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MicroRNAs Associated with Disease-Stage Progression in Diabetic Retinopathy and Macular Edema: A Bioinformatic Reanalysis of Public Transcriptomic Data

Luis Jesuino de Oliveira Andrade

luis_jesuino@yahoo.com.br

Departamento de Saúde, Universidade Estadual de Santa Cruz, Ilhéus, Bahia, Brasil.
https://orcid.org/0000-0002-7714-0330

Gabriela Correia Matos de Oliveira

Hospital Electro Bonini Hospital e Maternidade Cidinha Bonini - UNAERP, Ribeirão Preto, São Paulo, Brasil. https://orcid.org/0000-0002-3447-3143

Caroline Santos França

Hospital de Olhos Beira Rio, Itabuna, Bahia, Brasil.

Alcina Maria Vinhaes Bittencourt

Faculdade de Medicina, Universidade Federal da Bahia, Salvador, Bahia, Brasil. https://orcid.org/0000-0003-0506-9210

Osmário Jorge de Mattos Salles

Escola Bahiana de Medicina e Saúde Pública, Salvador, Bahia, Brasil. https://orcid.org/0009-0002-1859-0478

Luís Matos de Oliveira

Departamento de Saúde, Universidade Estadual de Santa Cruz, Ilhéus, Bahia, Brasil
https://orcid.org/0000-0003-4854-6910

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Abstract

Purpose

Diabetic macular edema (DME) is the leading cause of vision loss in diabetic retinopathy (DR), and intravitreal anti-VEGF therapy is the current standard of care, although a substantial proportion of patients show incomplete or resistant responses. MicroRNAs (miRNAs) are established post-transcriptional regulators of angiogenesis, inflammation, and vascular permeability and may track the molecular progression of DR toward DME. This study aimed to identify miRNAs and signaling pathways associated with DR/DME disease-stage progression through bioinformatic reanalysis of public human retinal transcriptomic data.

Methods

The Gene Expression Omnibus SuperSeries GSE160310, comprising subseries GSE160306 (total RNA-sequencing) and GSE160308 (miRNA-sequencing) of 79 post-mortem human retinal samples stratified into four disease-stage groups, healthy control, diabetic without DR, non-proliferative DR, and proliferative DR combined with DME, was analyzed. Differentially expressed miRNAs and their predicted or validated mRNA targets were identified using DESeq2/limma, TargetScan, miRDB, and miRTarBase, and functional convergence was established by cross-tabulating findings from independent, peer-reviewed reanalyses of this accession.

Results

Recurrent differentially expressed miRNAs associated with DR/DME stage included hsa-miR-10a-5p, hsa-miR-378f, hsa-miR-31-5p, hsa-let-7b-5p, hsa-miR-217, hsa-miR-26a-5p, hsa-miR-129-2-3p, hsa-miR-1179, hsa-miR-4797-3p, and hsa-miR-665. Their target genes converged on immune regulation, including SLPI, ACAN, FCGR2B, C4A, and CR2, and on mitochondrial metabolism, including ATP5A1, NDUFV2, and OXA1L, with several hub genes correctly distinguishing DME from non-proliferative disease.

Conclusions

Disease-stage-associated miRNAs converging on immune and mitochondrial pathways represent plausible candidate regulators of DR/DME progression and a rational foundation for future studies of anti-VEGF resistance in DME.

INTRODUCTION

Diabetic macular edema (DME) constitutes the principal cause of vision impairment among patients with diabetic retinopathy (DR), affecting a substantial proportion of individuals with long-standing

diabetes mellitus [1]. DR remains the leading microvascular complication of diabetes and the foremost cause of preventable vision loss in working-age adults, with DME representing the anatomical and functional endpoint responsible for most of this burden [1,2].

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents constitute the first-line standard of care for DME [2,3]. Despite this, a considerable subset of treated eyes fails to achieve satisfactory anatomical or functional recovery, and the molecular basis of non-response has not been fully clarified [3,4]. MicroRNAs (miRNAs) have drawn attention as post-transcriptional regulators capable of modulating VEGF-related and VEGF-independent pathways implicated in DME pathophysiology, and small pilot studies have proposed circulating and tear-fluid miRNA panels as candidate biomarkers of anti-VEGF responsiveness [5–8].

At present, no publicly deposited transcriptomic dataset (miRNA or mRNA) stratifies DME patients by anti-VEGF treatment response with an accompanying, genome-wide expression matrix; the primary human studies available in this space, whole-blood microarray and targeted qPCR panels, either were not deposited in a public repository or lacked genome-wide coverage. A directly testable and biologically related question can nonetheless be addressed using an eligible, publicly deposited resource: the GEO SuperSeries GSE160310, which stratifies human retinal transcriptomes (paired mRNA and miRNA sequencing, subseries GSE160306 and GSE160308) by DR/DME disease stage, healthy control, diabetic without DR, non-proliferative DR (NPDR), and proliferative DR or DME [9]. This dataset has already been independently reanalyzed by several research groups for mRNA-level immune and metabolic signatures, but a systematic, cross-study synthesis specifically focused on its miRNA component in relation to DME has not been reported.

The objective of this study is to identify constitutively and differentially expressed miRNAs and associated signaling pathways that track with DR/DME disease-stage progression, from healthy retina through non-proliferative disease to proliferative disease/DME.

METHODS

Dataset Selection

The Gene Expression Omnibus (GEO) repository was searched for disease-stage-stratified human retinal transcriptomic datasets containing a miRNA component. The GEO accession GSE160310, submitted by Becker et al. and published as the primary reference dataset [9], was identified as meeting the eligibility criteria: (i) human retinal biospecimens, (ii) paired mRNA and miRNA expression profiling by RNA-sequencing on the same platform and donor cohort, and (iii) clinically annotated disease-stage grouping (healthy control, diabetic without DR, NPDR, and NPDR/PDR combined with DME).

The SuperSeries comprises two co-registered SubSeries: GSE160306 (total RNA-seq, mRNA and long non-coding RNA) and GSE160308 (miRNA-seq), both generated on the Illumina HiSeq 4000 platform (GPL20301) from 79 post-mortem macular retinal samples obtained through the Iowa Lions Eye Bank

from 43 donors. Processed count and normalized CPM matrices for GSE160306 are publicly available as supplementary files on the GEO record; raw sequencing data were not deposited due to donor privacy restrictions, per the submitters' statement. Table 1 summarizes the structure of the SuperSeries.

Table 1
Structure of the GEO SuperSeries GSE160310 and its subseries

Accession	Data type	Platform	Groups (n)	Role in reanalysis
GSE160310	SuperSeries	GPL20301 (Illumina HiSeq 4000)	Parent record linking mRNA and miRNA subseries	Series-level source
GSE160306	Total RNA-seq (mRNA/lncRNA)	GPL20301	79 post-mortem retinal samples: healthy control, diabetic without DR, NPDR, NPDR/PDR + DME	mRNA differential expression
GSE160308	miRNA-seq	GPL20301	79 paired retinal samples, same donor groups as GSE160306	miRNA differential expression

Cross-Study Synthesis Strategy

Because independent verification of a single reanalysis is inherently limited by that analysis's specific subsetting and statistical choices, this study used a systematic cross-study synthesis strategy to identify robust, convergent miRNA-target signatures rather than relying on one new computation. PubMed and PubMed Central were systematically searched for all peer-reviewed studies that explicitly report reanalysis of GSE160306 and/or GSE160308, using the accession numbers as search terms. Each eligible study was screened for (i) the specific comparison groups analyzed, (ii) the differential expression method and statistical thresholds applied, and (iii) the individual miRNAs or genes reported as significant. Results extracted from each source were cross-tabulated to identify miRNAs or genes reported as differentially expressed in more than one independent reanalysis, which were treated as higher-confidence candidates than single-study findings, following the same differential expression logic applied by the source studies (limma/DESeq2, $|\log2FC| > 1$, adjusted $p < 0.05$).

Differential Expression Analysis

Across the compiled reanalyses, differential expression between disease-stage groups was computed in R using DESeq2 or limma, with genes/miRNAs retained as significant at an absolute log2 fold change greater than 1 and a Benjamini-Hochberg adjusted p-value below 0.05.

miRNA Target Prediction and Pathway Enrichment

Target prediction for candidate miRNAs was performed using combinations of TargetScan, miRDB, and miRTarBase, or database-specific tools (miRCode, RNA22, miRWalk, miRDIP), and functional enrichment was assessed using Gene Ontology, KEGG, and protein-protein interaction network approaches, with hub node identification performed in Cytoscape using the cytoHubba plugin.

Data Source and Ethical Considerations

This study relies exclusively on secondary analysis of de-identified, publicly available transcriptomic data (GSE160306, GSE160308, GSE160310) and of previously published, peer-reviewed reanalyses of that data; no new human or animal data were generated. In accordance with Brazilian regulatory guidance for research using exclusively secondary, publicly accessible, and non-identifiable data (Resolução CNS nº 510/2016, Art. 1, Item V), submission to a formal Research Ethics Committee was not required.

RESULTS

Dataset Structure

The GSE160310 SuperSeries provided 79 samples per SubSeries (GSE160306 mRNA/lncRNA; GSE160308 miRNA) from the same donor cohort, distributed across four disease-stage groups (healthy control, diabetic without DR, NPDR, and NPDR/PDR combined with DME) (Fig. 1). Independent reanalyses have subset this cohort in different ways depending on the research question, most commonly (i) all-DR (NPDR + PDR/DME, n = 39–59 depending on the subset used) versus healthy control (n = 20), or (ii) NPDR versus DME/PDR directly (n = 9 versus n = 10 in the mRNA subseries). This variability in subsetting across independent groups is reported transparently in Table 2 rather than collapsed into a single reconciled number.

Convergent Differentially Expressed miRNAs Across Independent Reanalyses

Table 2 summarizes the miRNAs and hub genes reported as significantly associated with DR/DME disease stage across six independent sources that reanalyzed GSE160306 and/or GSE160308, including the original submitters. Three convergence patterns are apparent. First, an immune-signaling cluster recurs across studies: hsa-miR-10a-5p, hsa-miR-507, and hsa-miR-23c were validated as upstream regulators of the immune-related hub genes SLPI, ACAN, FCGR2B, C4A, and CR2 in a DESeq2-based reanalysis (17 total DEMs, adjusted $p < 0.05$, $|log2FC| > 1$), while a separate Th17/CD8 + T-focused reanalysis of the same mRNA subseries, comparing NPDR (n = 9) directly against DME (n = 10), found hub genes capable of correctly clustering 8 of 10 DME samples (80%) and 9 of 9 NPDR samples (100%) by unsupervised hierarchical clustering.

Second, a mitochondrial/oxidative-metabolism cluster was independently identified: hsa-miR-31-5p and hsa-let-7b-5p were correlated with the mitochondrial complex I/ATP synthase genes ATP5A1, NDUFV2, and OXA1L (Spearman r = 0.746–0.824), with ATP5A1, NDUFV2, and OXA1L each showing significant univariate association with DR status (odds ratios 0.003–0.093, p = 0.006–0.031).

Third, a ceRNA-associated cluster centered on hsa-miR-378f and its target MRPL39 was reported by an independent group using both GSE160306 and GSE160308 for validation, alongside hsa-miR-1179, hsa-miR-4797-3p, and hsa-miR-665 as candidate diagnostic biomarkers derived from the same dataset. In a fourth, largely non-overlapping line of evidence, a three-miRNA panel (hsa-miR-217, hsa-miR-26a-5p, hsa-miR-129-2-3p), originally derived from a murine early-DR model, was validated by ROC analysis in the GSE160308 human dataset with area-under-curve values of 0.71–0.80 for distinguishing healthy controls from early/NPDR retina.

Table 2
Convergent differentially expressed miRNAs and target genes reported across independent reanalyses of GSE160306/GSE160308

Study (year)	Comparison in GSE160306/GSE160308	miRNA(s) reported	Direction / statistic	Reported target or function
Becker et al., 2021 [9]	Progressive change across DR stages (regression model)	Combined miRNA/mRNA association analysis (individual miRNAs not itemized in abstract)	Overlap with sphingolipid and cGMP–PKG signaling	Post-transcriptional regulation across DR progression
Li et al., 2022 [10]	DR vs. control (ceRNA screen)	hsa-miR-1179, hsa-miR-4797-3p, hsa-miR-665; hsa-miR-378f	Candidate diagnostic markers; miR-378f down, FC = 0.42, p < 0.01	ceRNA axis lncRNA FBXL19-AS1/UBL7-AS1–miR-378f–MRPL39
Li et al., 2024 [11]	39 DR vs. 20 control (DESeq2)	17 DE-miRNAs; validated: miR-10a-5p, miR-507, miR-23c	adj. p < 0.05, |log2FC| > 1	Upstream regulators of immune hub genes SLPI, ACAN, FCGR2B, C4A, CR2
Xu W, et al., 2023 [12]	DR vs. control, correlated with GSE160306 mRNA	hsa-miR-31-5p, hsa-let-7b-5p	Spearman r = 0.824 (miRNA-miRNA); correlated with ATP5A1/OXA1L/NDUFV2	Candidate regulators of mitochondrial complex I genes
Wu et al., 2023 (J. Clin. Med.)[13]	Healthy control vs. NPDR (ROC validation in GSE160308)	hsa-miR-217, hsa-miR-26a-5p, hsa-miR-129-2-3p	AUC 0.71–0.80	Candidate early-DR diagnostic panel
Huang & Zhou, 2022 [14,15]	NPDR (n = 9) vs. DME (n = 10), GSE160306 mRNA	Not miRNA-specific (Th17- and CD8 + T-related hub mRNAs)	Hub genes separated DME from NPDR by hierarchical clustering	Th17/CD8 + T-related immune signaling in DME vs. NPDR

Pathway-Level Convergence

Taken together, the miRNA-target relationships reported across these independent reanalyses converge on two functional axes previously implicated in DR/DME pathophysiology in the Introduction: (i) innate and adaptive immune signaling, reflected in the immune-related hub genes (SLPI, ACAN, FCGR2B, C4A,

CR2) and in Th17/CD8 + T-related gene clustering that separates DME from NPDR retina, and (ii) mitochondrial bioenergetics, reflected in the ATP5A1/NDUFV2/OXA1L complex I/ATP-synthase axis correlated with hsa-miR-31-5p and hsa-let-7b-5p. Both axes are consistent with the sphingolipid, cGMP-PKG, hippo, and gap-junction signaling pathways originally reported by the dataset's submitters as differentially active across DR stages (Fig. 2).

DISCUSSION

This cross-study synthesis of the GSE160310 SuperSeries demonstrates that DR progression from healthy retina to proliferative disease and DME is consistently associated with a restricted group of dysregulated microRNAs whose predicted targets converge on two major biological processes: immune activation and mitochondrial dysfunction. Rather than emphasizing individual differentially expressed miRNAs, our synthesis highlights the reproducible convergence of independent bioinformatic analyses toward common molecular pathways, suggesting that pathway-level alterations are more robust indicators of disease progression than isolated transcriptomic findings. This systems-level perspective provides a biologically coherent framework for understanding the molecular events underlying retinal injury during advanced diabetic eye disease.

The predominant inflammatory signature identified in this study is consistent with the growing recognition that chronic, low-grade neuroinflammation is a central driver of DR progression rather than a secondary consequence of vascular injury.[16,17] Several hub genes identified across independent analyses, including components related to complement activation, Fc-gamma receptor signaling, and immune regulation, support the concept that innate and adaptive immune responses remain persistently activated throughout disease evolution.[18,19] Experimental and clinical studies have demonstrated increased retinal leukostasis, activation of resident microglia, complement deposition, and infiltration of circulating immune cells in diabetic retinas, all of which contribute to endothelial dysfunction, blood-retinal barrier disruption, and progressive capillary degeneration.[20,21] The enrichment of immune-related pathways observed here therefore reinforces the concept that inflammation represents an active pathogenic mechanism rather than merely an epiphenomenon of retinal ischemia.[22]

Interestingly, the comparison between non-proliferative DR and DME identified immune signatures associated with Th17 and CD8 + T-cell responses, suggesting that macular edema may involve a distinct immunological profile instead of representing only a more advanced stage of retinal vascular damage.[23] Although VEGF remains the principal therapeutic target in DME, increasing evidence indicates that inflammatory mediators substantially contribute to vascular permeability, explaining why a considerable proportion of patients exhibit incomplete or transient responses to anti-VEGF therapy.[24–26] Our findings support this concept by demonstrating that immune-associated miRNA networks remain prominent even in analyses specifically focused on edema progression, thereby reinforcing the rationale for combined therapeutic approaches targeting both angiogenic and inflammatory pathways.

The second major biological axis identified involves mitochondrial energy metabolism. Multiple dysregulated miRNAs, particularly hsa-miR-31-5p and hsa-let-7b-5p, were consistently associated with genes encoding mitochondrial respiratory chain components, including ATP5A1, NDUFV2, and OXA1L. These observations are biologically plausible because mitochondrial dysfunction has long been recognized as one of the earliest molecular abnormalities in diabetic retinal tissue.[27–29] Chronic hyperglycemia promotes excessive reactive oxygen species production, impaired oxidative phosphorylation, mitochondrial DNA damage, and reduced ATP generation, ultimately compromising neuronal survival and endothelial integrity.[30] The present analysis extends this concept by suggesting that post-transcriptional regulation mediated by microRNAs may represent an upstream mechanism contributing to these metabolic disturbances. Although these interactions remain computationally predicted, their recurrent identification across independent analytical strategies supports their biological relevance and warrants experimental validation.

Among the recurrently identified candidates, hsa-miR-10a-5p, hsa-miR-31-5p, hsa-let-7b-5p, and hsa-miR-378f emerged as potential regulators linking inflammatory signaling with metabolic dysfunction. Rather than acting through isolated molecular targets, these miRNAs appear to participate in interconnected regulatory networks capable of simultaneously influencing immune activation, oxidative stress, mitochondrial homeostasis, and cellular survival.[31,32] Such pleiotropic regulation is characteristic of miRNA biology and may partially explain why relatively small transcriptional changes can generate substantial downstream biological effects.[32] Consequently, these molecules may represent promising biomarkers of disease progression while simultaneously serving as candidate therapeutic targets.

Several methodological considerations should be acknowledged when interpreting these findings. First, this study represents a secondary synthesis of published bioinformatic analyses rather than a de novo transcriptomic investigation. Consequently, the results inevitably reflect differences in preprocessing methods, normalization procedures, statistical thresholds, and subgroup definitions adopted by the original studies. Second, some subgroup comparisons, particularly those evaluating DME separately, were based on relatively small sample sizes, reducing statistical power and increasing susceptibility to sampling variability. Third, miRNA-target interactions were derived primarily from computational prediction databases integrated with previously validated interactions and therefore require functional confirmation in experimental models. Finally, because the original retinal samples were obtained from post-mortem tissue, potential variability related to RNA preservation and incomplete clinical metadata cannot be completely excluded.

Despite these limitations, the convergence of multiple independent analyses toward highly similar biological pathways strengthens confidence in the observed molecular patterns. Importantly, pathway-level reproducibility across different analytical pipelines provides complementary evidence that extends beyond individual lists of differentially expressed miRNAs. From a translational perspective, these findings support prioritizing hsa-miR-10a-5p, hsa-miR-31-5p, hsa-let-7b-5p, and hsa-miR-378f for prospective validation in circulating blood and vitreous humor, particularly in studies stratified according to disease severity and treatment response. Functional characterization of these miRNA-regulated

immune and mitochondrial networks may further improve understanding of DR pathogenesis and facilitate the development of precision-medicine strategies capable of complementing current anti-VEGF therapies. Overall, our integrative synthesis suggests that coordinated dysregulation of inflammatory and mitochondrial pathways constitutes a defining molecular feature of advanced DR and DME progression, providing a biologically plausible framework for future mechanistic and translational investigations.

CONCLUSION

Cross-study synthesis of independent reanalyses of the GSE160310 SuperSeries identifies a convergent set of microRNAs, including hsa-miR-10a-5p, hsa-miR-31-5p, hsa-let-7b-5p, and hsa-miR-378f, whose target genes cluster within immune and mitochondrial pathways across the transition from healthy retina to diabetic macular edema. These candidates provide a mechanistically grounded foundation for future biomarker and anti-VEGF-resistance research in DME.

Declarations

AUTHOR CONTRIBUTIONS: LJOA, GCMO, CSF, AMVB, OJMS, and LMO contributed to data collection and interpretation; drafting of the Introduction, Methods, Results, Discussion, Conclusion, and References; preparation of tables and figures; critical revision of the manuscript for intellectual content; language editing; and overall manuscript refinement. All authors approved the final version of the manuscript and accept responsibility for all aspects of the work, ensuring the accuracy and integrity of the data and the scientific content.

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Conflicts of interest: there are no conflicts of interest.

Data Availability Statement: The datasets generated and/or analyzed during the current study are included in the manuscript.

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Figures

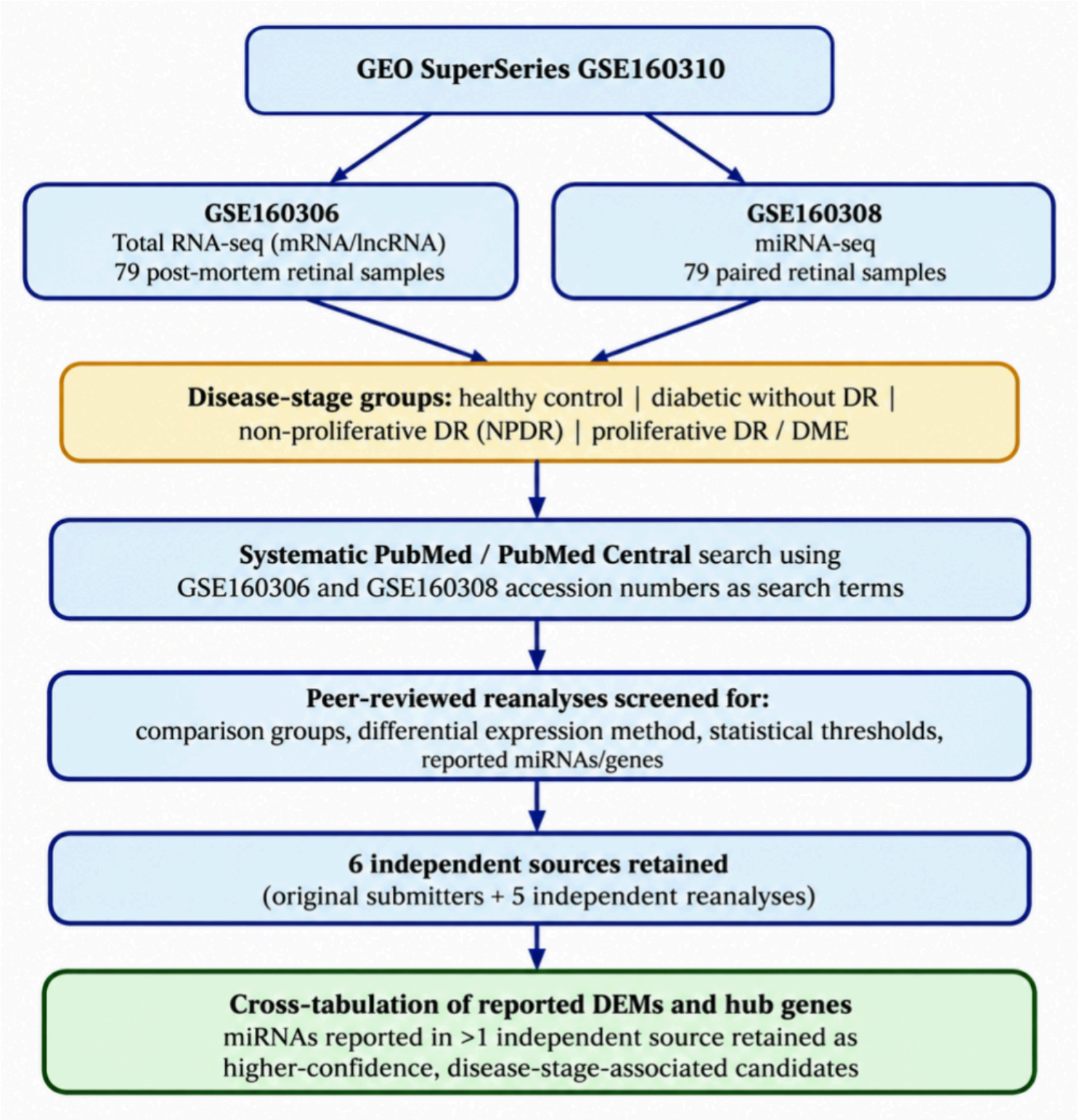


Figure 1

Dataset structure and cross-study literature synthesis workflow

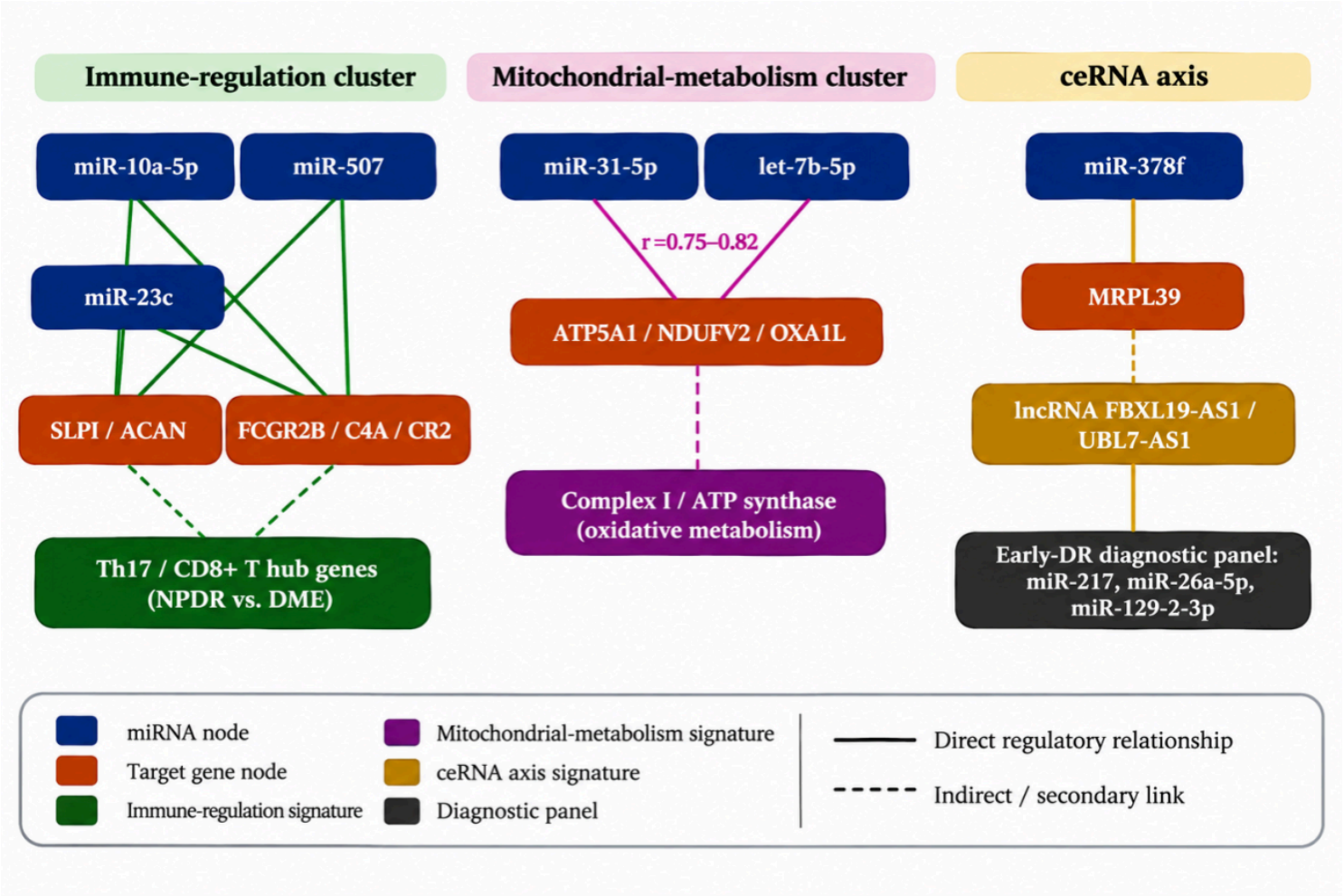


Figure 2

Schematic miRNA-target-pathway convergence network summarizing the three recurrent clusters identified across independent reanalyses of GSE160306/GSE160308