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Exploring the interplay between adipokine-mediated celastrol target genes and T cells in diabetic nephropathy: a mendelian randomization-based causal inference

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Abstract

Background Diabetic nephropathy (DN) is influenced by dysregulated adipokines, which play a key role in inflammation, immune responses, and lipid metabolism. However, the precise molecular mechanisms linking adipokine dysregulation, immune cell infiltration, and metabolic reprogramming in DN remain poorly understood. Celastrol, a bioactive lipid regulator, has been shown to mitigate renal immune-inflammatory damage by inhibiting the PI3K/Akt/NF-κB signaling pathway. Yet, its specific impact on adipokine-mediated immune responses and lipid metabolism in DN is unclear. This study aims to elucidate the interplay between adipokine-mediated target genes in DN and investigate how celastrol modulates these interactions.

Methods Gene expression profiles of DN patients were obtained from GEO datasets (GSE30122 and GSE30528) and analyzed for differentially expressed genes (DEGs) using the limma package. Gene set variation analysis (GSVA) was conducted to assess lipid metabolism pathways, while Mendelian randomization (MR) and Pearson correlation evaluated the association between DEGs and adipokines. Immune cell infiltration was analyzed using the IOBR R package (MCP-counter and xCell methods), followed by MR analysis of DN-related immune responses. Celastrol target genes were identified using the SEA database.

Results A total of 70 intersecting DEGs were identified. GSVA revealed that brown and beige adipocyte differentiation pathways were downregulated, while adipocyte-related pathways were upregulated in DN ($p < 0.05$). MR analysis demonstrated that adiponectin was negatively associated with DN (OR = 0.77, $P = 0.005$), whereas leptin (OR = 1.92, $P = 0.016$) and resistin (OR = 1.43, $P < 0.001$) were positively associated. Three key genes, MAGI2, FGF9, and THBS2 were linked to DN risk and T cell infiltration. THBS2 was positively correlated with T cell infiltration (OR = 0.51, $P = 6.7e\text{-}06$), while FGF9 (OR = -0.8, $P = 2.2e\text{-}16$) and MAGI2 (OR = 0.75, $P = 1.3e\text{-}13$) were negatively correlated. 22 celastrol target genes, including MAGI2, FGF9, and THBS2, were identified.

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Conclusion Our findings reveal that celastrol modulates DN progression through adipokine-immune crosstalk, with FGF9, MAGI2, and THBS2 emerging as key regulatory genes. These insights provide new avenues for biomarker discovery and therapeutic implications in the development of DN.

Keywords Diabetic nephropathy, Adipokines, Mendelian randomization, Immune infiltration, Immune cells, Celastrol

Introduction

Diabetic nephropathy (DN) is a leading cause of end-stage renal disease (ESRD) worldwide, and the prevalence of DN among adults with diabetes reaches as high as 30.9% in China [1, 2]. Blood glucose control and treatments that reduce urinary albumin do not fundamentally alter the course of DN [3]. The latest evidence-based guidelines recommend the use of sodium-glucose co-transporter 2 inhibitors, as well as angiotensin-converting enzyme inhibitors (ACEIs) / angiotensin receptor blockers (ARBs) and novel antihyperglycemic drugs. However, sodium-glucose co-transporter 2 inhibitors have not been shown to slow the progression of DN to ESRD [3]. Furthermore, due to the heterogeneity and complex mechanisms of diabetes-related kidney injury, there is still controversy regarding the current diagnosis and treatment of DN [4]. Therefore, it is urgent to explore strategies for early prevention and treatment of DN.

Lipids are the main energy source for the kidneys, and lipid metabolism disorders are closely associated with the occurrence and progression of DN [5]. Studies have indicated that the accumulation of cholesterol, phospholipids, triglycerides, fatty acids, and sphingolipids in the kidneys is related to the pathogenesis of DN [6]. Impaired fatty acid oxidation may lead to a disruption in the balance between fatty acid synthesis, uptake, and consumption, which in turn affects renal lipid metabolism and promotes the accumulation of intracellular lipids [7]. Dyslipidemia can damage the kidneys by enhancing lipid-mediated oxidative stress and inflammation, lipogenesis, ectopic lipid deposition, and changes in lipid distribution, metabolism, and β-oxidation [8]. Consequently, finding ways to alleviate DN progression by regulating lipid metabolism has become a key research focus [9].

Recent studies have shown that adipokines—bioactive peptides secreted by adipose tissue—play crucial roles in regulating lipid metabolism, insulin sensitivity, and inflammatory responses. Several adipokines, including leptin, adiponectin, and resistin, have been identified as important mediators of dyslipidemia [10]. Adiponectin is known to exert protective effects against metabolic disorders; Kawano et al. identified that adiponectin is an valuable marker for early DN detection [11], and adiponectin receptor agonists have been shown to improve renal function in type 2 diabetes (T2D) mouse models [12]. Leptin levels, commonly elevated in obesity and T2D, are associated with increased lipotoxicity and renal inflammation, which are central to DN pathogenesis. Resistin, initially recognized for its role in insulin resistance, is also implicated in lipid metabolism and inflammation. Huang et al. demonstrated that elevated levels of leptin and resistin are risk factors for DN in T2D patients with lower body mass index [13]. At the same time, another study showed that elevated plasma resistin is associated with DN risk in T2D patients [14]. While these adipokines have been widely studied, their exact causal roles in DN onset and progression remain unclear.

Celastrol—a natural quinone-methide triterpenoid compound derived from the root bark of *Tripterygium wilfordii*—has attracted growing attention for its role in preventing and mitigating various metabolic disorders. Our previous studies have shown that celastrol exerts anti-obesity effects by modulating interactions among systemic insulin sensitivity, adipose tissue inflammation, and skeletal muscle mitochondrial function [15, 16]. Additionally, celastrol has been shown to reduce *adipokine* resistin-associated matrix interactions and improve vascular smooth muscle cell migration [17]. These regulatory mechanisms function in immune responses, inflammation, and oxidative stress—all critical processes in DN pathogenesis. Recent research has demonstrated that celastrol significantly delays renal damage in DN [18]. Celastrol can lower blood glucose levels and renal function indices in db/db mice, alleviate morphological damage to kidney tissue, and induce significant anti-inflammatory effects [19]. Our recent report found that celastrol significantly enhances cell viability and reduces apoptosis in high glucose (HG)-treated HK-2 cells. Additionally, celastrol decreases pro-inflammatory cytokine levels and increases antioxidant enzyme activities, thereby mitigating fibrosis and oxidative stress induced by high glucose. These effects are primarily attributed to the inhibition of the PI3K/Akt/NF-κB signaling pathway [20]. Current evidence underscores its potential in modulating lipid metabolism, inflammation, and oxidative stress, presenting a promising therapeutic approach for managing dyslipidemia and suppressing DN progression.

Mendelian randomization (MR) is a robust epidemiological method that uses genetic variation as instrumental variables to estimate the causal effect of an exposure on an outcome, offering a feasible approach to overcome these limitations [21]. By applying MR, researchers can leverage genetic predispositions to elevated or decreased adipokine levels to elucidate their direct causal effects on DN. Recent studies suggest that celastrol acts as a leptin sensitizer, reducing body fat and leptin levels [22].

Moreover, celastrol exhibits significant regulatory effects on adiponectin and resistin levels [23]. Celastrol, a bioactive triterpenoid, has demonstrated promising renoprotective effects [20], but its role in adipokine-mediated immune modulation remains unexplored. To address this, we employed an MR approach combined with bioinformatics to elucidate adipokine-target gene interactions in DN. Specifically, this study focuses on leptin, adiponectin, and resistin, using a combined MR and bioinformatics analysis approach to investigate how genes associated with these adipokines contribute to DN susceptibility and progression. Understanding these causal relationships will not only deepen our knowledge of DN pathophysiology but may also pave the way for novel diagnostic biomarkers and therapeutic strategies targeting lipid metabolism.

Methods

Data acquisition

The expression profile datasets of DN patients GSE30122 (including 19 samples of DN and 50 normal samples) and GSE30528 (including 9 samples of DN and 13 normal samples) were downloaded from the GEO database (https://www.ncbi.nlm.nih.gov/geo). The disease samples primarily represent stages III-IV of DN, and all samples in these datasets were obtained from renal biopsies. The probes in the GEO datasets were changed to corresponding gene names using the R package "idmap3" (https://github.com/jmzeng1314/idmap3).

Identification of differentially expressed genes (DEGs) in DN

Differential expression analysis was performed on the GSE30122 and GSE30528 datasets to identify DEGs between normal and DN samples using the R package "limma". The criteria were set as P value < 0.05 and |log2 fold change| > 1. Subsequently, the intersecting genes between GSE30122 and GSE30528 were screened through a Venn diagram drawn using "VennDiagram".

Gene set variation analysis (GSVA) of lipid metabolism

Five GMT reference gene sets related to lipid metabolism were retrieved from MSigDB (https://www.gsea-msigdb.org/gsea/msigdb/), including: Brown_and_beige_adipocyte_differentiation, White_adipocyte_differentiation, Differentiation_.

of_white_and_brown_adipocyte, Adipocytes_diabetic_condition, and Adipocytes_.

normal_condition. Pathway enrichment scores were performed in GSE30122 using the R package "GSVA" and the differences in scoring results were statistically analyzed. Correlations between the selected intersection genes and pathway scores were also calculated. Significantly related genes were selected according to |correlation| > 0.6 and P value < 0.05.

MR analysis

We performed MR analysis to investigate the causal relationship between adipokines (adiponectin, leptin, and resistin), core genes (*FGF9*, *MAGI2*, *RRM2*, *VCAN*, *CD163*, *THBS2*), T-cell-related factors, and DN. GWAS data for these adipokines and genes were obtained from the IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/) and the GWAS Catalog (https://www.ebi.ac.uk/gwas/), using database IDs: ieu-a-1 (adiponectin), ieu-a-1003 (leptin), ebi-a-GCST90012034 (resistin), eqtl-a-ENSG00000102678 (*FGF9*), eqtl-a-ENSG00000187391 (*MAGI2*), eqtl-a-ENSG00000171848 (*RRM2*), eqtl-a-ENSG00000038427 (*VCAN*), eqtl-a-ENSG00000177575 (*CD163*), eqtl-a-ENSG00000186340 (*THBS2*), GCST90001620 (HLA DR + T cell lymphocyte), and GCST90001918 (CD45 on HLA DR + T cell). For the outcome variable, GWAS data for DN (ebi-a-GCST90018832) were also retrieved. We selected instrumental variables (IVs) through correlation analysis with a P threshold of < 5e-05 and retrieved relevant data, including effect size (beta), standard error (SE), and P value for each SNP. To ensure IV independence, we used the clump_data function in the TwoSampleMR package to remove SNPs in linkage disequilibrium with parameters clump_r^2 = 0.001 and clump_kb = 10,000. MR analysis was conducted using the TwoSampleMR package with several statistical methods, including Inverse Variance Weighted (IVW), Maximum Likelihood, MR-Egger, Weighted Median, and Weighted Mode, to assess the causal relationship between exposures and the outcome. To evaluate heterogeneity, we applied the mr_heterogeneity function using the IVW and MR-Egger methods and results with P > 0.05 indicated robust findings. Pleiotropy was assessed using the mr_pleiotropy_test function with the MR-Egger intercept test.

Immune landscape analysis

The immune cell infiltration analysis was conducted to assess the abundance of immune cells in the GSE30122 cohort using the R package "IOBR," specifically employing the mcpcounter and xcell methods [24]. The immune cells with the same difference trend in the two methods were identified and subjected to Mendelian randomization analysis.

Association of adipokines-related DEGs and T cells

To further validate the association of these key DEGs and immune cells, Pearson correlation analysis was calculated for adipokines-related DEGs and T cells in GSE30122.

Relationship between core gene and Celastrol

Target genes of celastrol were predicted using SEA database (https://sea.bkslab.org/) to verify the relationship between drug and these key DEGs.

Statistical analysis

All analyses were performed using R version 4.3.2, and $P < 0.05$ was considered significantly different. MR analyses were performed based on the R package "TwoSampleMR". The differential statistical analysis method is t-test, and the correlation analysis method is Pearson.

Results

Identification of DEGs and their association with lipid metabolism in DN

There were 249 and 156 DEGs in the GSE30528 (Fig. 1A) and GSE30122 (Fig. 1B), respectively. After intersecting these DEGs, 70 DEGs were acquired and shown in the Venn diagram (Fig. 1C). In the GSVA pathway enrichment score, Brown_and_beige_adipocyte_differentiation had a lower score in DN. However, the scores for Adipocytes_diabetic_condition and Adipocytes_normal_condition were higher in the DN samples ($P < 0.05$, Fig. 1D-E). At the same time, according to the results of Pearson correlation analysis, 6 genes (*FGF9*, *MAGI2*, *RRM2*, *VCAN*, *CD163*, and *THBS2*) were significantly related to the above three lipid metabolism pathways with |Correlation| < 0.6 and $P < 0.05$ (Fig. 1F).

MR analysis was performed on adipokines-related DEGs and their association with DN

The GWAS data of adipokines (ieu-a-1003, ieu-a-1, ebi-a-GCST90012034) and DN (ebi-a-GCST90018832) were retrieved from the IEU OpenGWAS (https://gwas.mrcieu.ac.uk/). All three adipokines (adiponectin, leptin, and resistin) were associated with DN (Fig. 2A). Figure 2B-D showed the SNP effects of adiponectin, leptin, and resistin on DN, analyzed using IVW, MR Egger, and Weighted Median methods. Adiponectin is negatively associated with DN risk (IVW, OR = 0.77, $P = 0.005$, Fig. 2B). The IVW method suggests that higher adiponectin levels may have a protective effect, but the MR Egger method did not find a significant association, indicating potential interference from horizontal pleiotropy. Leptin is positively associated with DN risk (MR Egger, OR = 1.92, $P = 0.016$, Fig. 2C). Resistin shows a strong association with DN risk (IVW, OR = 1.43, $P < 0.001$, Fig. 2D), with both the IVW and Weighted Median methods supporting that higher resistin levels may promote the progression of DN. The *P* values for heterogeneity and pleiotropy tests were greater than 0.05, indicating the reliability of the results (Table S1-2).

Furthermore, we performed Pearson correlation analysis on six genes (*FGF9*, *MAGI2*, *RRM2*, *VCAN*, *CD163*, and *THBS2*) and adipokines, which were significantly negatively correlated with adipokines ($P < 0.05$, Fig. 3A). To further verify the association between these six genes and DN, the above gene GWAS data (eqtl-a-ENSG00000186340, eqtl-a-ENSG00000102678, eqtl-a-ENSG00000187391, eqtl-a-ENSG00000171848, eqtl-a-ENSG00000038427, and eqtl-a-ENSG00000177575) were considered exposure factors. Using R TwoSampleMR MR analysis, *MAGI2*, *FGF9*, and *THBS2* were associated with DN (Fig. 3B). SNP effect plots showed the relationship between these three genes and DN (Fig. 3C-E). *MAGI2* was negatively correlated with the risk of DN (IVW, OR = 0.83, $P = 0.001$, Fig. 3C), *FGF9* was negatively correlated with the risk of DN (IVW, OR = 0.89, $P = 0.002$, Fig. 3D), and *THBS2* was positively correlated with the risk of DN (MR Egger, OR = 1.12, $P = 0.003$, Fig. 3E). The *P* values for both the simultaneous heterogeneity and pleiotropy tests were greater than 0.05, indicating the reliability of the results (Table S3-4).

MR analysis of T cells and DN

The infiltration levels of immune cells in DN were further explored. Levels of T cells, monocytic lineage, and fibroblasts were significantly higher than those in normal controls in the mcpcounter method ($P < 0.05$, Fig. 4A), only T cells showed the same trend in the xcell method (Fig. 4B). The GWAS data of T cells (GCST90001620, GCST90001918) were downloaded from the GWAS Catalog database. T cell as the exposure factor, DN as the outcome factor, using R packages TwoSampleMR for MR analysis. Two types of T cells were related to DN (Fig. 4C). As shown in the SNP effect plot, HLA DR^+ T cell%lymphocyte and DN risk were positively correlated (IVW, OR = 1.09, $P = 0.032$, Fig. 4D). CD45 on HLA DR^+ T cells was positively correlated with the risk of DN (IVW, OR = 1.12, $P = 0.020$, Fig. 4E), which was consistent with the trend of T cell immune infiltration analysis. The P values for both the simultaneous heterogeneity and pleiotropy tests were greater than 0.05, indicating the reliability of the results (Table S5-6).

Relationship between three adipokine-related genes and T cells

In addition, the identified three adipokine-related gene expression levels were validated in the GSE30122 dataset. As shown in Fig. 5A-C, *THBS2* was highly expressed in DN, while *FGF9* and *MAGI2* were lowly expressed ($P < 0.05$), consistent with the trends observed in their MR analysis results. Pearson correlation analysis shows a positive correlation between *THBS2* and T cells, while *FGF9* and *MAGI2* are negatively correlated with T cells (Fig. 5D-F).

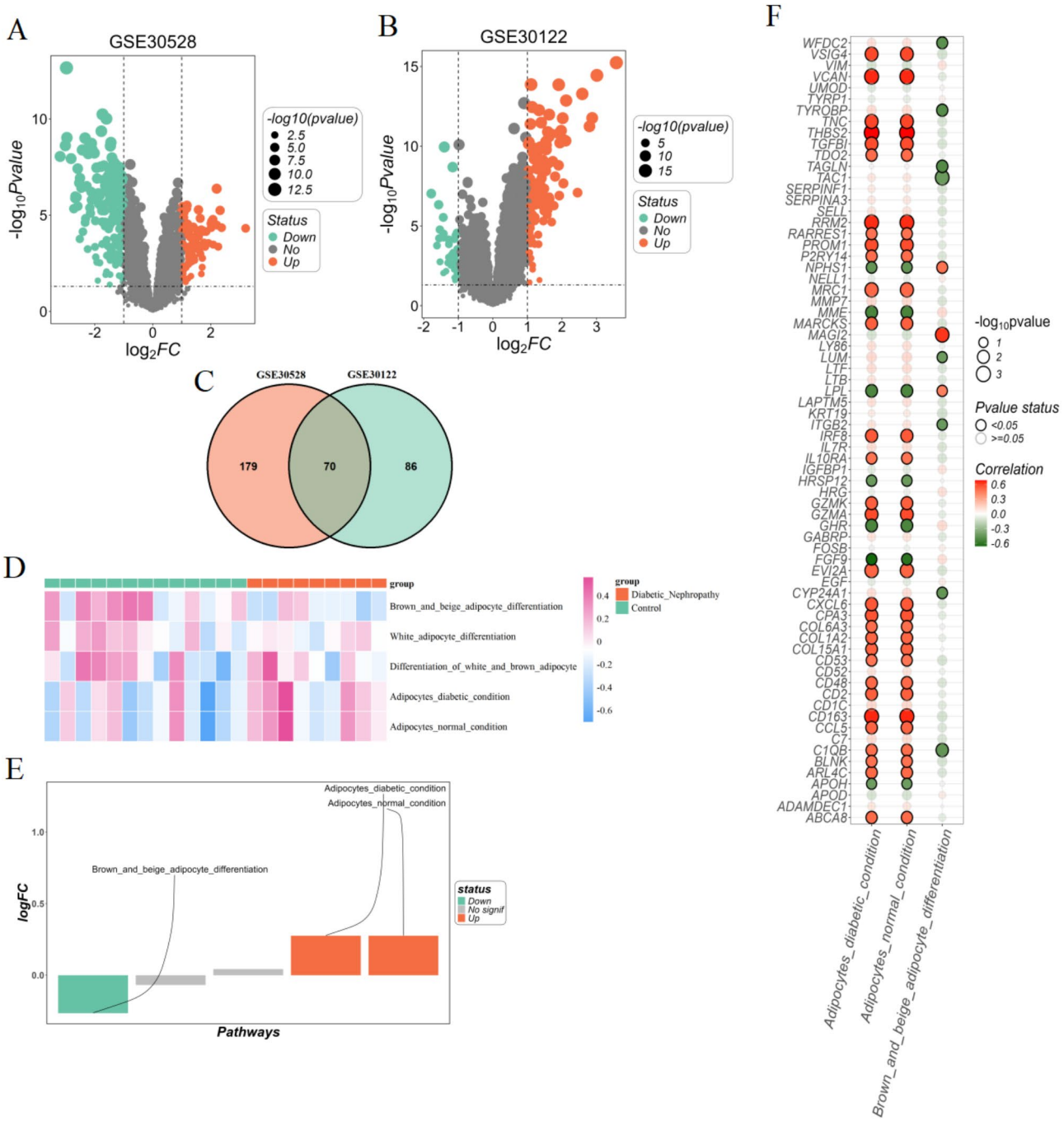

Fig. 1 Identification of DEGs and their association with lipid metabolism in DN
A-B. Volcano plot of different expressed genes (DEGs) between DN and normal in GSE30122 (A) and GSE30528 (B). **C.** Overlapping genes of DEGs in GSE30122 and GSE30528. **D-E.** Heatmap and barplot of GSVA scores. **F.** Correlation heatmap of 70 DEGs and lipid metabolism pathway

Relationship of MAGI2, FGF9, THBS2 and Celastrol

Twenty-two target genes of celastrol, including *MAGI2*, *FGF9* and *THBS2*(Fig. 6), were predicted using the SEA database (https://sea.bkslab.org/).

Discussion

Adipokines are closely associated with the progression of DN [25]. This study investigated the potential causal role of adipokine-related genes in the pathogenesis of DN. We identified six genes significantly negatively correlated with adipokines—adiponectin, leptin, or resistin—in DN. Among them, *MAGI2*, *FGF9*, and *THBS2* showed

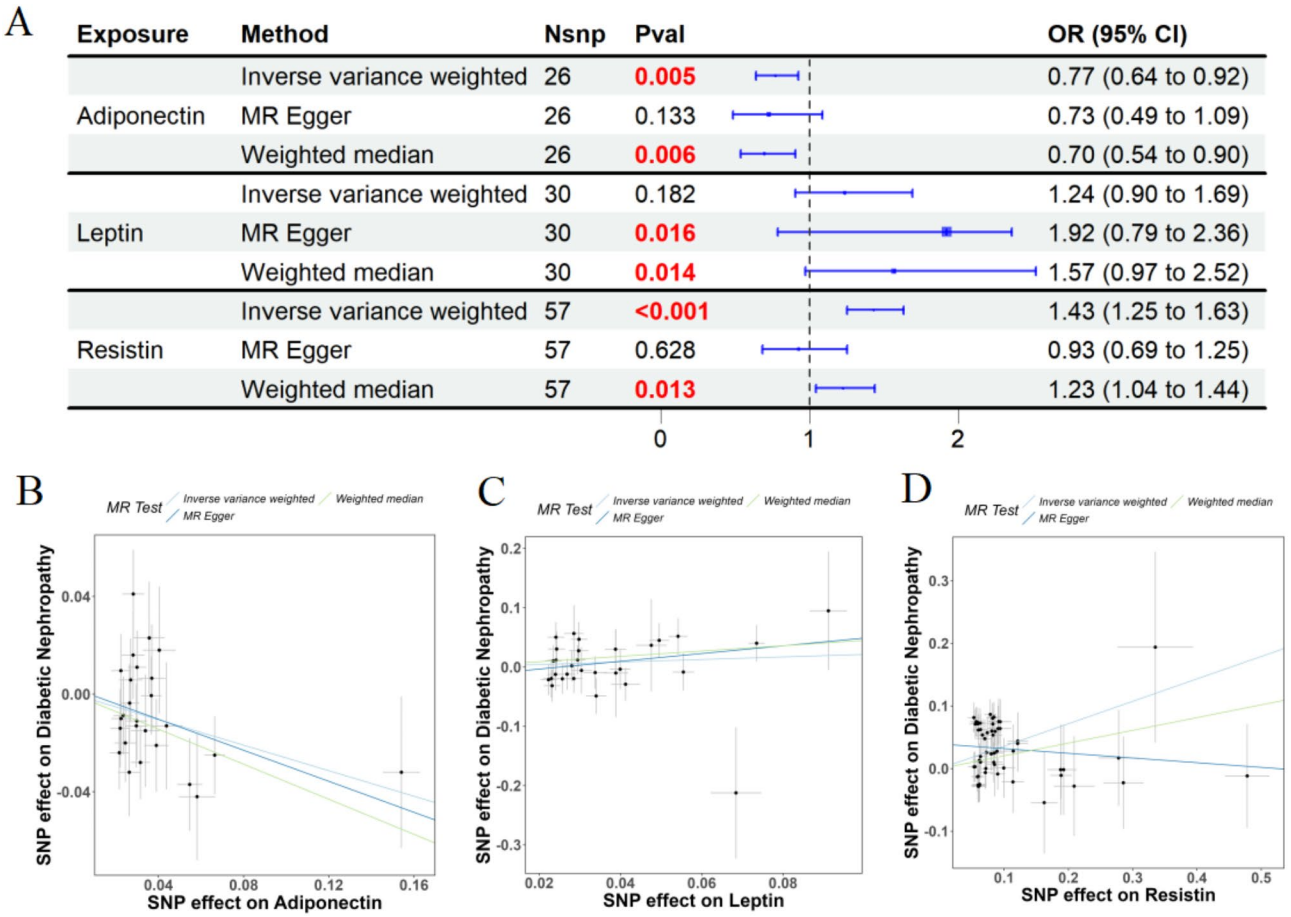

Fig. 2 MR analysis of adipokines and DN
A. MR risk forest of adipokines and DN. **B-D.** MR SNP effect plots for adipokines and DN

relationships with DN progression. Further immune infiltration and MR analysis revealed a strong association between T cells and DN risk, with significant correlations observed between the three identified genes and T cells.

First, pathway enrichment analysis indicated that the DN tissue had lower scores in brown and beige adipocyte differentiation. Brown adipose tissue is more energetically active than white adipose tissue in metabolic activities, with a greater number of mitochondria. Brown and beige adipocytes are not only thermogenic but also improve lipid metabolism through the secretion of specific factors [26]. Currently, activation of brown and beige cells is considered a potential target for treating obesity and T2D [26]. Our findings suggest that alterations in adipocyte differentiation may play a crucial role in DN by promoting lipid accumulation within renal tissue. Furthermore, our MR analysis revealed a link between specific adipokines—adiponectin, leptin, and resistin—and DN risk. Adiponectin is the most abundant adipokine in human plasma [27]. Previous studies have shown that low adiponectin is a major risk factor for metabolic disorders [28], and it may improve DN by inhibiting necrotic cell apoptosis [29]. Consistently, our findings indicate a negative correlation between adiponectin and DN risk. On the other hand, we found that both leptin and resistin are positively correlated with DN risk. Leptin levels are a risk factor for declining renal function [30]; leptin and resistin play crucial roles in insulin resistance-related kidney injury [31]. These findings provide further evidence for the distinct roles of adipokines in DN.

To further explore the specific mechanisms of lipid metabolism in DN, we identified 70 intersecting DEGs in the GSE30122 and GSE30528 datasets. Six genes—*FGF9*, *MAGI2*, *RRM2*, *VCAN*, CD163, and *THBS2*—were significantly associated with lipid metabolism pathways related to DN. Previous studies have shown that downregulation of *FGF9* in primary hepatocytes promotes lipid accumulation in cells [32]; *MAGI2*, regulated by *CLDN6*, influences fatty acid synthesis metabolism [33]; inhibition of *RRM2* limits the accumulation of intracellular toxic lipid peroxides [34]; *VCAN* is a lipid metabolism-related gene in gastric cancer [35]; *CD163* is a marker for M2 macrophages, and macrophages are associated with lipid metabolism in T2D [36]; *THBS2* has also

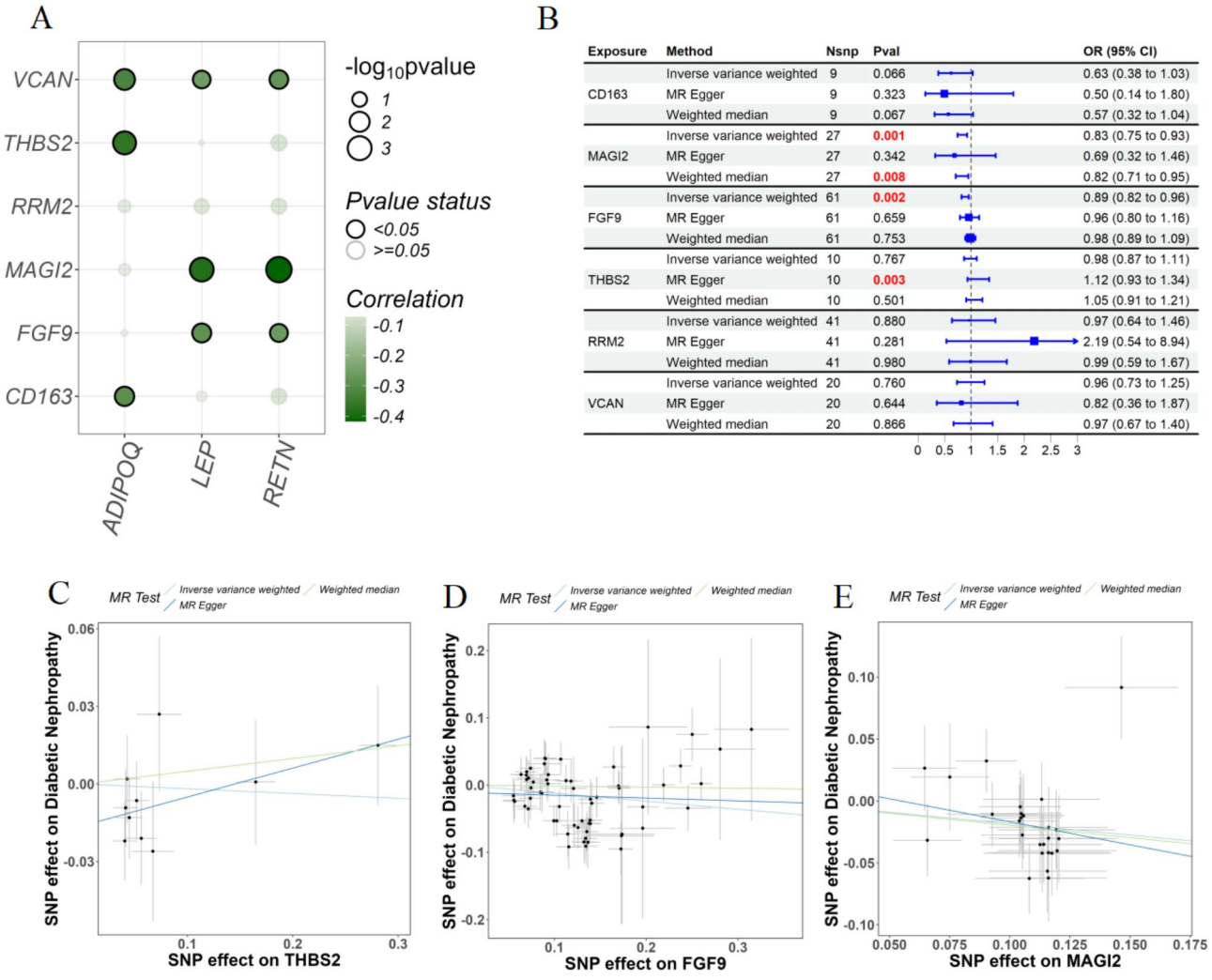

Fig. 3 MR analysis was performed on adipokines-related DEGs and their association with DN
(A) Association of adipokines and adipokines-related DEGs. **(B)** MR risk forest of adipokines-related DEGs and DN. **C-E.** MR SNP effect plots for adipokines-related DEGs and DN

been identified as a hub gene in T2D and is associated with lipid metabolism [37]. Our analysis also found a significant negative correlation between these six genes and adipokines, suggesting that as adipokine levels increase, the expression of these genes may decrease. Further MR analysis showed that *FGF9* and *MAGI2* are negatively correlated with DN risk, while *THBS2* is positively correlated. It has been reported that *FGF9* expression is significantly downregulated in high glucose-induced podocytes [38]. Currently, there is limited research on its specific role in DN. However, studies have shown that *FGF9* suppresses the expression of genes involved in adipogenesis and increases the expression of genes involved in fatty acid oxidation [32]. We hypothesize that the downregulation of *FGF9* may promote DN progression by facilitating lipid accumulation. Wang et al. confirmed the significant downregulation of *MAGI2* in DN, although the specific mechanism remains to be studied [39]. Qiu et al. pointed out that in breast cancer, *CLDN6* interacts with *MAGI2* to prevent *KLF5* from entering the nucleus, thereby inhibiting *SREBF1* transcription and ultimately suppressing palmitic acid-induced RAS palmitoylation [33]. Our results suggest that *MAGI2* may influence lipid metabolism regulation in DN through interactions with adipokines. In contrast, *THBS2* is upregulated in DN and positively correlated with DN risk. Previous studies have shown a significant increase in *THBS2* in T2D patients with nephropathy [40]. Mo et al. found that *THBS2* knockdown inhibited apoptosis in high glucose-induced human renal proximal tubular cells [41]. Our findings provide potential mechanisms for the roles of these genes in DN, where the downregulation of *MAGI2* and *FGF9*, as well as the upregulation of *THBS2*, may promote DN progression by influencing lipid metabolism.

In this study, we further investigated the role of celastrol in adipokine-mediated gene regulation. Using

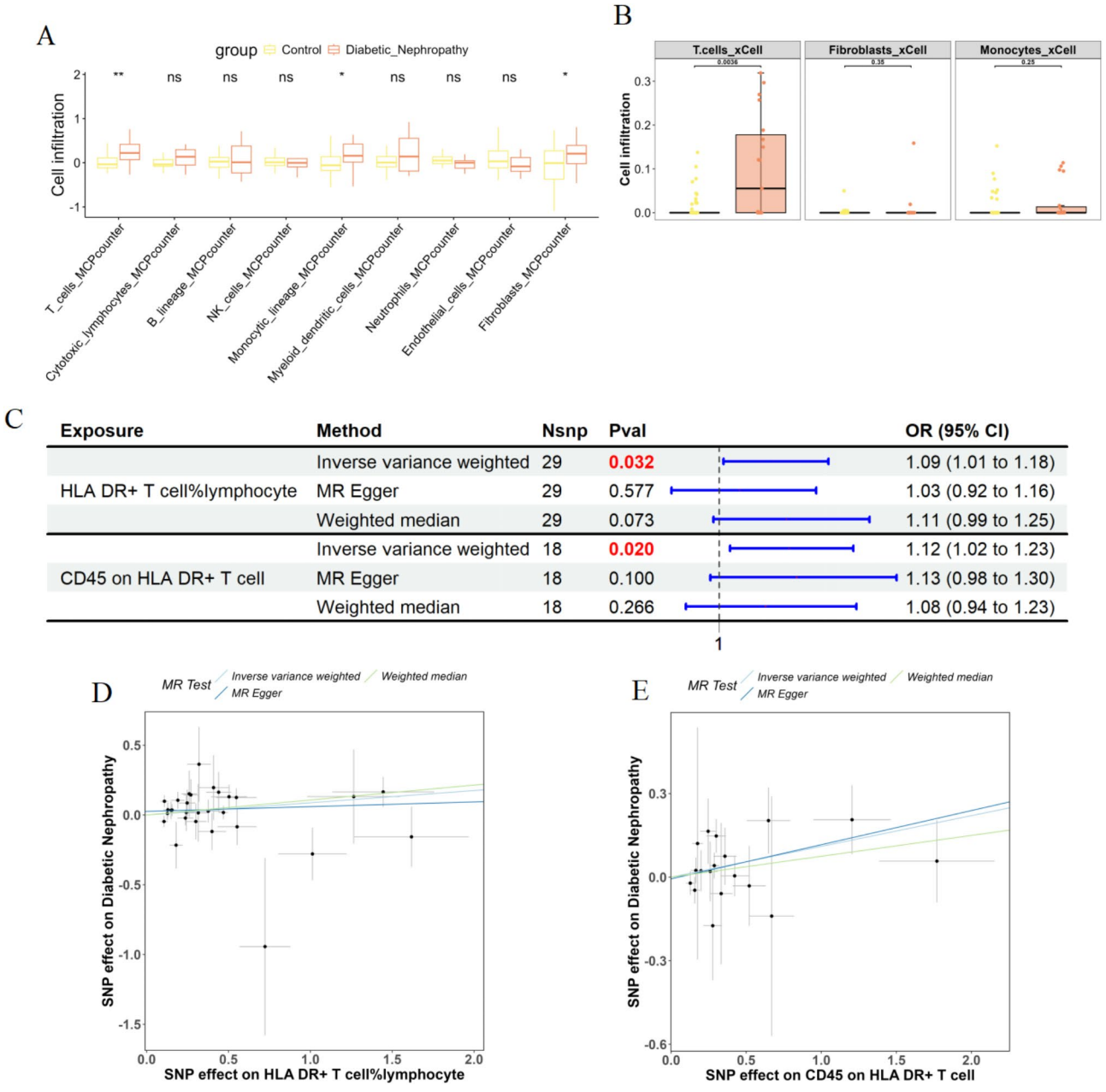

Fig. 4 MR analysis of T cells and DN
A-B. Immune infiltration analysis of mcpcounter and xcell. C. MR risk forest of T cell and DN. **D-E.** MR SNP effect plots for T cell and DN

predictions from the SEA database, *MAGI2*, *FGF9*, and *THBS2* were identified as potential target genes of celastrol. Our previous research demonstrated that celastrol significantly modulates adipokine levels, including adiponectin, leptin, and resistin, and influences key lipid metabolism pathways through the regulation of these adipokines [16]. These findings are consistent with the results of the present study. Based on the above results, we hypothesize that celastrol may regulate lipid accumulation and immune responses through its target genes, *FGF9*, and *THBS2*, promoting interactions between adipokines and their associated genes to play a critical role in the progression of DN.

In DN, dyslipidemia leads to glomerular injury and fibrosis, often accompanied by an inflammatory response [42]. Therefore, we conducted an immune infiltration analysis. Compared with normal controls, levels of T cells, monocyte lineage cells, and fibroblasts were higher in DN samples. Interestingly, GWAS data and MR analysis suggest a particular association between T cells and DN risk. T cell-mediated immunity promotes renal inflammation, fibrosis, and dysfunction, leading to the

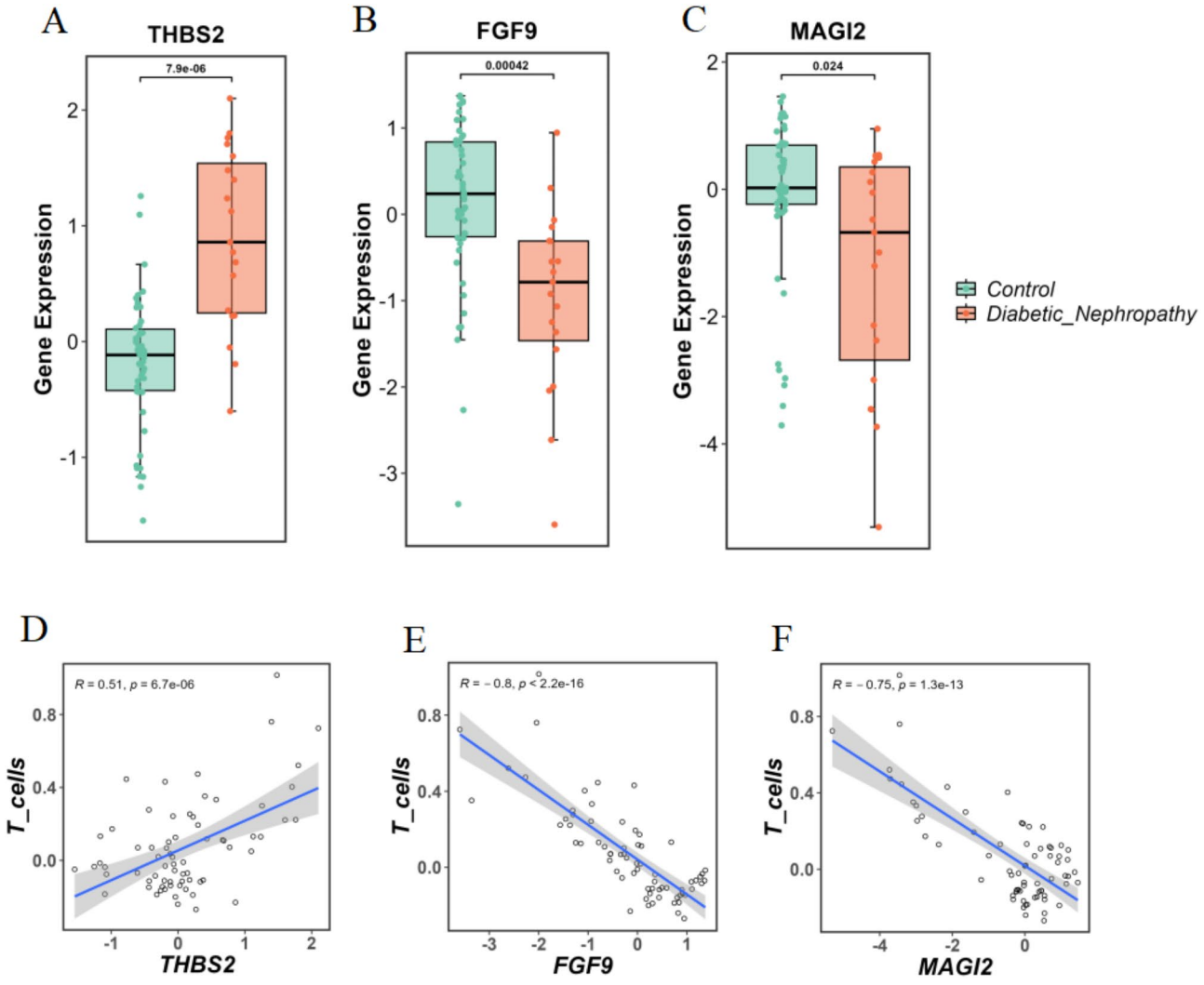

Fig. 5 Relationship of T cells and adipokines-related DEGs
A-C. Expression of FGF9, MAGI2, and THBS2 in GSE30122. **D-F.** Correlation of FGF9, MAGI2, and THBS2 with T cells

progression of chronic kidney disease [43]. Chen et al. indicated that dysregulation of immune checkpoint molecules on T cells disrupts renal homeostasis, triggering pathological inflammation and promoting DN progression [44]. Our findings did not show significant heterogeneity or multiplicity, strengthening the causal relationship between T cell infiltration and DN risk. Additionally, our data indicate a positive correlation between THBS2 expression and T cells, while *FGF9* and *MAGI2* exhibit a negative correlation. This is consistent with the above findings. Although there is currently rare research exploring the specific associations between these genes and T cells in DN, However, *THBS2* may influence the expression of PI3K by upregulating the TGF-β signaling pathway [45]. Additionally, the TGF-β signaling pathway is closely related to vascular inflammation in diabetic nephropathy [46]. We speculate that increased expression of *THBS2* in DN may promote T cell infiltration, thereby amplifying the immune response in DN. *FGF9* can induce the phosphorylation of ERK and AKT, as well as the activation of *CREB* and *Nrf2*, thereby exerting antioxidant functions [38]. Wang et al. found that *MAGI2* is negatively correlated with Tregs in DN [39]. Dysfunction of Tregs promotes autoimmunity and inflammation, and the imbalance between Th17 and Tregs contributes to the development of DN [47]. Decreased levels of *FGF9* and *MAGI2* may impair anti-inflammatory responses, exacerbating DN. The consistent trends observed in gene expression data and MR analysis support these explanations, suggesting that these genes may regulate T cell activity in DN.

However, there are a few limitations in this study that need to be addressed in future research. Firstly, the sample size of the dataset used in this study is relatively small, which may affect the reliability and generalizability of the results. Increasing the sample size in future studies could

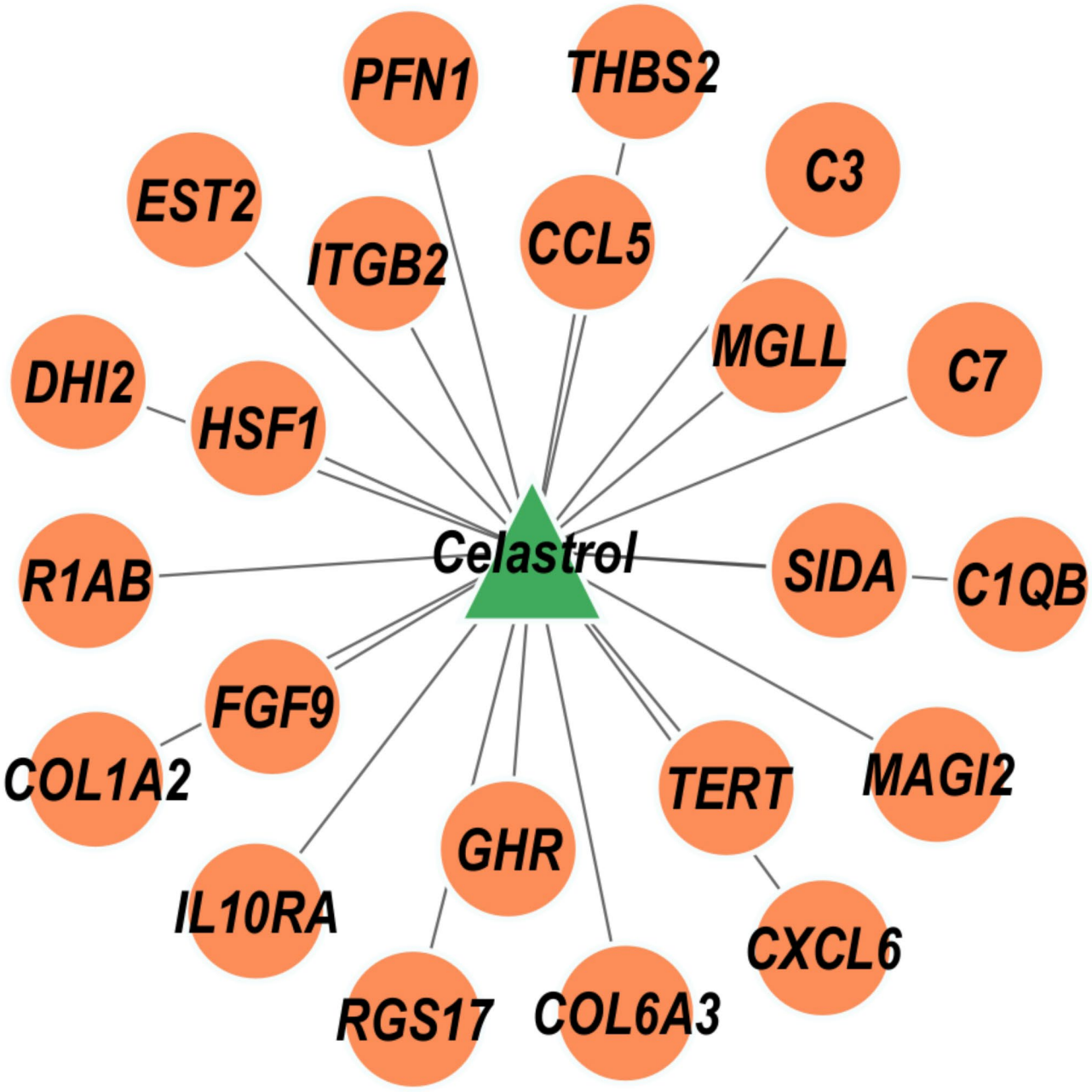

Fig. 6 Target genes network of *celastrol*
A. Relationship network between celastrol and target genes(the green triangle is celastrol, and the orange circle is the target gene)

help strengthen the robustness of our findings. Secondly, this study is based on publicly available databases, which lack comprehensive patient clinical characteristics and blood sample data, including routine blood tests and adipokine levels. This limitation restricts our ability to validate the direct associations between adipokine-mediated pathways and DN progression in a clinical setting. Future studies incorporating patient-level clinical data and blood biomarkers would provide a more comprehensive understanding of these interactions. Thirdly, although our bioinformatics analyses provide valuable insights, experimental validation is necessary to confirm the accuracy and applicability of these findings in DN pathophysiology and potential therapeutic strategies.

Conclusion

In conclusion, this study provides evidence for the involvement of adipokine-related genes in DN and identifies their association with T cells. Our findings indicate that adipokine dysregulation may influence lipid

metabolism pathways and lead to DN progression by promoting inflammation. Additionally, the celastrol's target genes including *MAGI2*, *FGF9*, and *THBS2* demonstrated significant correlations with T cells infiltrations. The relationship between adipokine-related genes, lipid metabolism, and T cells highlights their potential as therapeutic targets for DN. Importantly, the current study revealed the potential of celastrol as a novel therapeutic agent for DN, targeting adipokine-driven immune and metabolic dysregulation. Further research is imperatively needed to validate the therapeutic potential of targeting adipokine pathways and immune cells to mitigate DN progression.

Abbreviations

DN	Diabetic nephropathy
T2D	Type 2 diabetes
MR	Mendelian randomization
DEGs	Differentially expressed genes
GSVA	Gene set variation analysis

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-025-01665-0.

Supplementary Material 1

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Not applicable.

Author contributions
Xiaojuan Wang: Writing - original draft, Methodology, Investigation, Formal analysis and Data curation. Mohamad Hafizi Abu Bakar: Supervision, Conceptualization, Methodology, Writing - review & editing, Validation and Funding acquisition. Mohd Asyraf Kassim: Conceptualization, Resources, Writing - review & editing. Khairul Anuar Shariff: Conceptualization, Formal analysis, Resources, Writing - review & editing.JingWang and Manli Xu were responsible for the section of the paper related to the organization, analysis, and statistics of the data. All authors reviewed the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The data for this study were sourced from the public GEO database, and these datasets have obtained ethical approval from GEO and are de-identified. Therefore, ethical approval is not required for this study.

Consent for publication
All authors agreed to submit the manuscript.

Competing interests
The authors declare no competing interests.

Consent to participate
Not applicable.

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Publisher's note

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