BMC Medical Genomics

SYSTEMATIC REVIEW

Open Access

Discovering diabetes complications-related microRNAs: meta-analyses and pathway modeling approach

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Abstract

Purpose MicroRNAs(miRNA) play an important role in the pathogenesis of diabetic complications by regulating gene expression. The objective of this paper is to investigate micoRNA expression in diabetic nephropathy (DN), diabetic retinopathy (DR), diabetic neuropathy (DNP), and diabetic cardiopathy (DC). Methods: We conducted this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement and retrieved eligible microRNA-related studies of diabetic complications from PubMed, Embase, and Web of science databases. We enriched pathways corresponding to differentially expressed miRNAs using the miRPath tool on the DIANA website, and predicted their target genes with DIANA microT-CDS and TargetScan. Results: Although many of the selected studies were of high scientific quality, the results were heterogeneous. Among the 71 selected articles, 79 miRNAs were differentially expressed in various complications of diabetes, of which miRNA126, miRNA192 and 17 others were reported in at least two or more studies. A total of 156 target genes were predicted and 103 pathways were obtained by KEGG enrichment analysis. Conclusion: This comprehensive systematic evaluation provides experimental evidence statistics for miRNAs as circulating biomarkers and highlights promising biomarkers. These results provide preliminary data to further investigate the role of miRNAs in the diagnosis and therapeutic targets of human diabetic complications and support future broader longitudinal studies to better substantiate the role of dysregulated miRNAs as potential biomarkers and therapeutic targets of diabetic complications.

Keywords MicroRNA, Diabetes complications, Meta-analyses, Pathway modelling

Background

Diabetes is a metabolic disease characterized by chronic hyperglycemia and progressive microvascular and macrovascular complications, including nephropathy, cardiomyopathy, neuropathy, and retinopathy [1]. Diabetes is one of the fastest growing diseases worldwide and is expected to affect 783 million adults by 2045 [2]. Devastating macrovascular complications (diabetic cardiopathy(DC)) and microvascular complications (such as diabetic nephropathy(DN), diabetic retinopathy(DR), and diabetic neuropathy(DPN)) lead to increased mortality, blindness, renal failure, and decreased quality of life in individuals with diabetes [3]. The International

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diabetes Federation (IDF) predicts that by 2045, the burden of diabetes among people aged 20–79 years in the world will reach 12.2% (783.2 million), and the health expenditure related to diabetes is estimated to reach to 1054 billion US dollars [4]. The silent nature of diabetes and its vascular complications, the difficulty of detecting in the early clinical stage, and the limitations of current detection methods require safe and effective novel biomarkers to identify high-risk individuals for early and personalized intervention [5].

MicroRNAs (miRNAs) are small non-coding RNAs of 19–24 nucleotides that post-transcriptionally regulate gene expression through complementary base pairing with target mRNAs. Their regulatory functions can be synergistically integrated with transcription factors via shared signaling pathways [6]. MiRNAs function by partially binding to sequences in the 3′-untranslated region (3′-UTR) of their targets, interfering with translation but not damaging mRNA. According to research data on miRNA over the past 20 years, more than 60% of genes encoding human proteins are regulated by miRNA [7]. Studies have shown that miRNAs are associated with a variety of metabolic processes including glucose homeostasis, regulation of lipid metabolism, gluconeogenesis, adipogenesis, glucose transporter protein type 4 expression, insulin sensitivity and signaling [8]. Furthermore, the incidence of complications is correlated with suboptimal long - term glycemic control. The phenomenon in which the effects of hyperglycemia endure for an extended period even after blood glucose levels have returned to normal is known as metabolic memory [9, 10]. MicroRNAs (miRNAs) are capable of detecting fluctuations in blood glucose levels. They mediate the processes of gene expression associated with these changes, subsequently exerting an impact on cellular - level physiological processes, including the expression of genes related to inflammatory responses and oxidative stress. In this way, miRNAs mediate metabolic memory and thus influence the onset and progression of complications [5].

A growing number of miRNA signatures and interaction networks have now been identified for diabetes and its associated cardiorenal complications using established analytical techniques and platforms, and these short single-stranded molecules are emerging as potential diagnostic and predictive tools in human studies and may function as disease biomarkers and therapeutic targets [11]. Here, we provide a systematic overview to collect and summarize the current trials of blood miRNAs as promising diagnostic biomarkers for diabetic complications with a view to enriching the diagnostic indicators of diabetic complications.

Search strategy and eligibility criteria

We conducted this systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We have searched PubMed, ScienceDirect, and Web of Science for studies on miRNA expression profiles in diabetic complications published between 2002 and 2024 for the terms (miRNA in title/abstract, DN/DR/DPN/DC and expression) or (miRNA in title/abstract, DN/ DR/DPN/DC and profil*) or (miRNA, DN/DR/DPN/DC and expression in the title/abstract) or (miRNA, DN/DR/DPN/DC and profil* in the title/abstract). Articles meeting the following inclusion criteria were considered: (1) sample size of 10 or more patients; (2) blood specimens; (3) reports of miRNA expression levels; (4) reports of the diagnostic performance of the proposed biomarkers; (5) English-language literature; (6) randomized controlled or cohort studies; and (7) accepted or published papers. Manuscripts from case reports, conferences, editorial abstracts, and those without controls were excluded. In addition, relevant references were manually searched through the reference list of included studies to ensure literature coverage. All duplicates were removed using ENDNOTE's built-in "Find Duplicates" function. Two authors independently screened the title, abstract and full text and identified the full text that met the study eligibility criteria. The specific screening and extraction process is shown in Fig. 1.

Data extraction and quality assessment

Three investigators summarized the data that met the inclusion criteria into a customized Excel spreadsheet. The fourth author checked the extracted data for completeness and accuracy. Data extraction from the selected publications was done independently by the three authors using a standardized form. For each study, the following data were extracted: year of publication, first author in the article, number of people in the diabetic complication group and control group, specimen type, assay used, miRNA profile differentially expressed in patients versus controls, maximum adjusted effect size or p-value, and any of the following items (if available): sensitivity, specificity, Receiver Operating Characteristic(ROC), and Area Under the Curve(AUC), etc. Eligible articles were evaluated using MIAME guidelines 2.0 and MIQE guidelines for six items, including raw data on hybridization. The quality of each article was evaluated. All disagreements regarding the collected data were fully discussed by the investigators and a consensus was finally reached.

MicroRNA target gene prediction

DIANA-microT-CDS and Target Scan were used for target gene prediction of differentially expressed miRNAs. The target genes of motor up-regulated miRNAs and the target genes of motor down-regulated miRNAs were

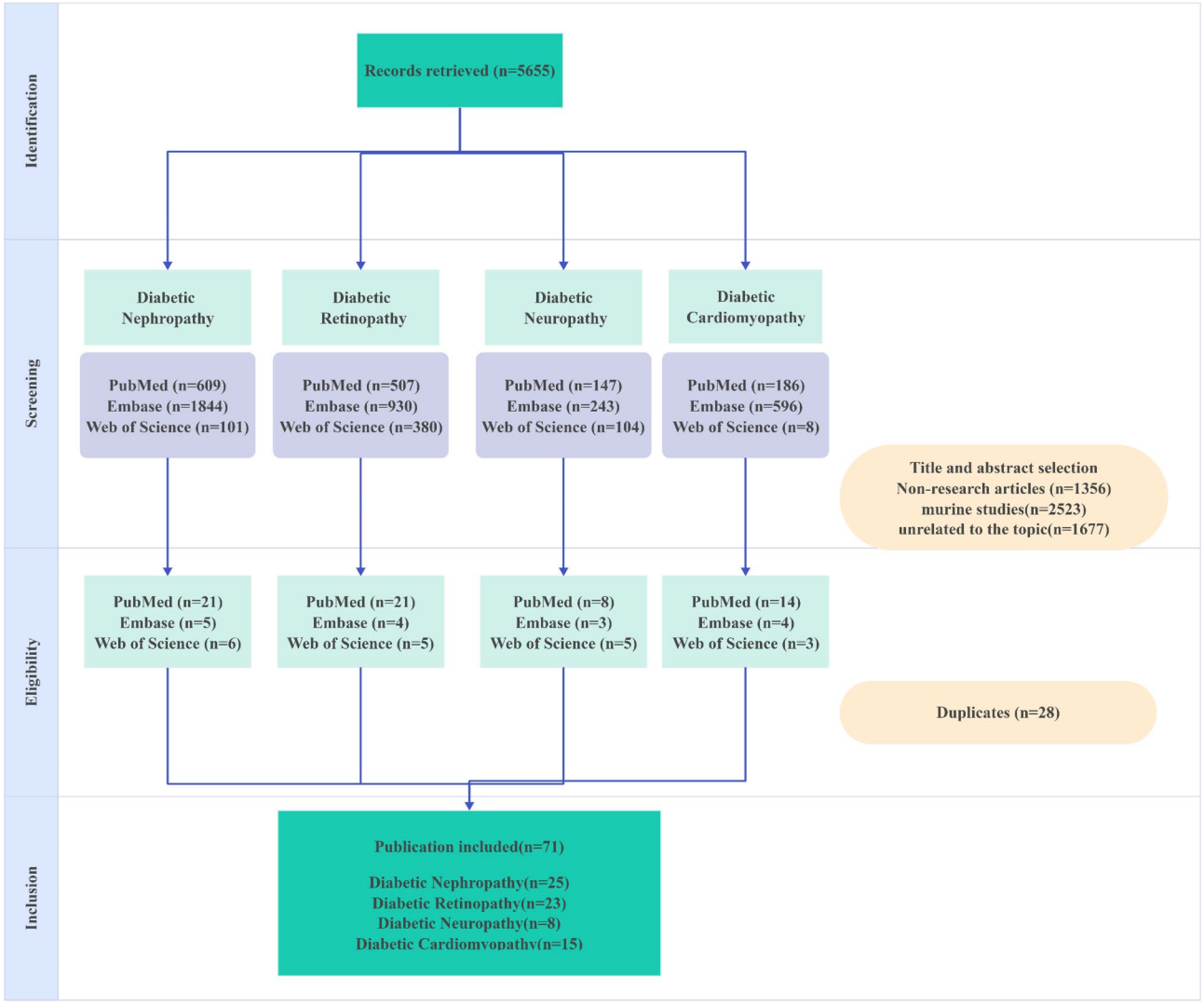

Fig. 1 Flow chart of literature screening

predicted, respectively. Due to the algorithmic differences between different prediction tools, genes predicted by both tools were selected as target genes for differentially expressed miRNAs to improve prediction accuracy. The results of specific target genes are shown in Table 1.

MicroRNA pathway analysis

DIANA is a miRNA target gene prediction platform developed by KiriakidouM based on experimental and computational biology methods, which records more comprehensive information related to miRNAs, genes and pathways. The DIANA-mirPath v.3 analysis tool is used to perform pathway analysis on differentially expressed miRNAs and predict the signaling pathways that miRNAs can affect. The analysis tool integrates the mainstream miRNA target gene database, and by inputting the differentially expressed miRNAs, the signaling pathways of the target genes can be calculated, so as to know which target genes' signaling pathways the miRNAs may act on to affect the differentially expressed miRNAs in diabetes complications. The results of diabetic retinopathy are shown in Fig. 2, the results of diabetic nephropathy are shown in Fig. 3, the results of diabetic neuropathy are shown in Fig. 4, the results of diabetic cardiopathy are shown in Fig. 5. The flow of the entire article is shown in Fig. 6.

Results

Selection of eligible studies

The Duplicates of the literature search and the detailed selection process of articles are given in Fig. 1. A total of 5655 eligible articles were retrieved from three databases, Pubmed, Embase, and Web of science, and a total of 1356 non-research articles, 2523 mouse model studies, and 1677 articles not related to the topic were excluded at the stage of screening abstracts and titles. Duplicates

Table 1 Target gene plots

miRNA ID	Number	target gene
DC		
hsa-miR-126-3p	22	PTPN9、PLXNB2、ITGA6
hsa-miR-130-3p	954	SLAIN1、MIER1、SKIDA1
hsa-miR-133a-3p	1148	SGMS2、KIAA0430、MAML1
hsa-miR-1-3p	1121	FNDC3A、HELZ2、SLC44A1
hsa-miR-204-3p	1577	TGFBR1、DLG5、FRMD5
hsa-miR-210-3p	16	IGF2、E2F3、B4GALT5
hsa-miR-21-3p	607	KIF26B、TMEM170B、NEK7
hsa-miR-223-3p	724	FBXW7、ACVR2A、FBXO8
hsa-miR-342-3p	988	KDM6B、PDGFRA、RFX3
hsa-miR-370-3p	702	TM9SF4、ERVV-2、SPDYE1
hsa-miR-450a-2-3p	462	NCR3LG1、ZNF207、CLIP3
hsa-miR-92-3p	355	LMLN、ATN1、WDR3
hsa-miR-9-3p	1372	FIGN、ONECUT2、ZNF664
hsa-miR-4505	1385	SYNGAP1、SEMA4F、POU2F1
hsa-miR-4743-3p	651	METTL15、GOLGB1、PDE8A
hsa-miR-4750-3p	377	SLC7A7、SLC25A41、MTF1
hsa-miR-199a-3p	672	DIO2、ADAMTSL3、ZHX1
DR		
hsa-miR-15a-3p	585	RNF13、ZNF654、NFRKB
hsa-miR-320a	1155	C12orf36、BPY2B、POU2F1
hsa-miR-495-3p	4153	ZFHX4、DDX3X、DGKH
hsa-miR-1281	118	LDB2、NYX、PPIF
hsa-miR-3197	108	ISOC1、NUTM2E、AC010536.1
hsa-miR-2116-3p	708	PABPN1、AL359091.2、MTCH2
hsa-miR-29a-3p	23	SIX3、BCL9、HEBP2
hsa-miR-200a-3p	1509	KLF12、ABL2、ZEB1
hsa-miR-152-3p	958	OSBPL11、C20orf112、MEOX2
hsa-miR-20-3p	4390	HMGN2、GABRG1、APOL2
hsa-miR-17-3p	1076	NFIB、FAM168B、TSHZ3
hsa-miR-126-3p	22	PTPN9、PLXNB2、ITGA6
hsa-miR-374a-3p	697	NOVA1、ZMAT3、VBP1
hsa-miR-221-3p	514	CLVS2、DGKH、SUGT1
hsa-miR-21-3p	607	KIF26B、TMEM170B、NEK7
hsa-miR-93-3p	1017	MED15、DST、PAXIP1
hsa-miR-210-3p	16	E2F3、B4GALT5、IGF2
hsa-miR-27-3p	2240	FBXW7、PLK2、SEMA7A
hsa-miR-200a-3p	1509	KLF12、ABL2、ZEB1
hsa-miR-10a-3p	1153	KIAA 1033、ATAD 2B、PSTN
hsa-miR-15a-3p	585	TP53TG3D、RHOBTB1、TP53TG3
hsa-miR-3976	557	PRR14、BTG 1、MTMR4
DN		
hsa-miR-31-3p	252	KRT36、VAT1L、UBE2H
hsa-miR-377-3p	1101	CFTR、STK35、RNF38
hsa-miR-192-3p	588	TMEM260、AKAP6、KPNB1
hsa-miR-126-3p	22	PTPN9、PLXNB2、ITGA6
hsa-miR-152-3p	958	OSBPL11、C20orf112、MEOX2
hsa-miR-451a	42	ATF2、OSR1、TBX1
hsa-miR-9-3p	1372	FIGN、ONECUT2、ZNF664
hsa-miR-130-3p	954	SLAIN1、MIER1、SKIDA1
hsa-miR-25-3p	873	CD69、FNIP1、HIPK3
hsa-miR-27a-3p	2240	FBXW7、PLK2、SEMA7A
hsa-miR-132-3p	1185	EP300、NACC2、MYCBP2

Table 1 (continued)

miRNA ID	Number	target gene
hsa-miR-320a	1155	C12orf36、BPY2B、POU2F1
hsa-miR-326	923	HNRNPA2B1、PPP1R3F、SRPR
hsa-miR-340-3p	223	ZNF850、TAPBP、TULP4
hsa-miR-660-3p	942	CTBP1、GOLGA6L2
hsa-miR-574-3p	39	TP53TG3、TP53TG3C、TP53TG3D
hsa-miR-223-3p	724	FBXW7、ACVR2A、FBXO8
hsa-miR-21-3p	607	KIF26B、TMEM170B、NEK7
hsa-miR-378a-3p	525	FOXG1、FAM179B、DSCAM
hsa-miR-16-1-3p	649	ZNF138、ZNF107、ZNF117
hsa-miR-29c-3p	23	SIX3、BCL9、HEBP2
hsa-miR-15a-3p	585	RNF13、ZNF654、NFRKB
hsa-miR-214-3p	1893	QKI、POU2F1、NAA15
hsa-miR-200a-3p	1509	KLF12、ABL2、ZEB1
hsa-miR-132-3p	1185	EP300、NACC2、MYCBP2
hsa-miR-223-3p	724	FBXW7、AC004076.7、ZNF773
hsa-miR-21-3p	607	KIF26B、TMEM170B、NEK7
DPN		
hsa-miR-155-3p	316	ZNF629、ZNF140、IGF1
hsa-miR-499a-3p	1080	TCF7L2、FOXN3、DOCK3
hsa-miR-199a-3p	672	DIO2、ADAMTSL3、ZHX1
hsa-miR-216a-3p	914	TMEM161B、CUX2、DKFZP779J2370
hsa-miR-377-3p	1101	CFTR、STK35、RNF38
hsa-miR-30d-3p	489	PITX2、ROCK2、PCLO
hsa-miR-128a-3p	1864	SZRD1、UBR1、VEGFC
hsa-miR-155-3p	316	CCDC65、ZNF629、ZNF140
hsa-miR-146a-3p	1227	RIOK3、FOXP2、NFAT5

Note: This table lists the differentially expressed micrornas found in diabetes complications, and gives the predicted number of target genes

were removed after combining the four complications obtained from the screening, and a total of 71studies were retained, of which the largest number of studies were on DR with 23 articles, 25 studies on DN, and 15 and 8 articles on DC and DPN, respectively. A total of 75 differentially expressed miRNAs were reported in the screened eligible literature.

Quality assessment results

The MIAME guidelines 2.0 and MIQE guidelines were used to assess the quality of the 71 eligible studies. The risk assessment analysis of the included articles is shown in Fig. 7, where we found that 39.4% of the literature was rated as high risk for not giving the raw data in the article. In terms of data processing analysis, only 11.3% of the articles had vague descriptions. 46.5% of the articles gave detailed annotations of the underlying sample (e.g. tissue, sex, and age) and experimental factors and their values (e.g., compounds and doses in dose-response studies), and 32.3% of the articles were rated as high risk.

MicroRNAs and diabetic nephropathy

A total of 27 differentially expressed miRNAs were described in the literature screened for DN, with miRNA126 and miRNA192 occurring three and four times, respectively, and Tayel SI et al. [9]assessed that the expression levels of these two miRNAs were significantly downregulated in DN patients. In the massive proteinuria group, miRNA126 expression was significantly and positively correlated with blood glucose levels, HbA1c levels, eGFR, TC levels, LDLc levels and miRNA192 expression. In contrast, in the massive proteinuria group, miRNA192 expression was positively correlated with PBG and negatively correlated with age and creatinine levels. This difference may explain the correlation of miRNA expression with early indicators of DN and the dyslipidemia observed in these patients. Ebadi Z et al. [12] also demonstrated through animal experiments that captopril and spironolactone target miRNA192 and alter its expression, playing an important role in the diagnosis and treatment of DN. Bijkerk R et al. [13] first conducted pre-screening of miRNA profiles in three healthy patients and eight DN patients, followed by a formal study with a larger number of participants, confirming that DN patients had lower circulating levels of 11 miRNAs (miR25, -27a, -126, -130b, -132, -152, -181a, -320, -326, -340, and −660) compared to healthy controls.

The study identified the most significantly enriched miRNAs and pathways in DN. The top three significantly enriched miRNAs were miR-27, miR-29, and miR-17.

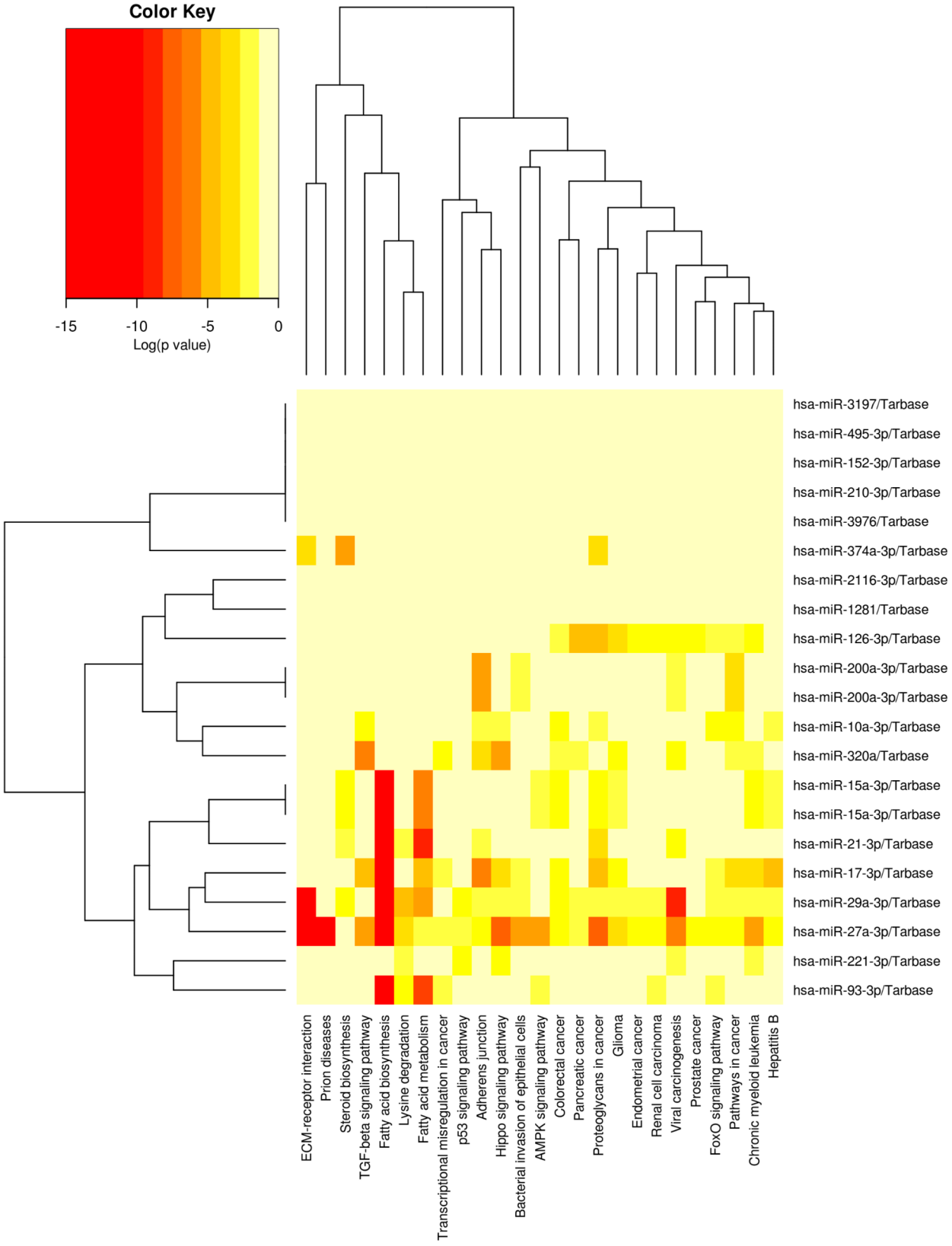

Fig. 2 Heatmap of microRNA pathway enrichment analysis in diabetic retinopathy. Note: This is a map of microRNA pathway enrichment in diabetic retinopathy. The abscissa represents the signaling pathways, while the ordinate lists differentially expressed microRNAs. The color gradient indicates statistical significance, with red showing a high significance level and yellow indicating no significance

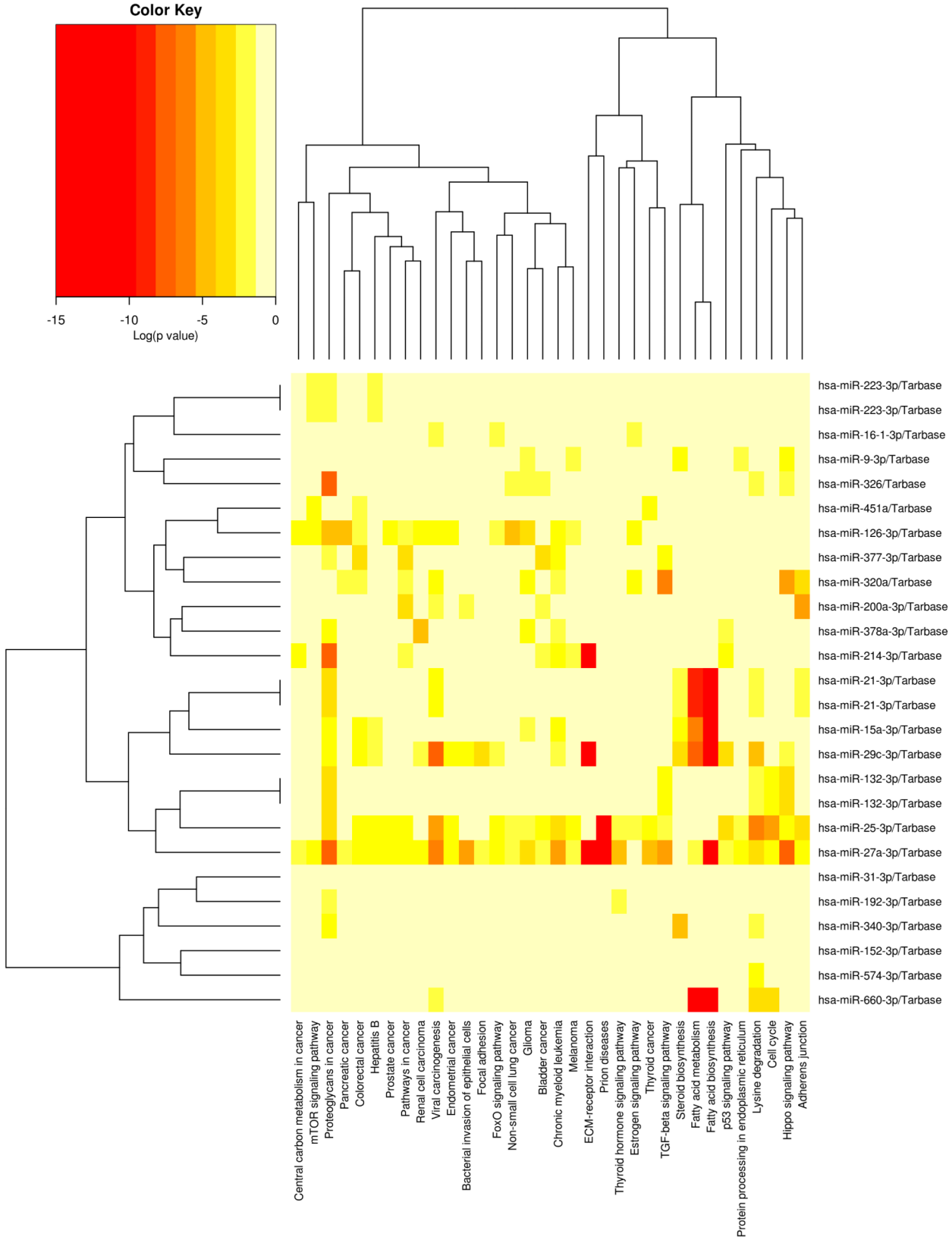

Fig. 3 Heatmap of microRNA pathway enrichment analysis in diabetic nephropathy. Note: This is a map of microRNA pathway enrichment in diabetic nephropathy. The abscissa represents the signaling pathways, while the ordinate lists differentially expressed microRNAs. The color gradient indicates statistical significance, with red showing a high significance level and yellow indicating no significance

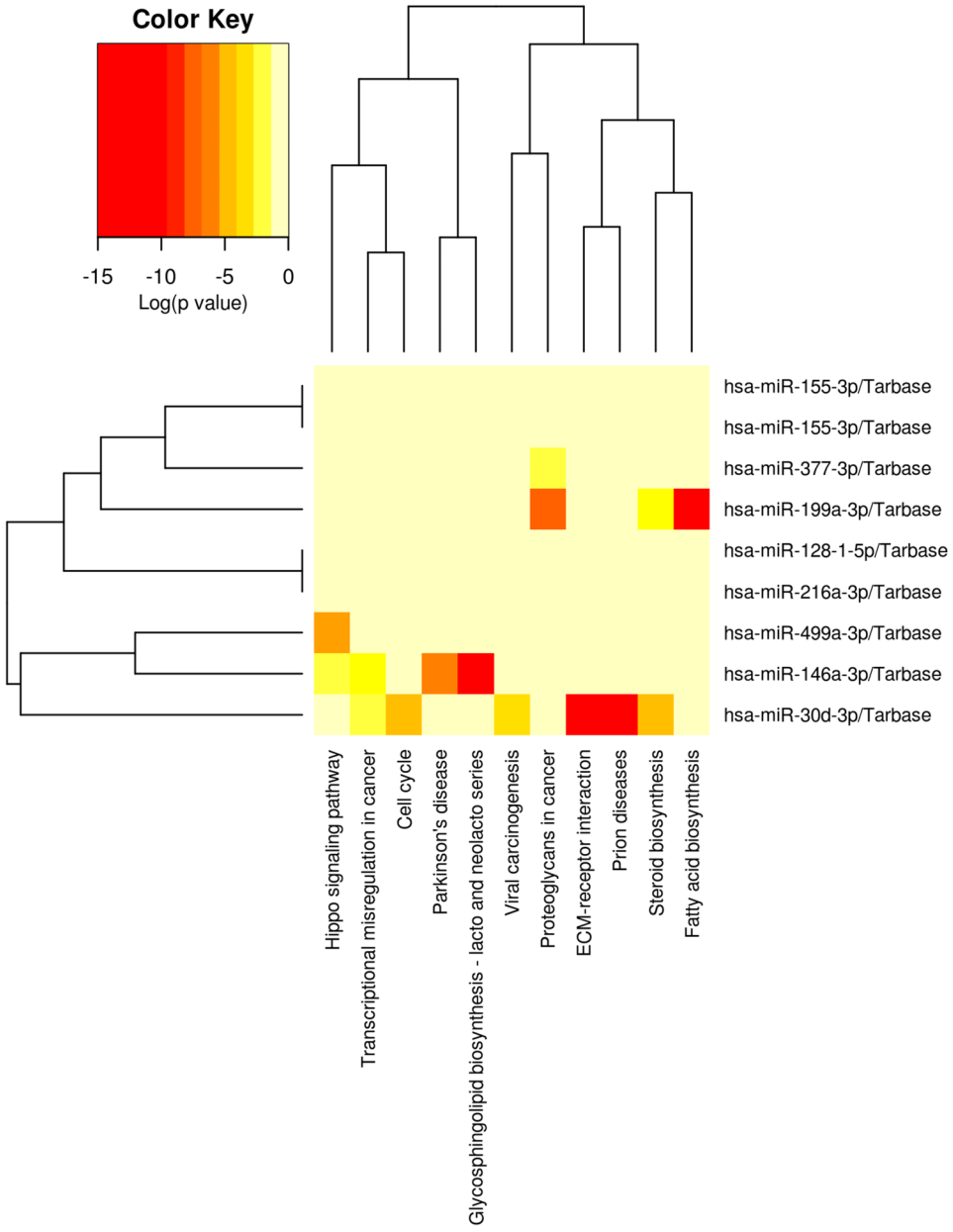

Fig. 4 Heatmap of microRNA pathway enrichment analysis in diabetic neuropathy. Note: This is a map of microRNA pathway enrichment in diabetic neuropathy. The abscissa represents the signaling pathways, while the ordinate lists differentially expressed microRNAs. The color gradient indicates statistical significance, with red showing a high significance level and yellow indicating no significance

The fatty acid synthesis pathway and fatty acid metabolism pathway exhibited the most prominent enrichment. Additionally, the viral carcinogenesis pathway and Hippo signaling pathway also demonstrated significant enrichment.

MicroRNAs and diabetic retinopathy

There are 23 publications on DR with 22 miRNAs detected, and Santovito D et al. [14] performed logistic regression analysis using circulating levels of miR-25-3p, miR-320 b, and miR-495-3p as a covariate model. The overall model yielded statistical significance (Cox and Snell R2 = 0.526, $p < 0.001$), the ROC curve demonstrated the accuracy of the model (AUC = 0.931,95% CI:0.853-1.000, sensitivity and specificity 85%, $p < 0.001$), and the coefficient associated with DR severity ($p = 0.79$, $p < 0.001$) greater than that of individual miRNAs. This reflects the performance of multiple miRNA detection models that better match clinical needs. Several studies have not only explored differentially expressed miRNAs but also explored the mechanisms through experiments. Ji H et al. [15] showed for the first time that NOTCH 2

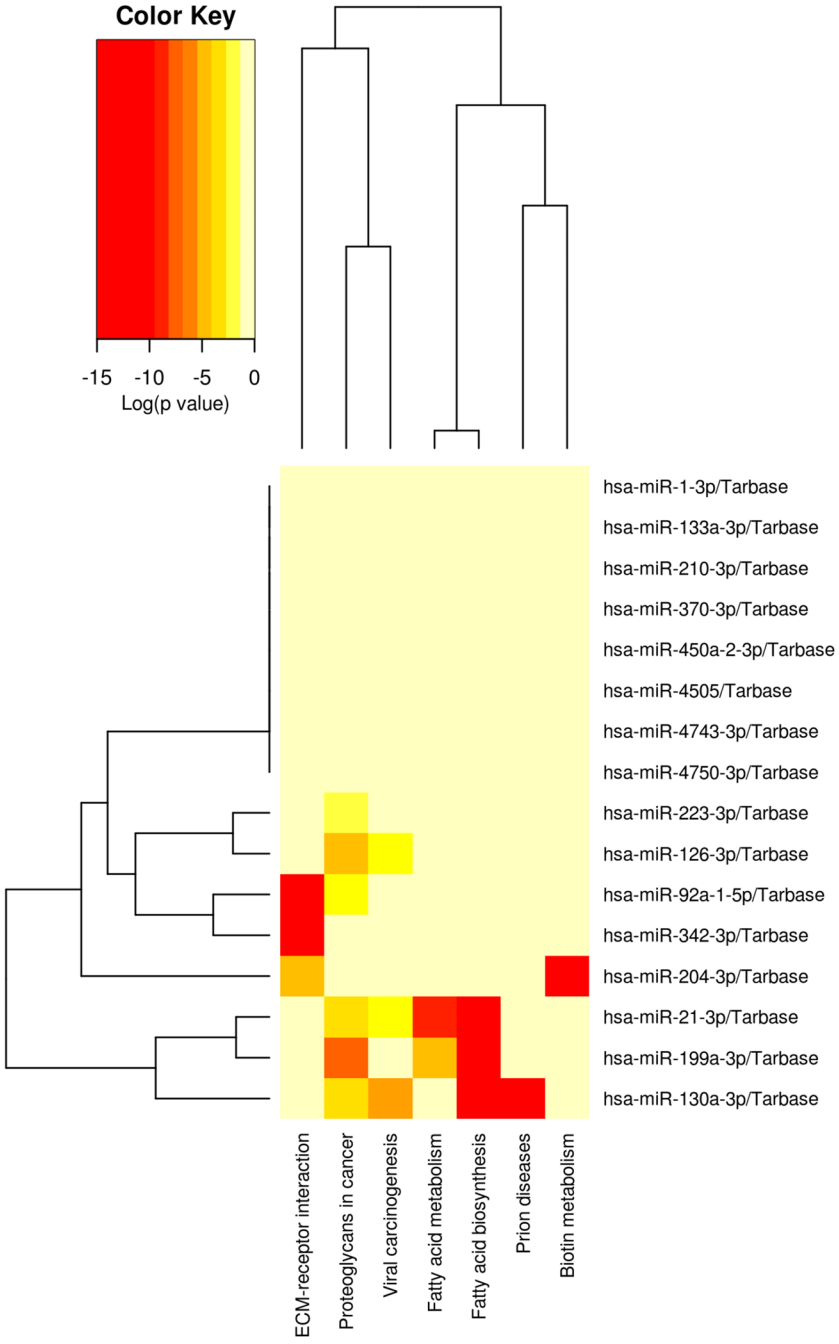

Fig. 5 Heatmap of microRNA pathway enrichment analysis in diabetic cardiopathy. Note: This is a map of microRNA pathway enrichment in diabetic cardiopathy. The abscissa represents the signaling pathways, while the ordinate lists differentially expressed microRNAs. The color gradient indicates statistical significance, with red showing a high significance level and yellow indicating no significance

is a target gene for the effective biomarker miR-2116-5p. It was hypothesized that circulating miR-2116-5p may promote neointima formation through VEGF-DLL-Notch signaling and Jagged signaling pathways. Zeng Y et al. [16] found that miR-29b3p inhibited SIRT 1 expression by binding to the 3-UTR of SIRT 1 using a dual luciferase reporter gene assay in HEK-293 T cells. miR-29b-3p was confirmed to promote HRMEC apoptosis by HG-$CoCl_2$-induced culture model of HRMEC apoptosis. Statistically and mechanistically, they demonstrated that miR-29b-3p may be an important regulator of vascular injury in DR progression.

The pathway analysis results demonstrated that miR-27 exhibited the most significant enrichment characteristics, suggesting its potential central regulatory role in DR. Notably, both the fatty acid synthesis pathway and fatty

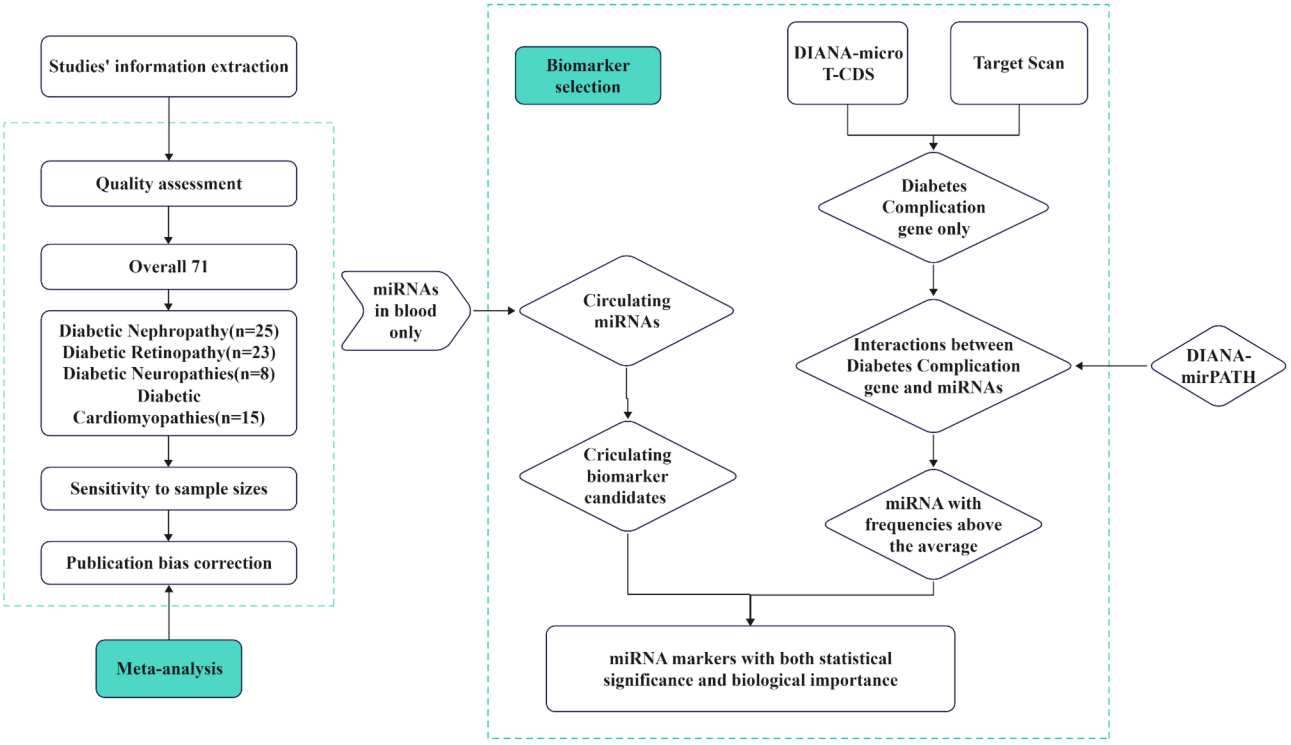

Fig. 6 Flow-process diagram. In the left box is the literature screening and meta-analysis process, screening out the differentially expressed microRNA in each complication, and on the right is the bioinformatics target gene prediction and pathway analysis of the selected microRNA

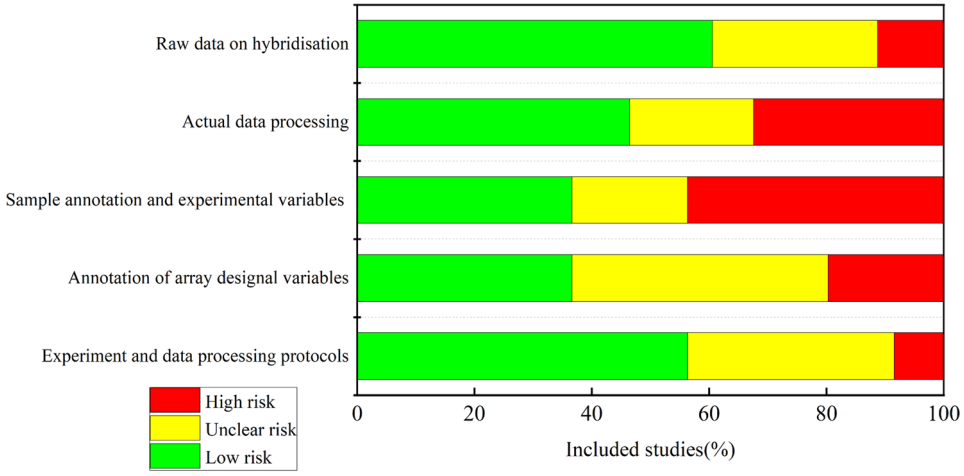

Fig. 7 Quality assessment according to the MIAME guideline

acid metabolic pathways were significantly enriched, and these biological processes were found to be closely associated with miR-93, miR-27, miR-29, miR-17, miR-21, and miR-15.

MicroRNAs and diabetic neuropathy

Expression of miRNA polymorphisms due to genetic variants affects the development of diabetic complications. Ciccacci C et al. [17] found that the variant allele of rs11888095 SNP in miRNA128 was significantly associated with higher risk of DPN (OR = 4.89, $P = 0.02$) and higher DPN severity ($P = 0.026$). The C allele of rs2910164 SNP in miRNA 146 A was associated with a lower risk of developing DPN (OR = 0.49, $P = 0.09$) and cardiovascular autonomic neuropathy(CAN) (OR = 0.32, $P = 0.052$). On the other hand, the variant allele of rs895819 SNP in miRNA 27 A was significantly associated with a high risk of early CAN (OR = 3.43 and $P = 0.023$).

Among the pathways enriched by DPN, ECM-receptor ineraction was the most significant, which was closely related to three mirnas. miR199 mediated Fatty acid biosynthesis was also significantly enriched.Furthermore, miR-30 was found to participate in multiple biological processes through its regulatory involvement in several significantly enriched pathways related to neuropathic pathogenesis.

MicroRNAs and diabetic cardiopathy

Bielska A et al. [18] conducted a miRNA expression profiling study and systematically summarized and validated the diagnostic significance of miR-615-3p, miR-3147, miR-1224- 5p, miR-5196- 3p, miR-6732- 3p and miR-548b-3p for DC, all tested miRNAs showed high diagnostic value (AUC = 0.779 ± 0.877) and more significantly they found that the miRNAs tested were more effective than the non-specific inflammatory parameters inflammatory mediators like chemokines CXCL12 and macrophage migration inhibitory factor (MIF).

Regarding the association of the four complications, among the types of miRNAs that were differentially expressed, we found that miRNA126 was frequently present. Mu YZ et al. [19] found that high sugar inhibited the proliferation of THP-1-derived macrophages and promoted intracellular miR-126 expression; miR-126 mediated the inhibitory effect of high sugar on the proliferation of THP-1-derived macrophages by upregulating the proliferation inhibitory factor BAX, caspase-3 expression and down-regulation of proliferation promoting factors PIK3R2 and Bcl-2. Tang ST et al. [20] also found that miR-126 may inhibit inflammation and ROS production in high glucose-treated endothelial cells by regulating HMGB1 expression. Pei CZ et al. [21] found that high levels of miR-126 promoted CXCR4 expression and LOC homing through ERK/VEGF and Akt/eNOS signaling pathways and prevented vascular injury by targeting KLF-8 to maintain stemness.

Seven signaling pathways were co-enriched in DC. Notably, the fatty acid synthesis and metabolism pathway was significantly enriched and demonstrated concordant enrichment in both DN and DR. Additionally, the ECM-receptor interaction pathway was significantly associated with three miRNAs. Furthermore, miR-130 exhibited marked correlations with multiple pathways, suggesting its potential role as a critical regulatory miRNA in the pathogenesis of DC.

KEGG pathway enrichment analysis

The miRNAs associated with four diabetic complications annotated through KEGG pathway enrichment analysis. Based on an in-depth analysis of these miRNAs, an enrichment summary of the pathways they are involved in was conducted. In the graphical representation of the results, the intensity of color indicates the strength of the correlation. Specifically, in DR, miRNAs 27, 29, and 17 are involved in a relatively large number of pathways; in DN, miRNAs 29, 25, and 27 participate in an even broader range of pathways; in DPN, miRNAs 30, 146, and 199 are involved in a greater number of pathways; while in DC, miRNAs 130, 21, and 199 are implicated in a considerable number of pathways. Following the enrichment analysis of the correlations between miRNAs and various pathways across the four complications, the following key representative pathways were identified: The fatty acid biosynthesis pathway is associated with seven miRNAs involved in the process of retinopathy, all showing strong correlations. Notably, this pathway is also strongly correlated with six miRNAs in DN and three miRNAs in DC. The fatty acid metabolism pathway ranks second in terms of enrichment in both DR and DN. This finding provides valuable insights into the connections between different diabetic complications, particularly the relationship between DN and DR. Due to the relatively poor blood supply in neural tissues, fewer miRNAs and pathways related to diabetic neuropathy have been identified in the literature. However, the ECM receptor interaction pathway shows a strong correlation with miRNA 30 in DPN, as well as with miRNAs 92, 342, and 204 in diabetic cardiopathy. These findings provide important leads for further research.

Discussion

Complications of the macrovascular system (DC) and microvascular complications system (DN, DR, and DPN) are a major cause of morbidity and mortality in patients with diabetes [22, 23] and carry a significant economic burden. Here, we describe the results of a systematic review of the contribution of miRNAs as biomarkers in the field of diabetic complications, and although the 71 relevant studies screened validated 75 miRNAs, only a very small number of miRNAs were co-validated or deeply developed to confirm their potential utility as biomarkers for diabetic complications.

MiRNAs provide a common link between the different complications of diabetes mellitus. Diabetes complicated by renal and cardiovascular disease has differentially expressed common miRNAs such as miR-29 and miR-126. Oxidative stress-induced glycated tissue damage and fibrosis are major drivers of vascular injury, and the potential mechanism by which miRNA29 plays an important role in the development of glomerular fibrosis may be related to TGF-β/SMAD 3 signaling pathway regulation or expression of peroxisome proliferator-activated receptor-γ (PPAR-γ) signaling [24]. MiR-126 promotes vascular endothelial growth factor (VEGF) signaling by inhibiting two negative regulators of the VEGF pathway, among others [25]. MiRNA-126 targets downstream

proteins such as EVH1 domain-containing protein 1 (Spred1), phosphoinositide-3-kinase regulatory subunit 2 (PIK3R2), which promote angiogenesis, reduces vascular inflammation, regulates autophagy and reduces endothelial cell apoptosis [26–28]. These studies reveal the feasibility of intervening by targeting the same mechanisms of miRNAs among diabetic complications and thus achieving prevention and delay of multiple complications.

Emerging evidence indicates that microRNA regulatory networks modulate key signaling pathways by influencing target gene expression, playing pivotal roles in the pathogenesis and progression of various diabetic complications. Cross-complication pathway enrichment analyses reveal significant enrichment of the fatty acid biosynthesis pathway in all subphenotypes. Notably, the fatty acid metabolism pathway is also markedly enriched in both DN and DR. These findings are strongly corroborated by target gene profiling, which identifies shared molecular targets such as NFIB—a transcription factor critical for adipocyte differentiation and epigenetic regulation—and FBXW7, an E3 ubiquitin ligase governing the degradation of lipid-synthesizing transcription factors. Functional validation comes from Yoshihik et al., whose metabolomic analyses demonstrated significantly elevated activity of the fatty acid biosynthesis pathway in the serum of patients with diabetic chronic complications ($P = 0.002$) [29]. Hyperglycemic environments upregulate the expression of key lipogenic enzymes, including acetyl-CoA carboxylase (ACC), fatty acid synthase (FASN), and stearoyl-CoA desaturase-1 (SCD1), in the liver and adipose tissue. This dysregulation results in excessive production of saturated fatty acids such as palmitate, driving CD36-mediated lipotoxic metabolite accumulation. Such lipotoxicity triggers metabolic dysfunction, endoplasmic reticulum stress, and systemic inflammation, culminating in multi-organ damage. Furthermore, these metabolites exacerbate insulin resistance, thereby disrupting glucose homeostasis [30]. In DR, lipotoxic compounds activate nuclear receptor NR4A1, enhancing downstream target gene GFAT2 expression and amplifying hexosamine biosynthetic pathway (HBP) activity. This leads to aberrant O-GlcNAcylation of retinal proteins [31]. Conversely, short-chain fatty acid synthesis attenuates oxidative stress and NF-κB signaling, partially mitigating diabetic nephropathy [32]. In the cardiovascular system, elevated fatty acid synthesis and metabolism impair cardiac β-adrenergic receptor resilience, accelerating myocardial dysfunction [33]. Additionally, activation of extracellular signal-regulated kinases 1/2 (ERK1/2) upregulates lipid metabolism genes—peroxisome proliferator-activated receptor alpha (PPARα), carnitine palmitoyltransferase 1 A (CPT1A), and fatty acid synthase (FASN)—contributing to myocardial remodeling in diabetic cardiomyopathy [34]. Collectively, these insights underscore the therapeutic potential of targeting fatty acid synthesis and metabolic pathways for protecting multiple organs in diabetes.

The expression level of miRNA is also related to the development stage of complications of diabetes. Qin LL et al. found that the risk of PDR increases when the content of miR-126 is below 5.02. When the content is higher than 8.43, it is more likely to be NPDR. When the content of miR-126 ranges from 5.02 to 8.43, it is a critical stage in the development of PDR. At this stage, endothelial cell damage is most severe, and NPDR rapidly develops into PDR [35]. The expression level of miRNA377 in diabetes nephropathy was progressively increased in the mi albuminuria group and the large albuminuria group ($P < 0.005$). The expression of miR-377 in the large amount of albuminuria group was 3.4 times higher than that in the normal control group [36]. Not only does miRNA play a significant role in early diagnosis of diseases, but the above studies also demonstrate the potential of miRNA as an indicator of disease progression, which can guide treatment and medication.

The articles we have selected have studied circulating miRNAs, and non-cellular miRNAs in blood are good diagnostic biomarker candidates for use in a variety of physiopathological conditions, including cancer, neurodegeneration, diabetes and other diseases [37]. Differences in miRNA detection exist between different types of extracellular biological fluids (e.g., serum, plasma, urine, and saliva) and between extracellular and cytosolic fluids (e.g., whole blood), and circulating miRNAs are considered the best source for research and clinical applications.A study by Mostafa Abdelsalam in patients with DN showed that the urinary miRNA-451 area under the curve was 0.427, while plasma miRNA-451 reached an area under the curve of 0.625 for a cut-off value of 19.5, plasma miRNA-451 had a sensitivity of 95.5% and specificity of 95.6% [38] demonstrating the validity of circulating miRNAs as biomarkers. In addition, miRNAs in blood are resistant to temperature fluctuations, pH changes, and repeated cycles of freezing and thawing [39]. Moreover, circulating miRNAs exhibit long half-lives, relatively consistent and sensitive changes in different pathophysiological processes, and high assay stability.

Regarding the type of blood samples, the results showed that 84.74% of the studies used plasma or serum as subjects, and only 13.5% of the studies used whole blood for the tests, and two studies analyzed miRNA levels in blood mononuclear cells, although blood is an easily accessible tissue, whole blood biomarkers are more likely to reflect blood characteristics rather than disease-induced phenomenon. In particular, cell-derived vesicles (called exosomes) release miRNA into the extracellular fluid, which may be associated with different pathological conditions. The level of cell-free miRNA in serum is considered to

be a reliable indicator of the progressive status of the disease. Serum miRNA has been reported to be stable for more than 10 days when stored at room temperature and for 10 years when stored at -20 ℃. Because the binding of miRNA to RNA-protein complexes containing arginine makes it rarely affected by RNase. A study on miRNA in cancer concluded that different blood sample types have advantages and disadvantages, suggesting that the use of different samples requires attention to their respective different collection and storage methods. When utilizing whole blood samples, it is advisable to employ PAXgene™ Blood RNA Tubes in strict accordance with the standardized protocols provided by the manufacturer (Qiagen), particularly regarding sample processing parameters critical for nucleic acid integrity.For plasma and serum collection, it is crucial to handle samples carefully, following strict guidelines for temperature, time and centrifugation. It is necessary to check and compensate for hemolysis in plasma and serum samples [40].

The results of the pathway analysis show that a single miRNA can regulate a wide range of different target genes. Specific miRNA therapeutic agents show potential as alternative treatment options with the possibility of halting or mitigating disease progression, but further research is needed to confirm their effectiveness. In the future, tissue/cell-specific miRNA regulators could be designed to target specific cells or organ systems involved in a disease state. For example, cell type-specific miRNA regulators could provide more targeted therapies in the area of diabetes-related diseases by coupling miRNA regulators with specific antibodies.

However, there are some limitations of our study: (1) Our results may be subject to publication bias due to the limited number of studies involved. (2) The search language was limited to English; therefore, there may be language bias. (3) Because of the small number of populations involved, there may be bias from the population. (4) Heterogeneity appears in most meta-analyses, including different reference controls, miRNA extraction, and cutoff values that may affect heterogeneity. (5) Due to the limited number of studies, all results are from studies using different blood components, which may yield different miRNA profiles.(6) Different miRNA detection technologies have different limitations, and the test standards are not uniform, which may affect the accurate determination of miRNA expression profiles.

Through our study, we identified the potential of miRNAs as mediators of intercellular communication in the diagnosis and therapeutic treatment of diabetic complications. MiRNAs reveal intrinsic connections between different complications and exhibit different expression levels at different stages of complication onset, which can guide the diagnosis and severity assessment of complications. These findings hold promise for guiding the diagnosis and severity assessment of complications, yet further validation in large - scale, diverse clinical settings is essential. In the selection of samples for testing, non-cellular miRNAs in blood, especially in plasma, are diagnostically effective. The rich results of pathway enrichment analysis on pathways and related target genes provide effective value for more accurate miRNA specific identification and target determination.

Conclusion

The potential utility of various miRNAs validated in the screening literature for diabetes complications lies in their involvement in processes such as oxidative stress and inflammation within procedures like glucose and lipid metabolism and insulin resistance via multiple pathways. They also participate in the maintenance of metabolic memory. In the future, the diagnosis and treatment of complications of diabetes based on circulating miRNA is very promising to improve the understanding of the complex mechanism of miRNA imbalance, and standardization research through prospective trials can transform current research into clinical application. At the same time, we found that modular biomarkers bound to multiple biomarkers converge on the same or related biological pathways, resulting in better sensitivity and specificity expression than a single miRNA, which has great potential in clinical transformation.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12920-025-02144-1.

Supplementary Material 1

Acknowledgements

Thank you to all the authors for their contributions and the support of the Chinese Academy of Traditional Chinese Medicine, Beijing University of Traditional Chinese Medicine, and Changchun University of Traditional Chinese Medicine for this article.

Author contributions

Yin Ruiyang wrote the main manuscript body, Zhang Yanjiao and Fang Xinyi prepared the drawings, Zhang Yuxin, Miao Runyu, Yao Yiqi and Guan Huifang assisted in literature screening and Tian Jiaxing provided guidance. All authors reviewed the manuscripts.

Funding

This work is supported by National Natural Science Foundation of China (82474323), CACM Realistic Project (2024-QNQS-12), High Level Chinese Medical Hospital Promotion Project (HLCMHPP20230CZ40907), CACMS Outstanding Young Scientific and Technological Talents Program (ZZ13-YQ-026), GAMIMD Special Fund (2022LYJSZX12), CACM-PDEC Dose-effect relationship research Project (202428-002).

Data availability

The data used to support the findings of this study are available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate
This paper does not involve clinical trials. So there are no clinical trial number, egistry, trial registration number, and data of registration.

Informed consent
N/A.

Consent for publication
All authors agree to the publication of this article.

Competing interests
The authors declare no competing interests.

Received: 13 March 2024 / Accepted: 11 April 2025
Published online: 15 May 2025

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