Research Article

Multiomics Integrated Analysis Identifies SLC24A2 as a Potential Link between Type 2 Diabetes and Cancer

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Received 8 September 2021; Accepted 11 April 2022; Published 13 May 2022

Academic Editor: Carla Iacobini

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Background. So far, type 2 diabetes (T2D) is considered as an independent risk factor for various cancers, but the underlying mechanism remains unclear. Methods. SLC24A2 was first identified as a key gene strongly associated with fasting plasma glucose (FPG). Then, overlapped differentially expressed genes (DEGs) between T2D verse control and SLC24A2-high verse SLC24A2-low were extracted and imported into weighted correlation network analysis. Gene Ontology, Kyoto Encyclopedia of Genes and Genomes, and gene set enrichment analysis were used for functional enrichment analysis of DEGs. Least absolute shrinkage and selection operator was utilized to build a T2D prediction model. Timer and K-M plotters were employed to find the expression and prognosis of SLC24A2 in pan cancer. Results. Interestingly, both DEGs between T2D verse control and SLC24A2-high verse SLC24A2-low enriched in cancer-related pathways. Moreover, a total of 3719 overlapped DEGs were divided into 8 functional modules. Grey module negatively correlated with T2D and FPG and was markedly involved in ribosome biogenesis. Ten SLC24A2-related genes (RRP36, RPF1, GRWD1, FBL, EXOSC5, BCCIP, UTP14A, TWISTNB, TBL3, and SKIV2L) were identified as hub genes, based on which the LASSO model accurately predicts the occurrence of T2D (AUC = 0.841). In addition, SLC24A2 was only expressed in islet β cells and showed abnormal expression in 17 kinds of cancers and significantly correlated with the prognosis of 10 kinds of cancers. Conclusion. Taken together, SLC24A2 may link T2D and cancer by influencing the ribosome function of islet β cells and play different prognostic roles in different cancers.

1. Introduction

Type 2 diabetes mellitus (T2D) is a common chronic disease characterized by a high incidence rate, high disability rate, and high mortality worldwide. The World Health Organization (WHO) reported that diabetes will become the seventh leading cause of death by 2030. Epidemiological studies suggest that T2D was associated with various cancers such as breast cancer [1], liver cancer [2], lung cancer, pancreatic cancer, and prostate cancer [3–5]. For one thing, the incidence of cancer in T2D patients was higher than that in non-diabetic patients [6, 7]. Diabetes was also an independent poor prognostic factor of several cancers [8, 9]. For another, cancers and anticancer drugs lead to several adverse effects in T2D patients, such as microalbuminuria, diabetic retinopathy, and other acute diseases [10, 11]. Besides, a key gene, insulin receptor, mainly regulates the transformation of diabetes to cancer by enhancing insulin sensitivity, mediating antiapoptotic effects through combining with insulin growth factor 2 (IGF2), and leading to drug resistance in immunotherapy in immunotherapy [12–14]. Hence, it is urgent to find biomarkers and targets for early diagnosis of T2D.

Solute carrier (SLC) family, the second largest membrane protein family in human, is mainly responsible for the absorption and transportation of amino acids, nucleotides, glucose, inorganic ions, and drugs in the cell membrane [15–17]. SLC24A2 is a new Na/Ca exchanger, which has the ability to regulate calcium homeostasis in mammalian cells or tissues [18]. Studies have shown that calcium channels on the islet β cell membraneregulated intracellular
calcium signals, thereby affecting insulin secretion, which were closely related to the occurrence, development, and treatment of diabetes [19]. However, the role of SLC24A2 in diabetes remains unclear.

To further clarify the function of SLC24A2 in T2D and cancer, we comprehensively analyzed the expression and function of SLC24A2 and its related genes in multiple datasets through bioinformatics methods, constructed an efficient T2D prediction model using lasso algorithm, and then evaluated the correlation with cancer prognosis, which reveal the potential mechanism linking T2D and cancers and provided a new target for the diagnosis and treatment of T2D.

2. Materials and Methods

2.1. Data Collection and Preprocessing. The transcriptome and clinical data of 4 type 2 diabetes- (T2D-) related datasets (GSE76896, GSE20966, GSE25724, and GSE154126) were downloaded from the Gene Expression Omnibus (GEO) database. GSE76896 based on the GPL570 platform consists of pancreatic specimens from 55 diabetic (T2D) patients and 116 nondiabetic (ND) patients. Pancreases of 10 control and 10 T2D subjects from GSE20966 based on the GPL1352 platform were obtained. GSE25724 based on the GPL96 platform consists of human islets of 6 T2D patients and 7 ND subjects. Affymetrix Human Genome U133 Plus 2.0 Array (HG-U133_Plus_2), Affymetrix Human X3P Array (U133_X3P), and Affymetrix Human Genome U133A (HG-U133A) Array platform annotation information was used to annotate genes. Single-cell RNA-seq data of islets of T2D donors were obtained from GSE154126. The “limma” [20] R package was utilized to identify the differentially expressed genes (DEGs) between both T2D versus control and SLC24A2-high T2D versus SLC24A2-low T2D patients with a significance threshold of adjusted \( P < 0.05 \) and \( \left| \log FC \right| > 1.0 \).

2.2. Weighted Gene Coexpression Network Analysis (WGCNA). The overlapped DEGs in T2D versus control and SLC24A2-high T2D versus SLC24A2-low T2D patients were utilized to construct the weighted gene coexpression network analysis (WGCNA) with the “WGCNA” [21] R package. Firstly, the hierarchical clustering analysis of all genes was performed by hclust function. Then, the soft threshold was filtered with picki soft threshold function and selected when the independence was greater than 0.8. The correlation between gene module and clinical information was calculated. The minimum number of genes in the module was set to 30. A unique color label was assigned to each module.

2.3. Identification of Hub Genes. The gene contained in the grey module, which is the most closely related to T2D, was introduced into the STRING (http://www.string-db.org) database to construct the protein-protein interaction network. After that, the hub gene of the grey module was identified with “Cytohubba” [22] application of Cytoscape software (version 3.8.0).

2.4. Gene Set Enrichment Analysis. Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), and Gene Set Enrichment Analysis (GSEA) were analyzed using “clusterProfiler” [23] R package. The c5.bp.v7.3.symbols.gmt and c2.cp.kegg.v7.3.symbols.gmt in the MsigDB V7.2 database (http://www.gsea-msigdb.org/gsea/msigdb/) were used as reference gene sets.

2.5. Construction of LASSO Model and Receiver Operating Characteristic (ROC) Curve Analysis. Least absolute shrinkage and selection operator (LASSO) was constructed by “glmnet” [24] R package. According to the obtained regression coefficients, a model index was created for each sample. The weighted expression value of all selected genes was calculated as the following formula: index = \( \sum ExpGen1 \times Coef1 + ExpGen2 \times Coef2 + ExpGen3 \times Coef3 + \cdots \). The “Coef” derived from lasso Cox regression represents the regression coefficient of each gene, while “Exp” means the mRNA expression value of each gene. Then, GSE76896 dataset was randomly divided into training set (70%) and test set (30%). To evaluate the performance of LASSO model to recognize T2D independently, the ROC curves of the training set, test set, and SLC24A2 alone were analyzed by using “pROC” [25] R package.

2.6. Bioinformatics Analysis. The expression and prognosis of SLC24A2 in pan-cancer were analyzed by the TIMER 2.0 database (http://timer.comp-genomics.org/) and Kaplan-Meier plotter (http://www.kmplot.com/analysis/index.php?p=background), respectively.

2.7. Statistical Analysis. The “ggstatsplot” [26] R package was utilized to analyze the correlation between SLC24A2 and FPG in T2D patients. The “ggcorrplot” [27] R package was used to analyze the correlation among 10 hub genes in the grey module. The comparison between SLC24A2 in T2D and non-T2D was analyzed by two independent sample \( t \)-tests. \( P < 0.05 \) was considered statistically significant.

3. Results

3.1. Identification of SLC24A2 or T2D-Related Differentially Expressed Genes (DEGs). In the GSE76896 dataset, the mRNA expression level of SLC24A2 in the T2D group was significantly higher than that in the non-T2D group (logFC = 1.023, \( P = 3.01e^{-03} \)) (Figure 1(a)) and significantly negatively correlated with fasting plasma glucose (FPG) level (\( r = -0.43, P = 0.002 \)) (Figure 1(b)). Compared with healthy individuals, 7108 differentially expressed genes (DEGs) were identified in the T2D group, of which 3576 were upregulated and 3532 were downregulated (Figure 1(c)). The heat map showed all the gene expression with \( \left| \log FC \right| > 1.5 \) in T2D versus control and non-T2D group (Figure 1(d)). In addition, compared with the SLC24A2-low group, a total of 5952 DEGs were identified in the SLC24A2-high group, including 3414 upregulated genes and 2538 downregulated genes (Figure 1(e)). The heat map showed all the gene expression with \( \left| \log FC \right| > 1.5 \) in the SLC24A2-high versus SLC24A2-low group (Figure 1(f)). Finally, a total of 3719 overlapped genes were obtained in
Figure 1: Continued.
Relationship between SLC24A2 and FPG

$t_{\text{Student}}(47) = -3.31, p = 0.002, \rho_{\text{Pearson}} = -0.43, \text{CI}_{\text{95\%}} [-0.64, -0.17], n_{\text{pairs}} = 49

\log_e(BF_{01}) = -3.12, \rho_{\text{median}} = -0.41, \text{CI}_{\text{95\%}} [-0.62, -0.15], r_{\text{Cauchy}} = 0.71

Figure 1: Continued.
Figure 1: Continued.
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the T2D/non-T2D group and SLC24A2-high/SLC24A2-low group, which were considered as both SLC24A2- and T2D-related genes.

3.2. Weighted Correlation Network Analysis (WGCNA) Identifies T2D-Related Modules. To identify the key modules related to T2D, WGCNA was performed to analyze the mRNA expression matrix of the 3719 DEGs obtained in the previous step. The results showed that a total of 8 modules (Figure 2(b)) were identified when 17 was selected as the optimal soft threshold (Figure 2(a)). Grey module was negatively correlated with disease type ($r = -0.48$, $P = 5e-11$) and fasting blood glucose (FPG) ($r = -0.38$, $P = 2e-07$), while turquoise module was positively correlated with disease type ($r = 0.36$, $P = 2e-06$) and FPG ($r = 0.31$, $P = 3e-05$) (Figure 2(c)). In addition, the green module was also negatively correlated with T2D ($r = -0.41$, $P = 3e-08$) and FPG ($r = -0.34$, $P = 4e-06$) (Figure 2(c)). Next, the genes contained in the grey module, which is the most relevant to T2D and FPG, were selected for further analysis. GO enrichment analysis results showed that genes in the grey module were significantly enriched in several biological processes, such as ribonucleoprotein complex biogenesis, ribosome biogenesis, and positive regulation of fat cell differentiation, and mainly participated in cellular components, such as exoribonuclease complex and exosome (Figure 2(d)). Finally, the Cytohubba algorithm was used to identify 10 hub genes, including RRP36, RPF1, GRWD1, FBL, EXOSC5, BCCIP, UTP14A, TWISTNB, TBL3, and SKIV2L (Figure 2(e)). The correlation analysis showed an extensive regulatory relationship between 10 hub genes and SLC24A2 (Figure 2(f)).

3.3. Gene Set Enrichment Analysis (GSEA) of SLC24A2 or T2D-Related DEGs. Gene set enrichment analysis (GSEA) showed that compared with the SLC24A2-low group, the DEGs in the SLC24A2-high group were mainly enriched in some biological processes including anatomical structure formation involved in morphogenesis, animal organ morphogenesis, antimicrobial humoral response, and biological
Figure 2: Continued.
Figure 2: Continued.
Figure 2: Continued.
adhesion (Figure 3(a)) and several KEGG pathways, such as bladder cancer, pathways in cancer, prostate cancer, small-cell lung cancer, and type II diabetes mellitus (Figure 3(c)). Similarly, compared with the control group, the DEGs in the T2D group were significantly enriched in several biological processes, such as anatomical structure formation involved in morphogenesis, cytokine-mediated signaling pathway, epithelial cell differentiation, and epithelium development (Figure 3(b)) and notably enriched in pathways in cancer, small-cell lung cancer, bladder cancer, autoimmune thyroid disease, and type I diabetes mellitus KEGG pathways (Figure 3(d)). Interestingly, they shared anatomical structure formation involved in morphogenesis biological process and 4 cancer or diabetes-related KEGG pathways including pathways in cancer, bladder cancer, small-cell lung cancer, and type I/II diabetes mellitus, suggesting that SLC24A2 may be a linkage between T2D and multiple cancers.

3.4. The Cell Source of SLC24A2 and Hub Genes Was Determined with scRNA-seq Dataset. The higher expression of SLC24A2 in T2D patients was significantly observed in GSE20966 (P = 0.0011) and GSE25724 (P = 0.0023) datasets (Figures 4(a) and 4(b)). After excluding cells with the mitochondrial gene expression ratio more than 5%, all cells from T2D samples were clustered into 7 clusters (islet α cells, islet β cells, ductal cells, acinar cells, mesenchymal cells, pancreatic polypeptide cells, and PP cells) by UMAP dimension reduction method in the GSE154126 dataset (Figure 4(c)).
Running enrichment score

Rank in ordered dataset

(a) GO_ANATOMICAL_STRUCTUREFORMATION_INVOLVED_IN_MORPHOGENESIS 0 0
GO_ANIMAL_ORGAN_MORPHOGENESIS 0 0
GO_ANTIMICROBIAL_IMMUNE_RESPONSE 0 0
GO_BIOLOGICAL_ADHESION 0 0
GO_BLOOD_VESSEL_MORPHOGENESIS 0 0
GO_CELLULAR_RESPONSE_TO_INFLAMMATION 0 0
GO_CELLULAR_RESPONSE_TO_LIPID 0 0

Figure 3: Continued.
Figure 3: Gene set enrichment analysis. (a) GO-biological processes enriched in T2D. (b) GO-biological processes enriched in SLC24A2-high. (c) KEGG pathways enriched in T2D. (d) KEGG pathways enriched in SLC24A2-high. GO: Gene Ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes.
Figure 4: Continued.
Results showed that SLC24A2 and its related 8 hub genes were all expressed in islet β cells (Figure 4(d)).

3.5. The LASSO Model Is an Effective Prediction Tool for T2D. Firstly, the expression matrices of 10 hub genes were extracted. After calculation by the LASSO algorithm, the non-zero regression coefficients of 8 genes were obtained, and the value of lambda.min is 0.04065766 (Figures 5(a) and 5(b)). The detailed risk score is calculated as the following formula: 
\[ \text{index} = \text{RRP36} \times (-0.6339354) + \text{RPF1} \times (-1.4930099) + \text{GRWD1} \times (-0.4587730) + \text{FBL} \times (-0.3610982) + \text{BCCIP} \times (-0.4258075) + \text{TWISTNB} \times (-2.3570415) + \text{TBL3} \times (-0.1784551) + \text{SKIV2L} \times (-0.4068790). \]

ROC curve showed that the AUC of SLC24A2 for independently predicting T2D was 0.6856 (Figure 5(d)), while 8-gene model reached 0.8410 in the training set and 0.6712 in the test set, indicating that the LASSO model may be an efficient tool to explore early biomarkers for diagnosis of T2D (Figure 5(c)).

3.6. Pan-Cancer Analysis of SLC24A2. Consistent with previous enrichment analysis of DEGs, SLC24A2 showed the abnormal expression in 17 cancers including bladder cancer (BLCA), prostate cancer (PRAD), and lung cancer (LUAD and LUSC) (Figure 6(a)). In detail, SLC24A2 was notably lower expressed in glioblastoma (GBM), kidney renal clear cell carcinoma (KIRC), and kidney renal papillary cell carcinoma (KIRP) (all \( P < 0.05 \)) than in adjacent tissues (Figure 6(a)), whose lower expression significantly correlated with high survival time in KIRC (HR = 1.49, \( P = 0.011 \)) and KIRP (HR = 2.05, \( P = 0.016 \)) (Figure 6(b)). Additionally, SLC24A2 observably elevated in other cancers (Figure 6(a)), which was significantly correlated with the poor prognosis of BLCA (HR = 1.37, \( P = 0.045 \)), head and neck squamous cell carcinoma (HNSC) (HR = 1.43, \( P = 0.016 \)), lung adenocarcinoma (LUAD) (HR = 1.33, \( P = 0.062 \)), stomach adenocarcinoma (STAD) (HR = 1.78, \( P = 0.00061 \)), and uterine corpus endometrial carcinoma (UCEC) (HR = 1.97, \( P = 0.00086 \)) but significantly correlated with the good prognosis of patients with esophageal cancer (ESCA) (HR = 0.39, \( P = 0.044 \)), liver hepatocellular carcinoma (LIHC) (HR = 0.62, \( P = 0.0071 \)), and lung squamous cell carcinoma (LUSC) (HR = 0.72, \( P = 0.017 \)) (Figure 6(b)). That is to say, although SLC24A2 may play different roles in different cancers, they were all closely related to prognosis.

4. Discussion

As we all know that type 2 diabetes (T2D) is a common chronic disease, usually accompanied by a variety of complications including cancer, however, the association between T2D and cancer has not yet been fully elucidated. Meanwhile, this lacks effective biomarkers for early diagnosis of T2D. Increasing evidences have demonstrated that the SLC...
Figure 5: Continued.
family plays a key role in the pathogenesis and diagnosis of both T2D and cancer [28–30]. However, the function of SLC24A2 needs to be fully clarified and further explored.

Firstly, we found that SLC24A2 was significantly upregulated in T2D patients within 3 datasets (GSE76896, GSE76896, and GSE76896) and negatively correlated with fasting plasma glucose (FPG) in GSE76896, suggesting that SLC24A2 might be a potential inhibitor of T2D through lowering blood glucose. SLC24A2, also known as NCKX2, is a sodium/potassium/calcium exchanger of the solute carrier

Figure 5: The LASSO model for predicting T2D. (a, b) LASSO model. (c) ROC analysis of train set and validation set. (d) ROC analysis of SLC24A2. LASSO: least absolute shrinkage and selection operator; ROC: receiver operating characteristic curve.
Figure 6: Expression and prognostic analysis of SLC24A2 in pan cancer. (a) The expression of SLC24A2 in pan cancer. (b) Prognostic analysis of SLC24A2 in pan cancer.
family, which was first reported to be associated with retinal diseases [18]. In recent years, SLC24A2 has been found as a tumor microenvironment-related gene to be related to the prognosis of esophageal squamous cell carcinoma [31]. Nonetheless, no reports have confirmed the association between SLC24A2 and T2D. It is well known that islet alpha cells and islet beta cells jointly regulate the level of blood glucose. In this study, scRNA-seq analysis revealed that SLC24A2 was only expressed in islet beta cells, suggesting that SLC24A2 may regulate blood glucose by affecting the function of islet beta cells. Therefore, this is the first study to clarify the potential mechanism of SLC24A2 in the occurrence and development of T2D.

To further reveal the role of SLC24A2 in the pathogenesis of T2D, we used the WGCNA algorithm to find key modules among DEGs both related to SLC24A2 and T2D. WGCNA is an effective way to search for coexpressed gene modules and to explore the association between gene networks and different phenotypes, which has been applied to the exploration of key genes in various diseases including T2D [32–34]. On this basis, we further identified 10 hub genes by the Cytohubba algorithm, namely, RRP36, RPF1, GRWD1, FBL, EXOSC5, BCCIP, UTP14A, TWISTNB, TBL3, and SKIV2L. One study showed that the methylation level of GRWD1 was associated with insulin resistance [35]. GWAS analysis revealed that SKIV2L was associated with inflammation status in patients with metabolic diseases such as diabetes [36]. Previous studies showed that RRP36, RPF1, FBL, and BCCIP affected ribosomal function and rRNA processing [37–39]. In addition, EXOSC5, UTP14A, TWISTNB, and TBL3 were closely related to the occurrence or prognosis of several cancers [40–43]. Together with the results of GO enrichment analysis, we believed that abnormal ribosome function may be one of the causes of T2D complicated with cancer. Coincidently, Peng et al. also found that the shared DEGs of T2D and colorectal cancer (CRC) patients were significantly enriched in the ribosomal pathway in the study of T2D complicated with CRC patients [44].

Interestingly, we found broad correlations between 10 hub genes and SLC24A2, indicating that a comprehensive analysis of SLC24A2-related regulatory network members could serve as potential markers for early diagnosis of T2D. Therefore, the LASSO algorithm was introduced to further analysis. The LASSO algorithm could construct a penalty function to obtain a more refined model based on regularization, which has been widely used in the exploration of tumor biomarkers [45]. After that, an efficient 8-gene (RRP36, RPF1, GRWD1, FBL, BCCIP, TWISTNB, TBL3, and SKIV2L) T2D prediction model was obtained, whose AUC reached 0.84 and 0.67, respectively, in training set and test set. Thus, LASSO is a promising tool for early diagnosis of T2D and has a high potential value.

It is also noteworthy that the DEGs between high- and low-SLC24A2 groups were enriched in T2D and several cancer pathways such as bladder cancer and non-small-cell lung cancer. Meanwhile, the DEGs between T2D and normal controls were also enriched in some cancer pathways including bladder cancer and non-small-cell lung cancer. That is to say, the shared DEGs imported into WGCNA, as well as SLC24A2, could explain the coexistence of T2D and cancer to some extent. Therefore, in addition to the analysis of PPI network and LASSO-prediction model for shared DEGs mentioned above, we also focused on the prognostic value of SLC24A2 in pan cancers. The results showed that SLC24A2 played opposite roles in different types of cancers due to the tissue specificity of SLC24A2.

In order to achieve better clinical application, we could make full use of SLC24A2 and its related genes for early clinical diagnosis. In addition, we could develop SLC24A2 inhibitors for clinical research. Although we explored the role of SLC24A2 between T2D and cancers through a multomics approach, this study still has some limitations. On the one hand, it is necessary to verify the prognostic value and robustness of the model in expanded samples. On the other hand, we also need to further verify the potential mechanism through in vivo and in vitro experiments to promote clinical application and transformation.

5. Conclusion

In summary, we used bioinformatics methods and multiple algorithms to integrate multiple RNA-seq datasets and scRNA-seq dataset and found that SLC24A2 may prevent the occurrence of T2D complicated by cancer via maintaining the ribosome function of islet beta cells and play different prognostic roles in cancers.

Data Availability

All data used in this study are from public databases, including GEO, TCGA, and K-M plotter. Detailed information could be found in the method section of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

This is the original article unpublished in any other publication.

References

[1] C. Debras, E. Chazelas, B. Srour et al., “Glycaemic index, glycaemic load and cancer risk: results from the prospective NutriNet-Santé cohort,” International Journal of Epidemiology, vol. 51, no. 1, pp. 250–264, 2021.
[2] Y. Hu, X. Zhang, Y. Ma et al., “Incident type 2 diabetes duration and cancer risk: a prospective study in two US cohorts,” Journal of the National Cancer Institute, vol. 113, no. 4, pp. 381–389, 2021.
[3] Z. Xiao, S. Gaertner, A. Morresi-Hauf et al., “Metformin triggers autophagy to attenuate drug-induced apoptosis in NSCLC cells, with minor effects on tumors of diabetic patients,” Neoplasia, vol. 19, no. 5, pp. 385–395, 2017.
[4] J. Cho, R. Scragg, and M. S. Petrov, “Postpancreatitis diabetes confers higher risk for pancreatic cancer than type 2 diabetes:
results from a nationwide cancer registry,” *Diabetes Care*, vol. 43, no. 9, pp. 2106–2112, 2020.

[5] K. Hemminki, X. Li, J. Sundquist, and K. Sundquist, “Risk of cancer following hospitalization for type 2 diabetes,” *The Oncologist*, vol. 15, no. 6, pp. 548–555, 2010.

[6] K. Reinholdt, L. T. Thomsen, C. Munk et al., “Incidence of HPV-related anogenital intraepithelial neoplasia and cancer in men with diabetes compared with the general population,” *Epidemiology*, vol. 32, no. 5, pp. 705–711, 2021.

[7] J. Tan, Y. You, F. Guo, J. Xu, H. Dai, and P. Bie, “Association of elevated risk of pancreatic cancer in diabetic patients: a systematic review and meta-analysis,” *Oncology Letters*, vol. 13, no. 3, pp. 1247–1255, 2017.

[8] A. Franko, L. Berti, J. Hennenlotter et al., “Increased expressions of matrix metalloproteinases (MMPs) in prostate cancer tissues of men with type 2 diabetes,” *Biomedicines*, vol. 8, no. 11, 2020.

[9] S. Umetsu, H. Mizukami, T. Saito et al., “Diabetes, an independent poor prognostic factor of non-B non-C hepatocellular carcinoma, correlates with dihydroxyrimidinase-like 3 promoter methylation,” *Scientific Reports*, vol. 10, no. 1, p. 1156, 2020.

[10] A. Milluzzo, A. Tumminia, V. Vella et al., “Short-term adverse effects of anticancer drugs in patients with type 2 diabetes,” *Journal of Chemotherapy*, vol. 31, no. 3, pp. 150–159, 2019.

[11] A. Milluzzo, M. Barchitta, A. Maugeri, A. Agodi, and L. Sciaccia, “Body mass index is related to short term retinal worsening in type 2 diabetes patients treated with anticancer drugs,” *Minerva Endocrinology*, 2022.

[12] A. Belfiore, F. Frasca, G. Pandini, L. Sciaccia, and R. Vigneri, “Insulin receptor isoforms and insulin receptor/insulin-like growth factor receptor hybrids in physiology and disease,” *Endocrine Reviews*, vol. 30, no. 6, pp. 586–623, 2009.

[13] A. Belfiore, R. Malaguarnera, V. Vella et al., “Insulin receptor isoforms in physiology and disease: an updated view,” *Endocrine Reviews*, vol. 38, no. 5, pp. 379–431, 2017.

[14] V. Vella, A. Milluzzo, N. M. Scalis, P. Vigneri, and L. Sciaccia, “Insulin receptor isoforms in cancer,” *International Journal of Molecular Sciences*, vol. 19, no. 11, 2018.

[15] M. Wiktor, W. Wiertelak, D. Maszczak-Senczko, P. J. Balwierz, B. Szulc, and M. Olczak, “Identification of novel potential interaction partners of UDP-galactose (SLC35A2), UDP-N-acetylglucosamine (SLC35A3) and an orphan (SLC35A4) nucleotide sugar transporters,” *Journal of Proteomics*, vol. 249, p. 104321, 2021.

[16] A. D. Woodward, S. J. Holcombe, J. P. Steibel, W. B. Staniar, C. Colvin, and N. L. Trottier, “Cationic and neutral amino acid transporter transcript abundances are differentially expressed in the equine intestinal tract,” *Journal of Animal Science*, vol. 88, no. 3, pp. 1028–1033, 2010.

[17] H. Li, E. R. Gilbert, Y. Zhang et al., “Expression profiling of the solute carrier gene family in chicken intestine from the late embryonic to early post-hatch stages,” *Animal Genetics*, vol. 39, no. 4, pp. 407–424, 2008.

[18] D. Sharon, H. Yamamoto, T. L. McGee et al., “Mutated alleles of the rod and cone Na-Ca+K-exchanger genes in patients with retinal diseases,” *Investigative Ophthalmology & Visual Science*, vol. 43, no. 6, pp. 1971–1979, 2002.

[19] G. M. Grodsky, “A new phase of insulin secretion. How will it contribute to our understanding of beta-cell function?,” *Diabetes*, vol. 38, no. 6, pp. 673–678, 1989.

[20] M. E. Ritchie, B. Chipson, D. Wu et al., “Limma powers differential expression analyses for RNA-sequencing and microarray studies,” *Nucleic Acids Research*, vol. 43, no. 7, p. e47, 2015.

[21] P. Langfelder and S. Horvath, “Fast R functions for robust correlations and hierarchical clustering,” *Journal of Statistical Software*, vol. 46, no. 11, 2012.

[22] C. H. Chin, S. H. Chen, H. H. Wu, C. W. Ho, M. T. Ko, and C. Y. Lin, “cytoHubba: identifying hub objects and subnetworks from complex interactome,” *BMC Systems Biology*, vol. 8, 2014.

[23] G. Yu, L. G. Wang, Y. Han, and Q. Y. He, “clusterProfiler: an R package for comparing biological themes among gene clusters,” *Omics: A Journal of Integrative Biology*, vol. 16, no. 5, pp. 284–287, 2012.

[24] J. Friedman, T. Hastie, and R. Tibshirani. “Regularization paths for generalized linear models via coordinate descent,” *Journal of Statistical Software*, vol. 33, no. 1, pp. 1–22, 2010.

[25] X. Robin, N. Turck, A. Hainard et al., “pROC: an open-source package for R and S+ to analyze and compare ROC curves,” *BMC Bioinformatics*, vol. 12, no. 1, p. 77, 2011.

[26] I. Patil, “Visualization with statistical details: The ggstatsplot approach,” *Journal of Open Source Software*, vol. 6, no. 61, p. 3167, 2021.

[27] A. Kassambare, ggcorrplot: Visualization of a correlation matrix using ggplot2, R Package, 2016.

[28] A. Bansal, S. Balasubramanian, S. Dhawan, A. Leung, Z. Chen, and R. Natarajan, “Integrative omics analyses reveal epigenetic memory in diabetic renal cells regulating genes associated with kidney dysfunction,” *Diabetes*, vol. 69, no. 11, pp. 2490–2502, 2020.

[29] T. Sun, F. Bi, Z. Liu, and Q. Yang, “SLC7A2 serves as a potential biomarker and therapeutic target for ovarian cancer,” *Aging*, vol. 12, no. 13, pp. 13281–13296, 2020.

[30] J. Xu, N. Wijesekara, R. Regeenes et al., “Pancreatic β-cell-selective zinc transporter 8 insufficiency accelerates diabetes associated with islet amyloidosis,” *JCI Insight*, vol. 6, no. 10, 2021.

[31] D. Zhang, C. Qian, H. Wei, and X. Qian, “Identification of the prognostic value of tumor microenvironment-related genes in esophageal squamous cell carcinoma,” *Frontiers in Molecular Biosciences*, vol. 7, article 599475, 2020.

[32] L. Li, Z. Pan, S. Yang, W. Shan, and Y. Yang, “Identification of key gene pathways and coexpression networks of islets in human type 2 diabetes,” *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, vol. 11, pp. 553–563, 2018.

[33] Y. Hu, L. J. Tan, X. D. Chen, J. Greenbaum, and H. W. Deng, “Identification of novel variants associated with osteoporosis, type 2 diabetes and potentially pleiotropic loci using pleiotropic cFDR method,” *Bone*, vol. 117, pp. 6–14, 2018.

[34] A. Fatima, R. M. Connaughton, A. Weiser et al., “Weighted gene co-expression network analysis identifies gender specific modules and hub genes related to metabolism and inflammation in response to an acute lipid challenge,” *Molecular Nutrition & Food Research*, vol. 62, no. 2, 2018.

[35] H. Yao, S. Mo, J. Wang et al., “Genome-wide DNA methylation profiles of phlegm-dampness constitution,” *Cellular Physiology and Biochemistry: International Journal of Experimental Cellular Physiology, Biochemistry, and Pharmacology*, vol. 45, no. 5, pp. 1999–2008, 2018.
[36] A. T. Kraja, D. I. Chasman, K. E. North et al., “Pleiotropic genes for metabolic syndrome and inflammation,” Molecular Genetics and Metabolism, vol. 112, no. 4, pp. 317–338, 2014.

[37] G. Clerget, V. Bourguignon-Igel, N. Marmier-Gourrier et al., “Synergistic defects in pre-rRNA processing from mutations in the U3-specific protein Rrp9 and U3 snoRNA,” Nucleic Acids Research, vol. 48, no. 7, pp. 3848–3868, 2020.

[38] L. Kater, M. Thoms, C. Barrio-Garcia et al., “Visualizing the assembly pathway of nucleolar Pre-60S ribosomes,” Cell, vol. 171, no. 7, article e1514, pp. 1599–1610, 2017.

[39] C. Ye, B. Liu, H. Lu et al., “BCCIP is required for nucleolar recruitment of eLF6 and 12S pre-rRNA production during 60S ribosome biogenesis,” Nucleic Acids Research, vol. 48, no. 22, pp. 12817–12832, 2020.

[40] D. Kraus, A. Glassmann, C. Golletz, G. Kristiansen, J. Winter, and R. Probstmeier, “Zona pellucida protein 2 (ZP2) is expressed in colon cancer and promotes cell proliferation,” Cancers, vol. 13, no. 8, 2021.

[41] J. Zhang, P. Ren, D. Xu et al., “Human UTP14A promotes colorectal cancer progression by forming a positive regulation loop with c-Myc,” Cancer Letters, vol. 440, pp. 106–115, 2019.

[42] L. Wang, J. Huang, M. Jiang, Q. Chen, Z. Jiang, and H. Feng, “CAMK1 phosphoinositide signal-mediated protein sorting and transport network in human hepatocellular carcinoma (HCC) by biocomputation,” Cell Biochemistry and Biophysics, vol. 70, no. 2, pp. 1011–1016, 2014.

[43] R. B. Reddy, S. S. Khora, and A. Suresh, “Molecular prognosticators in clinically and pathologically distinct cohorts of head and neck squamous cell carcinoma-a meta-analysis approach,” PLoS One, vol. 14, no. 7, article e0218989, 2019.

[44] W. F. Peng, F. Bai, K. Shao, L. S. Shen, H. H. Li, and S. Huang, “The key genes underlying pathophysiology association between the type 2-diabetic and colorectal cancer,” Journal of Cellular Physiology, vol. 233, no. 11, pp. 8551–8557, 2018.

[45] A. Zhang, J. Yang, C. Ma, F. Li, and H. Luo, “Development and validation of a robust ferroptosis-related prognostic signature in lung adenocarcinoma,” Frontiers in Cell and Developmental Biology, vol. 9, article 616271, 2021.