the center of the protein-protein interaction network as the core genes. The peripheral blood T cells were more elevated in the T1DM subjects than the normal subjects. *RAB11A*, *CASP3*, and *SIRT1* are autophagy-associated genes. *RAB11A* and *CASP3* were positively correlated with most immune cells, while SIRT1 was negatively correlated with most immune cells.

Conclusions: Autophagy-related genes (i.e., *RAB11A*, *CASP3*, and *SIRT1*) and immune cells (i.e., T and B cells) may play important regulatory roles in the development of T1DM. Our findings provide novel insights into and potential targets for T1DM prediction and treatment.

Keywords: Type 1 diabetes (T1DM); autophagy; immunity; biomarkers; bioinformatics

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Introduction

Type 1 diabetes mellitus (T1DM) is an abnormal nutrient metabolism disease caused by the autoimmune destruction of pancreatic islet β-cells, which often results in absolute insulin deficiency (1,2). The global incidence of T1DM increases by approximately 3% per year, but the incidence varies widely between regions, such that there is an annual incidence of 57.6 per 100,000 in Finland but only 0.1 per 100,000 in China (3-5). Additionally, T1DM tends to occur in younger individuals, with children and adolescents accounting for approximately 90% of all T1DM patients in Europe and the United States, and T1DM is the most common form of childhood diabetes in most parts of the world (4,6). As T1DM is incurable and requires lifelong insulin therapy to maintain blood glucose levels, and the metabolic disorders caused by T1DM have serious adverse effects on children, adolescents, and pregnant women of childbearing age, T1DM is an important disease that seriously threatens the health of young adults and children and adolescents (7,8).

Despite extensive research, the pathogenesis of T1DM has not been fully elucidated. T1DM is an autoimmune disease caused by T cells; programmed cell death protein 1 (PD-1) is expressed in activated T cells, and programmed death-ligand 1 (PD-L1) deficiency acts directly on pathogenic T cells and increases individuals' susceptibility to T1DM, while regulatory T cells and B cells prevent T1DM independently of the PD-1/PD-L1 pathway (9). Additionally, natural killer (NK) cells, Th1 cells, and regulatory T cells have been found to play important roles in the development of T1DM (10,11). In recent years, the positive effects of autophagy on organisms' health have been widely recognized, and various studies have established that there is a close relationship between chronic metabolic diseases and autophagy, and more specifically, that the dysregulation of autophagy may affect the normal function of the body, and thus lead to the development of chronic metabolic diseases (12-14). Autophagy in the pathogenesis of T1DM is mainly reflected in the induction of antioxidant responses in cells, the reduction of endoplasmic reticulum stress, and the prevention of islet β-cell apoptosis, but excessive autophagy can lead to islet β-cell damage and death (15-17). As an intracellular protein degradation pathway and an organismal defense mechanism, diabetes affects cellular autophagy through oxidative stress response, endoplasmic reticulum stress, and mammalian target of rapamycin (mTOR)-dependent signaling pathways (18-20). In addition, autophagy significantly controls the immune response by regulating the function of immune cells and cytokine production (21).

Currently, the diagnosis of T1DM remains clinical, and there is a lack of sensitive and effective biomarkers that can be used as early predictors of T1DM. The roles of genes related to T1DM pathogenesis, immune cells, and autophagy, and their relationships to T1DM have not yet been clarified. Thus, this study sought to uncover potential biomarkers related to autophagy in T1DM using a bioinformatics approach and to provide a theoretical basis for predicting T1DM and developing targeted therapeutic agents. We present the following article in accordance with the STREGA reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1812/rc).

Methods

Raw data

We acquired the transcriptome data of GSE30211 (including 302 T1DM samples and 422 healthy samples) from the Gene Expression Omnibus database. The sequence data from the different platforms were merged and normalized for further analysis. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Differentially expressed genes (DEGs) between the T1DM and healthy samples

Using Limma package in R software, a differential analysis of the T1DM and healthy samples was conducted to identify the DEGs. The heatmap and volcano map of the DEGs were generated using the ggplot2 package.

Functional enrichment analysis of the DEGs

We performed a Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) functional enrichment analysis using the clusterProfiler package in R, and the results were displayed using the ggplot2 package.

Construction of the protein-protein interaction (PPI) network

The PPI network of the DEGs was constructed using Search Tool for the Retrieval of Interacting Genes/Proteins

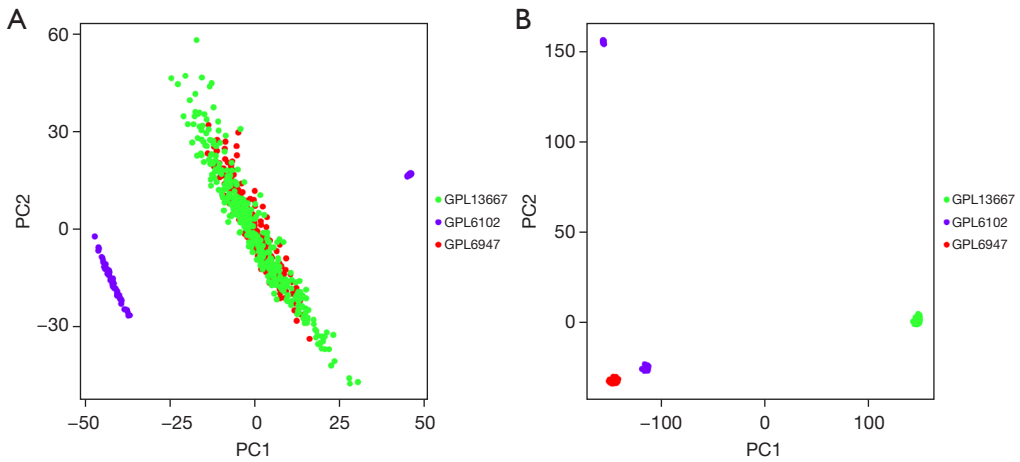

Figure 1 PCA analysis before and after data normalization. (A) PCA analysis after data normalization; (B) PCA analysis before data normalization. GPL13667, GPL6102 and GPL6947 are three different sequencing platforms. PCA, principal component analysis; PC1, principal component 1; PC2, principal component 2.

(STRING; https://string-db.org/) and displayed using Cytoscape software. The cytoHubba plugin was used to calculate the top 10 proteins for the number of link nodes.

Acquisition of hub autophagy genes of T1DM

Autophagy-related genes were obtained from the Human Autophagy Database. The T1DM autophagy-related hub genes were obtained from the intersection of the DEGs. The top 10 PPI genes and the autophagy-related genes were displayed using the VennDiagram package.

Immune-infiltration analysis of T1DM

We conducted a single-sample gene set enrichment analysis (ssGSEA) to analyze the immune landscapes of the T1DM and healthy samples. We compared the infiltration of 28 immune cells in T1DM patients and healthy samples. Further, we also analyzed the relationship between the abundance of the 28 immune cells and the hub autophagy-related genes in T1DM.

Statistical analysis

All the statistical analyses were performed in R software. The difference analysis and correlation analysis were performed using the Wilcoxon and Spearman tests, respectively. A P value <0.05 was considered statistically significant.

Results

Principal component analysis (PCA) of raw transcriptome data before and after data normalization

The PCA indicated that the principal components of the gene expression levels of the 3 platforms were at the same level after standardization (*Figure 1A*); however, before normalization, the principal components of the gene expression levels differed significantly (*Figure 1B*).

DEGs in T1DM

The T1DM-related DEGs showed that compared to the healthy samples, 301 genes were upregulated and 267 genes were downregulated in the T1DM samples (*Figure 2*).

Functional enrichment analysis of the T1DM-related DEGs

The results of the GO functional enrichment analysis of the T1DM-related DEGs indicated that the top 5 biological processes in T1DM were blood coagulation, hemostasis, coagulation, the regulation of small GTPase-mediated signal transduction, and platelet activation, while the top 5 cell components were the cell leading edge, lamellipodium, cortical cytoskeleton, nuclear inner membrane, and tetraspanin-enriched microdomain, and the top 5 molecular functions were the transferase activity transferring alkyl or aryl (other than methyl) groups, glutathione transferase

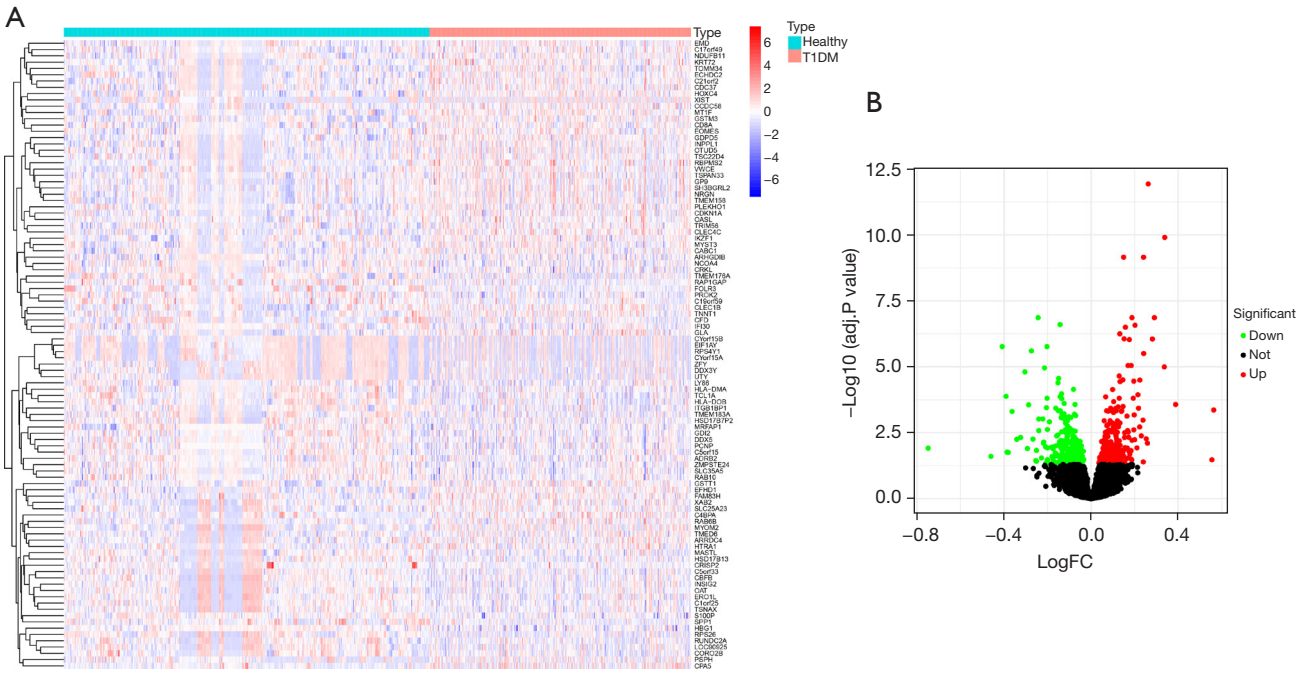

Figure 2 DEGs in T1DM. (A) Heatmap of the top 50 DEGs in T1DM; (B) volcano plot of all the DEGs in T1DM; red and green represent the upregulated and downregulated genes, respectively. DEGs, differentially expressed genes; FC, fold change; T1DM, type 1 diabetes mellitus.

activity, glutathione binding, oligopeptide binding, and GDP-dissociation inhibitor activity (*Figure 3A,3B*).

The results of the KEGG analysis indicated that the top 10 enrichment pathways were endocytosis, hematopoietic cell lineage, nucleocytoplasmic transport, glutathione metabolism, platinum drug resistance, the metabolism of xenobiotics by cytochrome P450, the drug metabolism of other enzymes, the extracellular matrix-receptor interaction, the chemical carcinogenesis of deoxyribonucleic acid adducts, and the drug metabolism of cytochrome P450 (*Figure 3C,3D*).

Top 10 ranked proteins of the PPI network

The PPI network of the DEGs indicated that the top 10 ranked proteins of the DEGs in the PPI network were *RAB11A* (a member of the RAS oncogene family), protein tyrosine phosphatase non-receptor type 11 (*PTPN11*), lamin A/C (*LMNA*), heat shock protein family A (*HSP70*), heat shock protein family A member 4 (*HSPA4*), cluster of differentiation 8A (*CD8A*), caspase 3 (*CASP3*), exportin 1 (*XPO1*), SRC proto-oncogene, non-receptor tyrosine kinase (*SRC*), SMAD family member 4 (*SMAD4*), and sirtuin 1 (*SIRT1*) (*Figure 4*).

Acquisition and expression levels of the T1DM autophagy-related genes

The intersection of the DEGs, PPI network, and autophagy-related genes showed that T1DM had the following 3 autophagy-related genes: *CASP3*, *RAB11A*, and *SIRT1* (*Figure 5A*). *CASP3*, *RAB11A*, and *SIRT1* were more lowly expressed in the T1DM samples than the healthy samples (*Figure 5B-5D*).

ssGSEA analysis of immune infiltration in the T1DM and healthy samples

Compared to the healthy samples, activated CD8 T cells, NK cells, activated dendritic cells, and monocytes were highly infiltrated in T1DM, while activated B cells, mature B cells, and Mast cells were lowly infiltrated in T1DM (*Figure 6A*). The correlation analysis showed that *CASP3* and *RAB11A* were positively correlated with the abundance of most immune cell infiltrates, while *SIRT1* was negatively correlated with the abundance of most immune cell

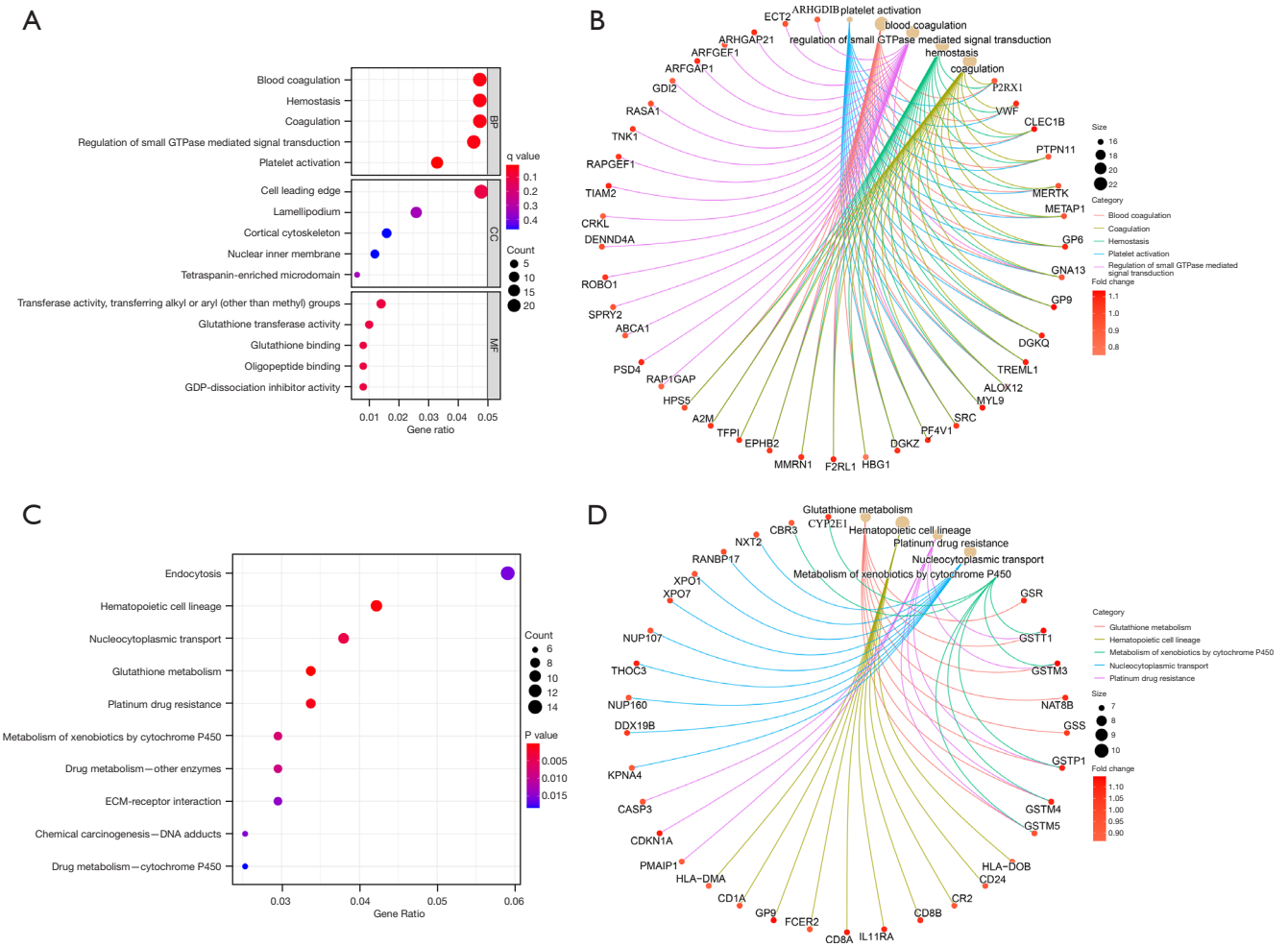

Figure 3 Functional enrichment analysis results of the T1DM-related DEGs. (A) Bubble diagram of the GO enrichment function analysis; (B) circle diagram of specific enrichment genes involved in the biological process; (C) bubble diagram of the top 10 KEGG pathways; (D) circle diagram of the specific enrichment genes of the top 5 signaling pathways. The size of the bubble represents the number of enrichment genes, and the color represents the q value and P value. DEGs, differentially expressed genes; ECM, extracellular matrix; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; T1DM, type 1 diabetes mellitus.

infiltrates (*Figure 6B*).

Discussion

Patients with diabetes mellitus often have immune abnormalities, such as reduced immune cells and reduced NK cell activity, and are at high risk of developing various infections (22). Diabetes is one of the most common comorbidities in patients and is a potential risk factor for the poor prognosis of patients with Middle-East respiratory syndrome, severe acute respiratory syndrome, coronavirus disease 2019, and cancer (23-26). Identifying and analyzing the signaling pathways associated with the development of T1DM will extend understandings of the pathogenesis of T1DM and provide a basis for the early diagnosis and treatment of T1DM and the prevention of concomitant diseases.

In this study, based on the GSE30211 data set, 422 healthy samples and 320 T1DM cases were analyzed, and 568 DEGs were obtained in both groups, of which 301 genes were upregulated and 267 genes were downregulated. The results of the functional and pathway enrichment analysis showed that the DEGs were closely associated with autophagy and immunity, which led us to speculate that

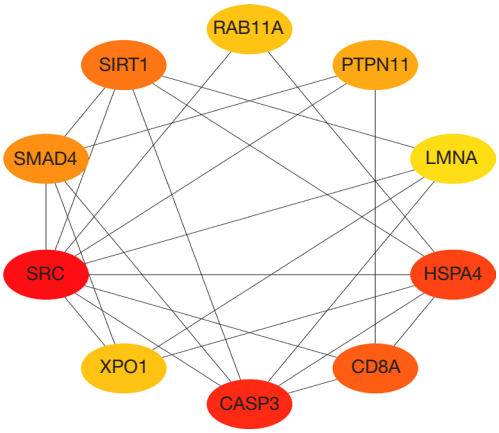

Figure 4 Top 10 ranked proteins of the PPI network. The connection represents the interaction between proteins; the redder the color, the higher the number of links. CASP3, caspase 3; CD8A, cluster of differentiation 8A; HSPA4, heat shock protein family A member 4; LMNA, lamin A/C; PPI, protein-protein interaction; PTPN11, protein tyrosine phosphatase non-receptor type 11; RAB11A, member RAS oncogene family; SIRT1, sirtuin 1; SMAD4, SMAD family member 4; SRC, SRC proto-oncogene, non-receptor tyrosine kinase; XPO1, exportin 1.

these molecules are active in T1DM pathogenesis. *RAB11A*, *PTPN11*, *LMNA*, *HSP70*, *HSPA4*, *CD8A*, *CASP3*, *XPO1*, *SRC*, *SMAD4*, and *SIRT1* were located at the center of the PPI network as core genes, and thus have the potential to be therapeutic targets for T1DM.

To screen for autophagy-related biomarkers in T1DM, we performed a cross-tab analysis and identified a total of 3 candidate autophagy-related biomarkers (i.e., *RAB11A*, *CASP3*, and *SIRT1*). *RAB11A* encodes a protein belonging to the Rab family of the small GTPase superfamily, which is associated with constitutive and regulatory secretory pathways and may be involved in protein transport (27). *RAB11A* plays an important role in the membrane receptor-mediated cytokinesis of macromolecules, and the high expression of *RAB11A* inhibits cellular autophagy and enhances the proliferation of pancreatic cancer cells (28,29). Recent research suggests that *RAB11A* may be an intra-nuclear module affecting T2DM (30). Multiple cell death modalities, such as apoptosis, autophagy, and necrosis, have been found to be associated with the pathogenesis of T1DM. The protein encoded by the *CASP3* gene is a member of the cysteine-aspartate protease family, and the sequential activation of cysteine plays a central role in the execution phase of apoptosis (31). Tumor necrosis factor activates *CASP3*, which causes apoptosis in T1DM islet β-cells (32). Recent research has shown that *CASP3* can predict the onset of diabetic events (33). However, the exact mechanism of *CASP3* in TIDM is not yet clear. *SIRT1*, a NAD-dependent protein deacetylase involved in the amelioration of several metabolic diseases, increases insulin sensitivity in the liver, and is strongly associated with insulin resistance in different pathological states (34). *SIRT1* regulates the activity of forkhead box O1 (FOXO1) through the regulation of the occurrence of autophagy (35). Additionally, *SIRT1* is a potential target for protecting pancreatic β-cells from hypoxic damage during islet transplantation (36). The above report is consistent with our findings that *RAB11A*, *CASP3*, and *SIRT1* are all lowly expressed in T1DM. Thus, these 3 genes represent promising biomarkers and therapeutic targets.

Additionally, we analyzed the differences in the levels of immune cells in T1DM and healthy subjects and found that activated CD8 T cells, NK cells, activated dendritic cells, and monocytes were higher in T1DM patients than normal subjects, and activated B cells, immature B cells, and mast cells were lower in T1DM patients than normal subjects, indicating that these immune cells play an important role in the development of T1DM. The maintenance of immune homeostasis is the result of an interaction between immune cells and regulatory immune cells. A study has reported that the proportion of both B cells and follicular helper T (Tfh) cells is significantly higher in T1DM patients than healthy patients, and the suppression of B cell function delays the onset of diabetes to some extent (37). Tfh cells play a key role in the process of helper humoral immunity by secreting interlukin-21, inducing the massive proliferation of B cells, and differentiating to form plasma cells (38). In relation to T cells, current studies have shown an increase in Th1 and Th17 cells and a decrease in regulatory T cell subpopulations during T1DM disease episodes (39,40). In the peripheral blood of children with T1DM, the percentage of intermediate T cells and memory T cells is increased, and both are positively correlated with and specific to T1DM (41). Our results showed that T cells were increased and B cells were decreased in patients with T1DM, which differed from the current report, suggesting that cellular immunity is activated, and humoral immunity is suppressed in T1DM patients, which in turn suggests that T1DM may be in a stable phase and may be an important cause of islet cell damage. Subsequently, we examined the correlations between *RAB11A*, *CASP3*, and *SIRT1* and immune cells, and found that *RAB11A* and *CASP3*

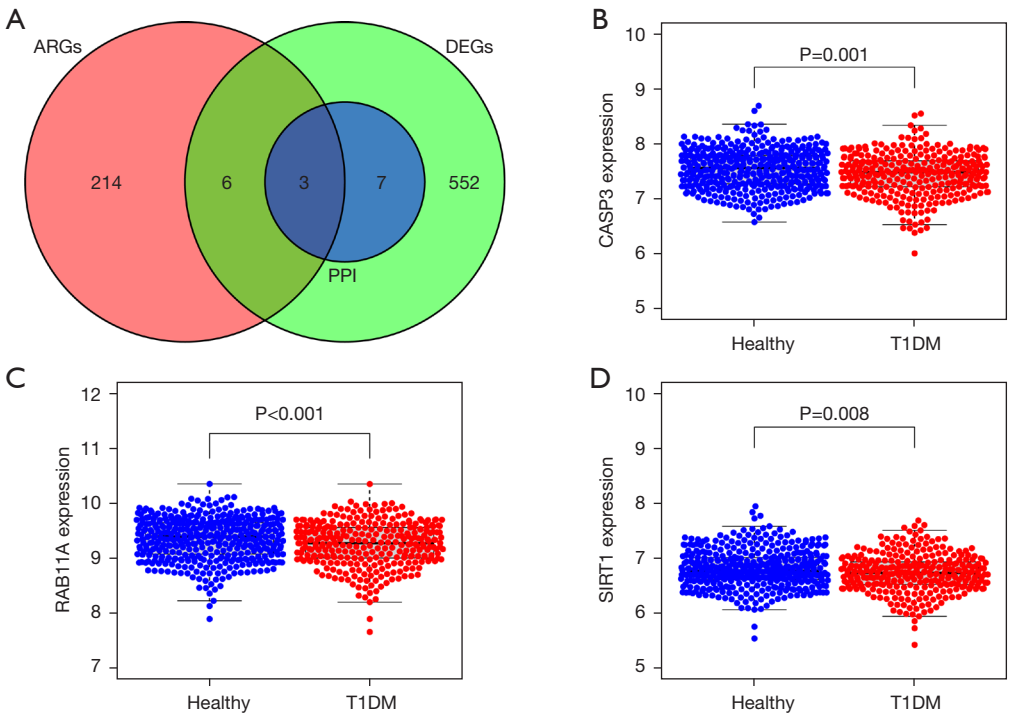

Figure 5 Acquisition and expression level of T1DM autophagy-related genes. (A) A Venn diagram showing the intersection of the DEGs, PPI network and autophagy-related genes; (B) expression level of *CASP3* in the healthy and T1DM samples; (C) expression level of *RAB11A* in the healthy and T1DM samples; (D) expression level of *SIRT1* in the healthy and T1DM samples. *CASP3*, caspase 3; DEGs, differentially expressed genes; *RAB11A*, member RAS oncogene family; *SIRT1*, sirtuin 1; T1DM, type 1 diabetes mellitus. ARGs, autophagy-related genes. PPI, protein-protein interaction.

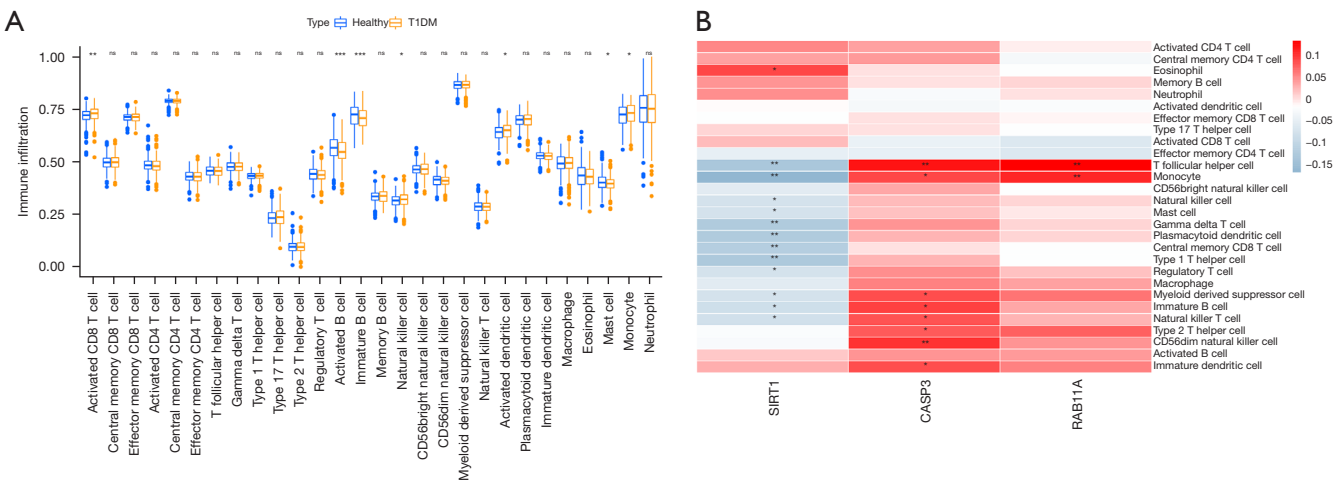

Figure 6 ssGSEA analysis of immune infiltration in the T1DM and healthy samples. (A) Boxplot of the difference analysis of immune cell infiltration levels in the healthy and T1DM samples; (B) heatmap of the correlation analysis of immune cell infiltration levels and the 3 autophagy-related genes of T1DM; red indicates a positive correlation, gray indicates a negative correlation. *, P<0.05; **, P<0.01, ***, P<0.001. *CASP3*, caspase 3; ns, not significant; *RAB11A*, member RAS oncogene family; ssGSEA, single-sample gene set enrichment analysis; *SIRT1*, sirtuin 1; T1DM, type 1 diabetes mellitus.

were positively correlated with most of the immune cells, and *SIRT1* was negatively correlated with most of the immune cells. Thus, *SIRT1* may be associated with T1DM stabilization, while *RAB11A* and *CASP3* may be associated with TIDM progression.

We systematically analyzed DEGs, autophagy-related genes, and immune cells and their relationships with T1DM. However, this study had a number of limitations, including that only a single data set was analyzed and that experimental validation is required. Further expansion of the data set and population and basic experiments need to be conducted to reveal the detailed mechanisms of autophagy-related genes in T1DM.

Conclusions

In this study, *RAB11A*, *CASP3*, and *SIRT1* were identified as potential autophagy-related biomarkers and clinical therapeutic targets in T1DM. This study revealed for the first time the association between autophagy-associated genes and immune cells. However, further experiments still need to be conducted to explore the functions and mechanisms of autophagy-related genes in T1DM.

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Footnote

Reporting Checklist: The authors have completed the STREGA reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1812/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1812/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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