Tohoku J. Exp. Med., 2024, **264**, 1-8

Four Genes with Seven Targeted Drugs might be Treatment for Diabetic Nephropathy and Acute Coronary Syndrome

Zhichao Zhou,[1] Fengcheng Lin,[1] Wenqi Wei[1] and Dongmei Liu[1]

[1]The Third Department of Cardiology, Zhanjiang Central Hospital, Guangdong Medical University, Zhanjiang, Guangdong, China

Diabetes nephropathy (DN) is a main risk factor for acute coronary syndrome (ACS), but the molecular mechanism is unknown. This research used bioinformatics approaches to uncover potential molecular mechanisms and drugs for DN and ACS. GSE142153 and GSE19339 were downloaded from the Gene Expression Omnibus (GEO) database. The mutually different expression genes (DEGs) detected in the GSE142153 and GSE19339 datasets were then subjected to Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis. After a protein-protein interaction network (PPI) analysis, hub genes and transcriptional regulators were tracked by Cytoscape Soft. Finally, potential therapeutic drugs were predicted by the DGIDB drug database. This study identified 274 mutual DEGs from the DN and ACS datasets. Functional analyses indicated that "RNA polymerase II" and the "IL-17 signaling pathway" might play an important role in DN and ACS. Through PPI network construction, the top ten genes were identified. Hub gene and transcription factor interactions were constructed. Seven drugs targeted at VEGFA, IL6, IL1B, and IL1A were evaluated. Four genes and seven drugs were evaluated that could provide a novel perspective for DN and ACS in the future.

Keywords: acute coronary syndrome; bioinformatics; diabetic nephropathy; differentially expressed genes; targeted drugs

Tohoku J. Exp. Med., 2024 September, **264** (1), 1-8.
doi: 10.1620/tjem.2024.J048

Introduction

Individuals afflicted with diabetes frequently encounter hyperglycemia, a condition marked by elevated blood glucose levels. This perturbation exerts a detrimental influence on numerous organs, with the renal system being notably susceptible, culminating in the potential manifestation of diabetic nephropathy (DN) (Qi et al. 2007). DN does not present early warning indicators and frequently emerges belatedly, characterized by elevated blood pressure, edema, excessive proteinuria, and/or compromised renal function (Anders et al. 2018). The therapeutic strategies conventionally encompass the modulation of glycemic concentrations and arterial pressure. Regrettably, these interventions often yield suboptimal outcomes. Furthermore, the precise molecular underpinnings of DN's pathogenesis remain shrouded in mystery, representing an enduring conundrum in medical research.

Acute Coronary Syndrome (ACS) constitutes a prevalent form of coronary thrombosis, a vascular malady that frequently culminates in symptoms such as unstable angina, myocardial infarction, or, in severe instances, may remain undifferentiated due to aberrations in cardiac rhythm (Berriche et al. 2014). Individuals afflicted with DN confront an amplified risk of ACS, manifesting as severe complications including heart failure and acute myocardial infarction. These conditions are associated with elevated mortality rates, surpassing those observed among patients unaffected by DN (Buntaine et al. 2016). A study showed that patients with DN and ACS had a two-fold higher put on the line of undefined during their hospital stay than those without these conditions (Franklin et al. 2004). Hence, it is

Received March 6, 2024; revised and accepted June 16, 2024; J-STAGE Advance online publication June 27, 2024

Correspondence: Wenqi Wei, The Third Department of Cardiology, Zhanjiang Central Hospital, Guangdong Medical University, Chikan District, Zhanjiang, Guangdong Province 524000, China.
e-mail: zhj_003@163.com
Dongmei Liu, The Third Department of Cardiology, Zhanjiang Central Hospital, Guangdong Medical University, Chikan District, Zhanjiang, Guangdong Province 524000, China.
e-mail: liudongmeibetty@163.com

critical to know the molecular pathogenesis of DN with ACS and to reduce the risk of hospitalization insurance or death.

In this study, bioinformatics methodologies were used to analyze the possible molecular mechanisms and medicines that could contribute to DN and ACS. GSE142153 and GSE19339 were retrieved from the Gene Expression Omnibus (GEO) database to discover the biological relationship between DN and ACS. We next looked for differentially expressed genes (DEGs) in the datasets. To comprehend genome-based expression investigations, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment of mutual DEGs were carried out. The protein-protein interaction network (PPI) was then used to search key genes for hub genes and transcriptional regulators. Finally, the DGIDB drug database was used to predict potential drugs.

Materials and Methods

Microarray data extraction

We obtained the microarrays from the GEO (https://www.ncbi.nlm.nih.gov/geo/) to identify the common genetic linked between DN and ACS. The DN dataset GSE142153 (the GPL6480 platform) included peripheral blood samples from 10 healthy individuals and 34 DN patients. The ACS dataset GSE19339 (GPL570 platform) included 4 healthy individuals and 4 ACS patients.

Identification of DEGs

The DEGs in peripheral blood samples from patients and the control group were analyzed using GEO2R software with $P < 0.05$, logFC > 1 as up regulation, and logFC < −1 for DEGs as down regulation. Following that, this study used Venn software to check for crossover DEGs.

GO and KEGG pathway enrichment

GO as well as KEGG analysis was performed using the DAVID database (https://david.ncifcrf.gov/) to investigate possible functions, including biological process (BP), molecular function (MF), and cellular component (CC) as well as pathways enriched in these DEGs. $P < 0.05$ denoted a statistically significant difference.

Protein-protein interaction (PPI) network construction and hub gene extraction

The STRING database (https://www.STRING-db.org) was used to build PPI networks to examine the relationships between DN and ACS. The study utilized Cytoscape software (v3.9.0) (https://www.cytoscape.org/) to visualize and analyze the PPI network. Additionally, the CytoHubba plugin in Cytoscape was to select the ten hub genes.

Recognition of transcription factors

The Network Analyst platform was used to identify topology-related transcription factors (TFs) from the JASPAR database (http://jaspar.genereg.net).

Building drug-gene interactions

We investigated drugs targeted to hub genes using the drug database (DGIDB: https://dgidb.genome.wustl.edu/).

Statistics analysis

A moderate t-test was used to identify DEGs. $P < 0.05$ denoted statistical significance.

Results

Common DEGs identification between DN and ACS

Firstly, 1,286 DEGs were discovered in DN, with 491 showing up-regulation and 795 showing down regulation. Similarly, we found 2,972 DEGs in the ACS dataset, with 1,399 up-regulation and 1,573 down regulation. Then, we identified 274 common DEGs (130 with up regulation and 144 with down regulation) between DN and ACS datasets. Fig. 1 shows a cross-analysis comparison for both data, and Table 1 lists all 274 differential genes.

GO as well as KEGG analysis

Fig. 2 shows DEGs were strongly linked to transcriptional regulation from the RNA polymerase II promoter in the BP category, the nucleus in the CC category, and protein binding in the MF category. According to the KEGG path-

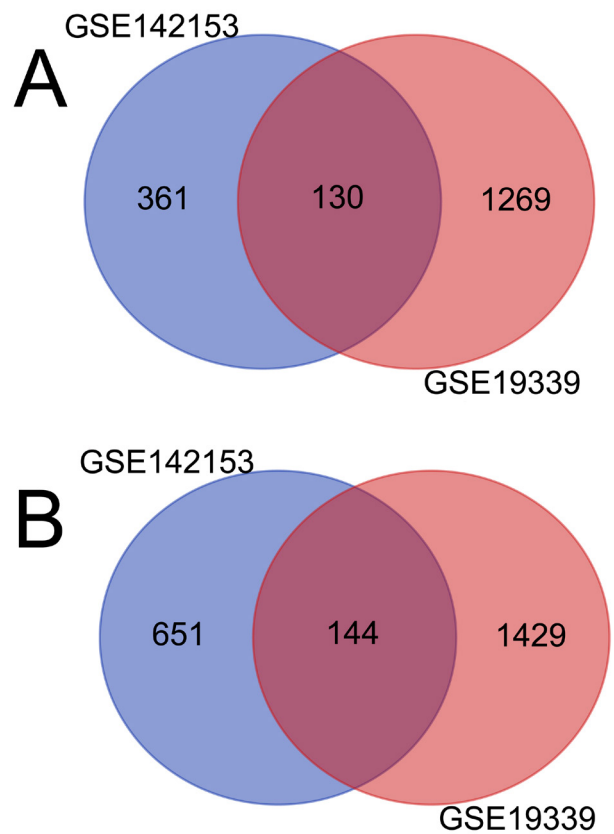

Fig. 1. Common differentially expressed genes (DEGs) identification.
(A) 130 common DEGs with up regulation.
(B) 144 common DEGs with down regulation.

Table 1. Differentially expressed genes (DEGs) identification.

Genes	Gene name
Up-regulated genes	*FSTL1, B3GNT5, CXCL3, C15orf48, NDST1, NR4A2, HES1, PLK3, ATF3, DUSP4, MYO6, GATA6, SOCS6, SLCO2A1, HBEGF, SLC2A3, ZNF331, PHLDA1, SDC2, PTGES, CCL7, SPRY2, CXCL8, PHACTR1, THBD, IFITM10, EMP1, HDGFRP3, NUAK1, LAMB3, SNAI1, SERPINB2, IER3, P2RY1, FZD7, MAP3K8, EGR2, IL1A, SMAD7, AVPI1, RAB20, SERTAD1, CCL20, OLR1, CD83, GK5, SC5D, GABARAPL1, PFKFB3, EREG, TNS1, PTX3, VEGFA, CDH11, DOCK4, BCOR, NR4A3, JOSD1, EGR3, OASL, CCL2, MMP1, IL6, CRNDE, CREM, ETF1, RGS1, CCRL2, GZF1, SLCO4A1, FOSL2, HSPA13, NOCT, GADD45G, SLC35F5, CCR1, GRASP, MAPK6, IL10, HIC1, TAF13, SLC16A6, SLC7A5, CXCL2, DENND1B, RASGEF1B, MELTF, ZBTB21, METRNL, PPIF, GJB2, STARD4, CALCRL, ICAM1, TMEM52B, SHB, HIF1A, PHLDA2, PDE4B, GPR84, SDC3, MAFB, TGIF1, CTNNAL1, CDKN1A, HNRNPLL, ADM, RNMT, SEMA3F, IL1B, SKIL, C11orf96, ELL2, F3, NINJ1, LMNA, SEMA6B, HAS1, GEM, PLAUR, WHRN, MAFF, FOSL1, INSIG1, BTG3, CH25H, SMAD6, ACKR3, SYAP1, ANKRD37*
Down-regulated genes	*TRAF3IP2-AS1, NIFK-AS1, SLC15A2, CASP6, ARL17A, ZNF718, HSPA1L, TRAF5, GIMAP1, LINC01410, SETDB1, RCSD1, LOC202181, PAQR8, SLAMF1, COX10, IGLV1–44, GABBR1, APBA2, VSIG1, LEF1-AS1, NAIP, TNFRSF17, SIRPG, ZNF781, ITGA6, ZNF514, DSC1, PCBD2, GIMAP6, LINC00662, PNISR, NR3C2, TCHP, TLR10, LHX4-AS1, IGKC, NUPL2, TCL1A, SIRT5, TRIM66, AQP3, TRIM52, IPCEF1, PDE7A, ZNF573, GVINP1, ADCY10P1, DDX17, ZNF559, SGK494, FBXL16, ZNF782, TRAF3IP3, ZC3H4, AK5, TNRC6C-AS1, TET1, ZNF789, CD200R1, ST6GAL1, ZNF404, PMS1, N4BP2L1, CX3CR1, MDS2, AATBC, ERGIC2, HGF, MYB, DNASE1, PCMTD2, ZNF248, GIMAP8, CYP2U1, AMN1, SKP2, MTHFSD, SEC31B, EFCAB7, ZRSR2, LOC100996455, STAP1, ABCD2, PARP11, CLEC4C, LEF1, RAD52, TPTE2P5, ZNF792, AK9, AP5M1, STX7, TMEM147-AS1, C20orf196, RBL2, OSGEPL1, OMA1, AMIGO1, PIN4, EPHX2, UBASH3A, TBC1D4, C11orf21, CD24, ZNF512, CLECL1, CCDC18-AS1, CCDC65, TRABD2A, TBC1D10C, SRSF1, KLHL22, USP34, C1orf74, METTL7A, LRRN3, PAIP2B, SUFU, CR2, ZNF337, HERC4, MTRF1, PGBD2, SLC25A12, QRSL1, CARF, FCRLA, TCF7, CLUAP1, ZNF30, CEPT1, METTL3, SLC14A1, STK38, IGH, STRN, PLXDC1, DENND2D, SCML4, CD40LG, MTERF2, JCHAIN, BCKDHB*

way analysis, the seven most affected pathways were "Herpes simplex virus 1 infection," "Pathways in cancer," "IL-17 signaling pathway," "Cytokine-cytokine receptor interaction," "Viral protein interaction with cytokine and cytokine receptor," and "Kaposi sarcoma-associated herpesvirus infection," and "Lipid and atherosclerosis."

PPI establishment and hub gene identification

Fig. 3A depicts the mutual DEGs-based PPI network had 183 nodes with 1,092 edges. The top ten DEGs were identified: IL6, CXCL2, IL1A, CCL20, IL10, ICAM1, CXCL3, CXCL8, IL1B, and VEGFA (Fig. 3B).

Regulating Network Construction

The hub gene is regulated by 39 transcription factors (TFs). Fig. 4 displays TFs and hub genes interaction network.

Evaluation of drug-gene interactions

VEGFA, IL6, IL1B, and IL1A were targeted to seven drugs. These probable compounds are listed in Table 2.

Discussion

DN is a prevalent and grave complication associated with diabetes, potentially precipitating ACS. The deterioration of ACS by DN transpires through multifaceted pathways: the dysregulation of sodium homeostasis and ensuing volume expansion, the provocation of inflammatory cytokine liberation, the diminution of capillary density, the accumulation of late-stage glycation end products, the perturbation of calcium regulation, and temporally variable insufficiency (Avogaro et al. 2019). The mortality rate for ACS patients with concurrent DN approximates double that of their counterparts without DN (Franklin et al. 2004). Nevertheless, the precise mechanism through which DN catalyzes the onset of ACS persists as an unresolved enigma.

This study used a bioinformatic method to investigate potential molecular mechanism and medicine. GO function analyses were used ontologies to represent biological information (Gene Ontology Consortium 2015). In this study, GO were mainly associated with RNA polymerase II promoter. The KEGG pathway analysis provides insight into cellular and organismal level functions (Kanehisa et al. 2021). These findings underscore the potential significance of RNA polymerase II and select inflammation pathways in the pathogenesis of diabetic DN and ACS.

PPI network was used to identify and predict protein interactions (Stojanova et al. 2013). The results showed that the PPI network had 1,092 edges and 183 nodes. In addition, the top ten genes from PPI network were screened, including: IL6, CXCL2, IL1A, CCL20, IL10, ICAM1, CXCL3, CXCL8, IL1B, and VEGFA.

IL-6 functions as a pleiotropic soluble modulator, orchestrating immune responses and hematopoiesis (Tanaka et al. 2014). Serum IL-6 concentrations serve as determinants of plaque stability and are intimately associated with ACS, wherein elevated levels are indicative of a grim prognosis and heightened mortality risk in ACS patients (Moe and Wong 2010). In the evolution of DN, IL-6 potentially influences podocytes, with IL-6 signaling correlating with podocyte hypertrophy.

CXCL2/CXCL3 play a significant role in coordinating immunocyte recruitment in inflammatory (Charo and Ransohoff 2006). CXCL2 possesses the capability to activate inflammatory vesicles through the recruitment of

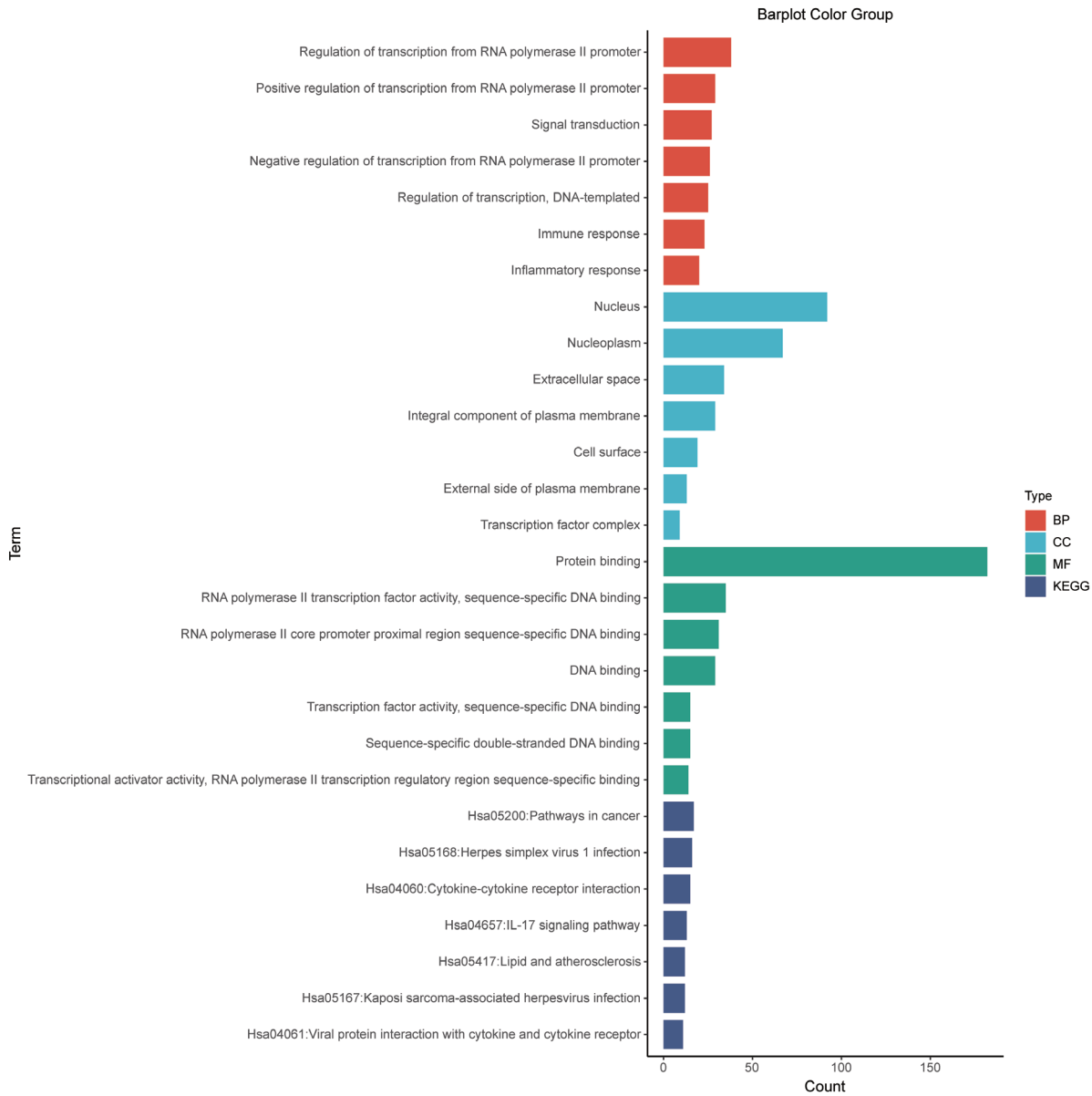

Fig. 2. Functional analyses of differentially expressed genes (DEGs) between diabetic nephropathy (DN) and acute coronary syndrome (ACS).
Red, blue, green, and dark indicated biological process (BP), molecular function (MF), and cellular component (CC), and KEGG pathway analyses, separately.

inflammatory cells at sites of inflammation, and these activated inflammatory vesicles can amplify the incidence of cardiovascular diseases. Van Gemst J.J. employed high-throughput proteomics to discern serum protein levels in AKI-D patients who exhibited renal function recovery and uncovered that CXCL2/CXCL3 was markedly associated, emerging as a novel predictive biomarker for renal recuperation (van Gemst et al. 2018).

CCL20 functions as a pivotal modulator of leukocyte migration during inflammatory responses. The deletion of the CCL20 receptor curtails endothelial inflammation and atherogenesis in mice predisposed to atherosclerosis (Calvayrac et al. 2011), suggesting that CCL20 serves as a mechanistic pathogenic component and could act as an endothelial inflammation biomarker. Conversely, the upregulation of CCL20 is often correlated with augmented macrophage infiltration into the renal tubular mesenchyme, signifying a potential link between CCL20 and renal macrophage infiltration in DN (Huang et al. 2014).

Some investigations have found that IL1B can induce vascular endothelial and renal tethered cell activation, making it a potential candidate for DN pathogenesis (Loughrey et al. 1998). According to a human case-control study, the –511T single nucleotide polymorphism (SNP) within the IL1B gene is associated with diminished IL-1B production in human monocytes and a reduced incidence of myocardial

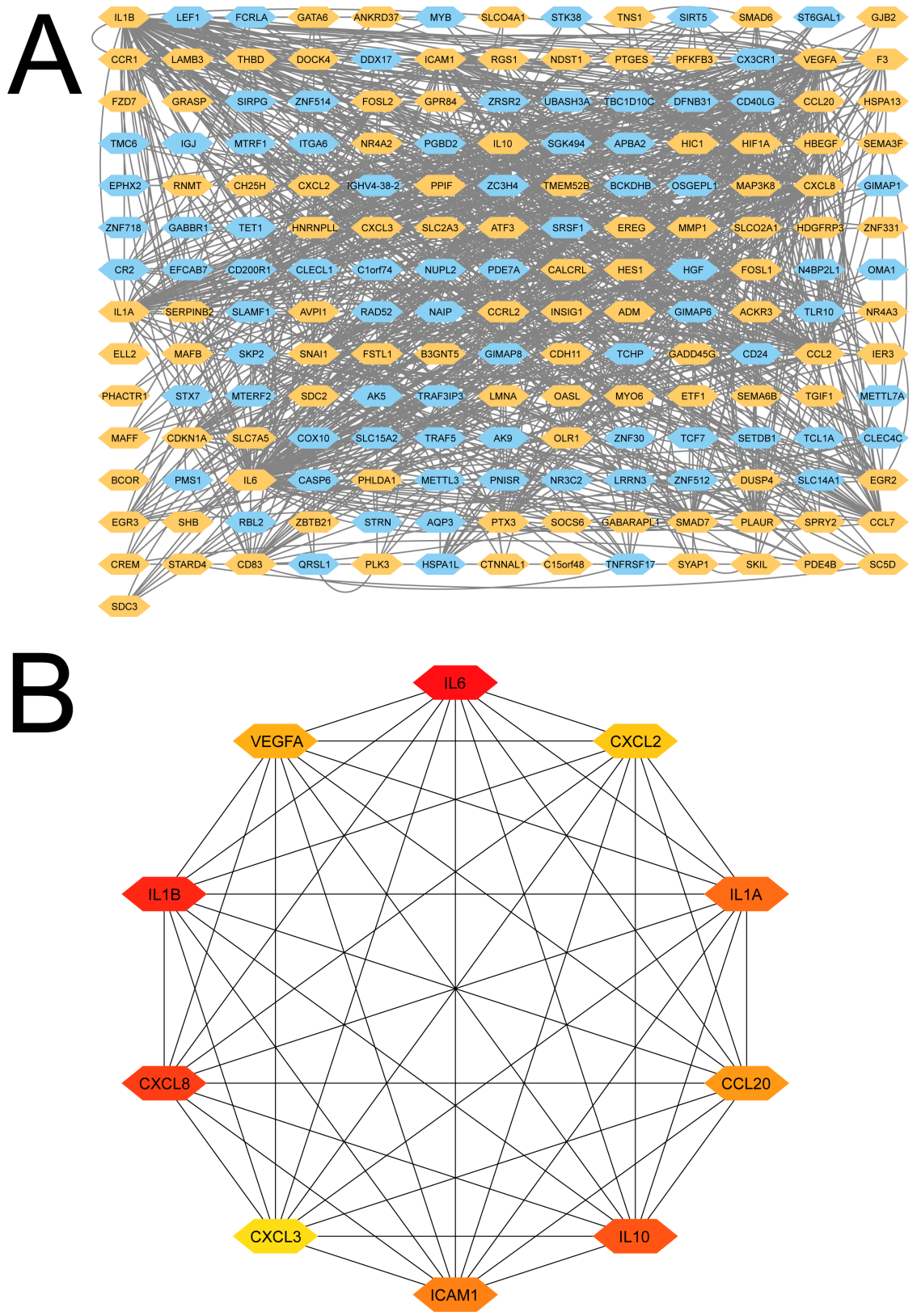

Fig. 3. Protein-protein interaction (PPI) network establishment and hub genes identification.
(A) PPI network of mutual genes. Genes in yellow and blue boxes represent up and down regulation genes separately.
(B) Ten most significant genes involved in the PPI network.

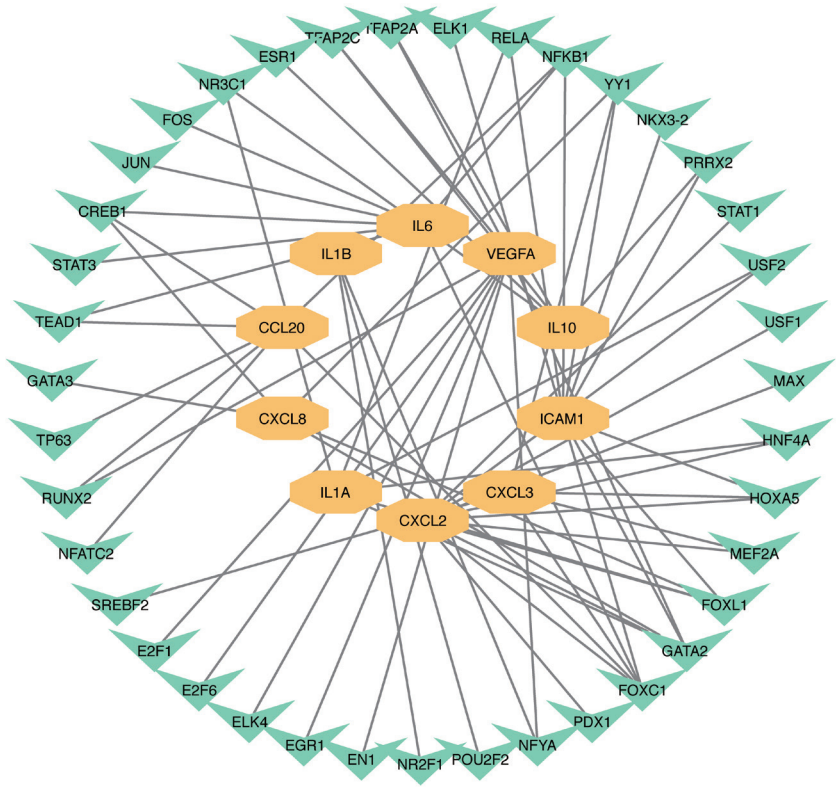

Fig. 4. The hub genes and transcription factors (TFs) interaction network. Green arrow represents TFs, yellow hexagonal indicates hub genes.

Table 2. Drugs targeted to hub genes.

Gene	Drug	Interaction types
VEGFA	PEGAPTANIB SODIUM	Antagonist
	BEVACIZUMAB	Antibody; Inhibitor
	AFLIBERCEPT	Binder; Antibody; Inhibitor
	RANIBIZUMAB	Inhibitor
IL6	SILTUXIMAB	Antagonist; Antibody; Inhibitor
IL1B	CANAKINUMAB	Binder; Antibody; Inhibitor
	RILONACEPT	Binder; Inhibitor
IL1A	RILONACEPT	Binder

infarction at a younger age (Iacoviello et al. 2005). This suggests that IL1B levels may influence arterial wall inflammation, thereby precipitating ACS.

Furthermore, another study demonstrated that when human proximal tubular renal HK-2 cells were treated with high glucose, there was a slight increase in IL-1A levels. This suggests that tubular cell-released IL-1α serves as a significant inflammatory factor contributing to kidney inflammation within DN (Salti et al. 2020).

Another hub gene, IL-10, is a specific anti-inflammatory molecule that reduces inflammatory infiltration and interstitial fibrosis in renal tissues; therefore, IL-10 is expected to delay the development of DN while improving the overall prognosis (Wei et al. 2022). In one study, baseline IL-10 levels in plasma were measured in 193 male ACS patients, and elevated baseline plasma IL-10 levels were significantly associated with a higher mortality rate and non-fatal myocardial infarction risk during the 5-year follow-up, suggesting that IL-10 may be a potential biomarker for ACS (Cavusoglu et al. 2011).

ICAM-1 is an adhesion receptor and cell surface glycoprotein that mediates the recruitment of circulatory leukocytes at inflammation sites. Elevated ICAM-1 levels in ACS cases after 24 hours indicate that ICAM-1 plays a significant role in leukocyte-endothelial cell interactions in ACS (Shyu et al. 1996). In contrast, in DN patients, ICAM1 gene transcription is enhanced in the nucleus, and ICAM1 mRNA levels are elevated on the endothelial cell

surface; as a result, ICAM1 may have a role in the occurrence of DN (Gu et al. 2012).

CXCL8, a powerful angiogenesis activator, is elevated in ACS patients' circulating erythrocytes. According to a related study, elevated CXCL8 levels are the major reason for renal neutrophil accumulation, which causes kidney injury in DM mice (Cui et al. 2017).

VEGF-A levels have been shown to correlate with inflammatory markers, suggesting that VEGF effectors and inflammatory systems in acute coronary syndrome (ACS) patients share phenotypic traits. VEGFA is a crucial source of glomerular podocytes, and both upregulated and downregulated podocyte VEGFA expression during renal development can lead to glomerular disease in mice (Eremina et al. 2006), making it vital to regulate VEGFA levels in glomeruli.

We also looked at how hub genes and TFs genes interacted. Certain DNA sequences are recognized by TF genes, which regulate target gene transcription and expression (Lambert et al. 2018). TFs are important for understanding disease progression. Our study found 39 TFs that regulate hub genes, implying a strong association between them.

We used the DGIDB drug database to identify possible therapeutic molecules for DN and ACS. VEGFA was matched to 4 drugs. Among the medications, "pegaptanib sodium" is a selective RNA aptamer that can inhibit VEGF from binding to its receptor, thereby reducing pathological angiogenesis. It has been utilized in the treatment of ocular vascular diseases, age-related macular degeneration, and other conditions (Apte 2008). Another targeted medication, "bevacizumab," is a humanized monoclonal antibody capable of binding to soluble VEGF-A isoforms. By binding to VEGF-A, "bevacizumab" obstructs the VEGF-VEGFR interaction, consequently inhibiting the activation of the VEGF pathway that promotes neovascularization. It is frequently used in the treatment of cancers, such as non-small cell lung cancer and metastatic breast cancer (Shukla et al. 2007).

"Aflibercept" is a fully humanized recombinant fusion protein that acts as a decoy, binding to placental growth factor and VEGF-A, thereby preventing the ligand from binding to its homologous receptors (Garcia et al. 2020). "Ranibizumab," a high-affinity recombinant Fab, is responsible for neutralizing all VEGFA isoforms and was approved by the FDA in June 2006 for treating wet age-related neovascularization (Ciombor et al. 2013). Some investigators have shown that serum VEGF has a valid diagnostic value for ACS (Huang et al. 2020), suggesting that VEGFA is a potential drug target for treating ACS. In contrast, "siltuximab" which binds to IL-6, represents the IL-6 chimeric mAb and is used to treat multicentric Castleman's disease, cytotoxic chemotherapy, and other conditions (Markham and Patel 2014).

Another hub gene is IL1B, which has two corresponding medications. One is "canakinumab," a monoclonal antibody (mAb) that blocks the IL-1β-regulated inflammatory pathway, and it has been used to prevent coronary artery disease (Ortega-Paz et al. 2021). Another medication targeting both IL1B and IL1A is "rilonacept," a soluble IL-1 receptor chimeric fusion protein that neutralizes IL-1A and IL-1B, showing promising results in a phase II study of recurrent/refractory pericarditis and may become widely available for cardiovascular diseases in the future (Abbate et al. 2020).

Conclusions

This study used bioinformatics methods to explore the correlation between DN and ACS, finding four genes and seven medications that could provide a novel perspective for DN and ACS in the future.

Conflict of Interest

The authors declare no conflict of interest.

References

Abbate, A., Toldo, S., Marchetti, C., Kron, J., Van Tassell, B.W. & Dinarello, C.A. (2020) Interleukin-1 and the Inflammasome as Therapeutic Targets in Cardiovascular Disease. *Circ. Res*., **126**, 1260-1280.

Anders, H.J., Huber, T.B., Isermann, B. & Schiffer, M. (2018) CKD in diabetes: diabetic kidney disease versus nondiabetic kidney disease. *Nat. Rev. Nephrol.*, **14**, 361-377.

Apte, R.S. (2008) Pegaptanib sodium for the treatment of age-related macular degeneration. *Expert Opin. Pharmacother.*, **9**, 499-508.

Avogaro, A., Bonora, E., Consoli, A., Del Prato, S., Genovese, S. & Giorgino, F. (2019) Glucose-lowering therapy and cardiovascular outcomes in patients with type 2 diabetes mellitus and acute coronary syndrome. *Diab. Vasc.. Dis Res.*, **16**, 399-414.

Berriche, A., Ammari, L., Abdelmalek, R., Kanoun, F., Aissa, S., Ghoubantini, A., Kilani, B. & Tiouiri Benaissa, H. (2014) Syndrome coronarien aigu sous traitement antiretroviral. *Tunis. Med.*, **92**, 690-693.

Buntaine, A.J., Shah, B., Lorin, J.D. & Sedlis, S.P. (2016) Revascularization Strategies in Patients with Diabetes Mellitus and Acute Coronary Syndrome. *Curr. Cardiol. Rep.*, **18**, 79.

Calvayrac, O., Rodriguez-Calvo, R., Alonso, J., Orbe, J., Martin-Ventura, J.L., Guadall, A., Gentile, M., Juan-Babot, O., Egido, J., Beloqui, O., Paramo, J.A., Rodriguez, C. & Martinez-Gonzalez, J. (2011) CCL20 is increased in hypercholesterolemic subjects and is upregulated by LDL in vascular smooth muscle cells: role of NF-kappaB. *Arterioscler. Thromb. Vasc. Biol.*, **31**, 2733-2741.

Cavusoglu, E., Marmur, J.D., Hojjati, M.R., Chopra, V., Butala, M., Subnani, R., Huda, M.S., Yanamadala, S., Ruwende, C., Eng, C. & Pinsky, D.J. (2011) Plasma interleukin-10 levels and adverse outcomes in acute coronary syndrome. *Am. J. Med.*, **124**, 724-730.

Charo, I.F. & Ransohoff, R.M. (2006) The many roles of chemokines and chemokine receptors in inflammation. *N. Engl. J. Med.*, **354**, 610-621.

Ciombor, K.K., Berlin, J. & Chan, E. (2013) Aflibercept. *Clin Cancer Res*, **19**, 1920-1925.

Cui, S., Zhu, Y., Du, J., Khan, M.N., Wang, B., Wei, J., Cheng, J.W., Gordon, J.R., Mu, Y. & Li, F. (2017) CXCL8 Antagonist Improves Diabetic Nephropathy in Male Mice With Diabetes and Attenuates High Glucose-Induced Mesangial Injury. *Endocrinology*, **158**, 1671-1684.

Eremina, V., Cui, S., Gerber, H., Ferrara, N., Haigh, J., Nagy, A., Ema, M., Rossant, J., Jothy, S., Miner, J.H. & Quaggin, S.E. (2006) Vascular endothelial growth factor a signaling in the

podocyte-endothelial compartment is required for mesangial cell migration and survival. *J. Am. Soc. Nephrol.*, **17**, 724-735.

Franklin, K., Goldberg, R.J., Spencer, F., Klein, W., Budaj, A., Brieger, D., Marre, M., Steg, P.G., Gowda, N., Gore, J.M. & Investigators, G. (2004) Implications of diabetes in patients with acute coronary syndromes. The Global Registry of Acute Coronary Events. *Arch. Intern. Med.*, **164**, 1457-1463.

Garcia, J., Hurwitz, H.I., Sandler, A.B., Miles, D., Coleman, R.L., Deurloo, R. & Chinot, O.L. (2020) Bevacizumab (Avastin®) in cancer treatment: A review of 15 years of clinical experience and future outlook. *Cancer Treat. Rev.*, **86**, 102017.

Gene Ontology Consortium (2015) Gene Ontology Consortium: going forward. *Nucleic Acids Res.*, **43**, D1049-1056.

Gu, H.F., Ma, J., Gu, K.T. & Brismar, K. (2012) Association of intercellular adhesion molecule 1 (ICAM1) with diabetes and diabetic nephropathy. *Front. Endocrinol.* (*Lausanne*), **3**, 179.

Huang, A., Qi, X., Cui, Y., Wu, Y., Zhou, S. & Zhang, M. (2020) Serum VEGF: Diagnostic Value of Acute Coronary Syndrome from Stable Angina Pectoris and Prognostic Value of Coronary Artery Disease. *Cardiol. Res. Pract.*, **2020**, 6786302.

Huang, C., Pollock, C.A. & Chen, X.M. (2014) High glucose induces CCL20 in proximal tubular cells via activation of the KCa3.1 channel. *PLoS One*, **9**, e95173.

Iacoviello, L., Di Castelnuovo, A., Gattone, M., Pezzini, A., Assanelli, D., Lorenzet, R., Del Zotto, E., Colombo, M., Napoleone, E., Amore, C., D'Orazio, A., Padovani, A., de Gaetano, G., Giannuzzi, P., Donati, M.B., et al. (2005) Polymorphisms of the interleukin-1beta gene affect the risk of myocardial infarction and ischemic stroke at young age and the response of mononuclear cells to stimulation in vitro. *Arterioscler. Thromb. Vasc. Biol.*, **25**, 222-227.

Kanehisa, M., Furumichi, M., Sato, Y., Ishiguro-Watanabe, M. & Tanabe, M. (2021) KEGG: integrating viruses and cellular organisms. *Nucleic Acids Res.*, **49**, D545-D551.

Lambert, S.A., Jolma, A., Campitelli, L.F., Das, P.K., Yin, Y., Albu, M., Chen, X., Taipale, J., Hughes, T.R. & Weirauch, M.T. (2018) The Human Transcription Factors. *Cell*, **175**, 598-599.

Loughrey, B.V., Maxwell, A.P., Fogarty, D.G., Middleton, D., Harron, J.C., Patterson, C.C., Darke, C. & Savage, D.A. (1998) An interluekin 1B allele, which correlates with a high secretor phenotype, is associated with diabetic nephropathy. *Cytokine*, **10**, 984-988.

Markham, A. & Patel, T. (2014) Siltuximab: first global approval. *Drugs*, **74**, 1147-1152.

Moe, K.T. & Wong, P. (2010) Current trends in diagnostic biomarkers of acute coronary syndrome. *Ann. Acad. Med. Singap.*, **39**, 210-215.

Ortega-Paz, L., Capodanno, D. & Angiolillo, D.J. (2021) Canakinumab for secondary prevention of coronary artery disease. *Future Cardiol.*, **17**, 427-442.

Qi, W., Chen, X., Gilbert, R.E., Zhang, Y., Waltham, M., Schache, M., Kelly, D.J. & Pollock, C.A. (2007) High glucose-induced thioredoxin-interacting protein in renal proximal tubule cells is independent of transforming growth factor-beta1. *Am. J. Pathol.*, **171**, 744-754.

Salti, T., Khazim, K., Haddad, R., Campisi-Pinto, S., Bar-Sela, G. & Cohen, I. (2020) Glucose Induces IL-1alpha-Dependent Inflammation and Extracellular Matrix Proteins Expression and Deposition in Renal Tubular Epithelial Cells in Diabetic Kidney Disease. *Fron.t Immunol.*, **11**, 1270.

Shukla, D., Namperumalsamy, P., Goldbaum, M. & Cunningham, E.T. Jr. (2007) Pegaptanib sodium for ocular vascular disease. *Indian. J. Ophthalmol.*, **55**, 427-430.

Shyu, K.G., Chang, H., Lin, C.C. & Kuan, P. (1996) Circulating intercellular adhesion molecule-1 and E-selectin in patients with acute coronary syndrome. *Chest*, **109**, 1627-1630.

Stojanova, D., Ceci, M., Malerba, D. & Dzeroski, S. (2013) Using PPI network autocorrelation in hierarchical multi-label classification trees for gene function prediction. *BMC Bioinformatics*, **14**, 285.

Tanaka, T., Narazaki, M. & Kishimoto, T. (2014) IL-6 in inflammation, immunity, and disease. *Cold Spring Harb. Perspect. Biol.*, **6**, a016295.

van Gemst, J.J., Kouwenberg, M., Rops, A., van Kuppevelt, T.H., Berden, J.H., Rabelink, T.J., Loeven, M.A. & van der Vlag, J. (2018) Differential binding of chemokines CXCL1, CXCL2 and CCL2 to mouse glomerular endothelial cells reveals specificity for distinct heparan sulfate domains. *PLoS One*, **13**, e0201560.

Wei, W., Zhao, Y., Zhang, Y., Jin, H. & Shou, S. (2022) The role of IL-10 in kidney disease. *Int. Immunopharmacol.*, **108**, 108917.