



# International Journal of Biological and Biomedical Research

## MicroRNA Networks in Systemic Lupus Erythematosus: From Compartment-Specific Biomarkers to Precision Immune Endotypes

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### Article Info

**E-ISSN:** 3107-7137

**Volume:** 02

**Issue:** 05

**Received:** 11-07-2026

**Accepted:** 09-08-2026

**Published:** 07-09-2026

**Page No:** 51-62

### Abstract

Systemic lupus erythematosus (SLE) is a heterogeneous systemic autoimmune disease in which defective immune tolerance, nucleic-acid sensing, type I interferon activation, T- and B-cell dysregulation, immune-complex formation and tissue injury interact as a self-reinforcing network. MicroRNAs (miRNAs) are short non-coding RNAs that fine-tune post-transcriptional gene expression and can simultaneously regulate multiple nodes of this network; their relevance to SLE therefore extends beyond simple differential expression to encompass epigenetic remodeling, extracellular-vesicle (EV) communication, inflammatory signaling and organ-specific injury. This critical narrative review synthesizes evidence published between 2020 and 2026 concerning miR-146a, miR-21, miR-155, miR-126, miR-150, miR-181a, miR-223, miR-125-family members, the miR-17~92 cluster and emerging EV-associated candidates, with particular emphasis on the compartment-dependence of miR-146a and on urinary/plasma EV biomarkers in lupus nephritis (LN). A regionally important Middle Euphrates cohort (Shlash *et al.*) is incorporated alongside international evidence to illustrate both the value and the limits of single-cohort biomarker studies. Across compartments, the literature supports miRNAs as important network regulators but does not support any single miRNA as a universal SLE biomarker: the direction and magnitude of change vary with cell type, biofluid, disease activity, treatment exposure and analytical workflow. We argue that clinical translation should move from single-miRNA discovery toward standardized, compartment-specific, multi-miRNA signatures that are analytically validated per the Minimum Information for Publication of Quantitative Real-Time PCR Experiments guidelines (MIQE 2.0), EV-characterized where relevant per the Minimal Information for Studies of Extracellular Vesicles guidelines (MISEV2023), and integrated with interferon activity, immune-cell endotype, renal biomarkers and longitudinal outcomes in prospective multicenter cohorts.

**DOI:** <https://doi.org/10.54660/IJBBR.2026.2.5.51-62>

**Keywords:** systemic lupus erythematosus, microRNA, miR-146a, miR-2, miR-155, lupus nephritis, extracellular vesicles, interferon, biomarkers, precision medicine

### 1. Introduction

#### 1.1. SLE As A Systems-Level Disorder

SLE is best understood as a systems-level disorder rather than a disease driven by a single cytokine or immune-cell population. Genetic susceptibility interacts with environmental triggers and epigenetic remodeling to alter nucleic-acid sensing, antigen presentation, lymphocyte activation, cytokine production, apoptosis and clearance of cellular debris. The resulting interferon-rich, immune-complex-laden environment feeds back into transcriptional and post-transcriptional regulation, creating a self-

reinforcing network rather than a linear pathway <sup>[1-6,58]</sup>. A recent synthesis of the molecular landscape of SLE reinforces this systems view, mapping how genetic risk loci converge on a limited number of convergent immune pathways rather than acting independently <sup>[58]</sup>.

## 1.2. Mirna Biology and Epigenetic Crosstalk

miRNAs generally associate with Argonaute proteins and guide the RNA-induced silencing complex toward complementary transcripts. Because one miRNA can regulate many transcripts and one transcript can be targeted by multiple miRNAs, their aggregate effect is network-like rather than single-target. In SLE, this creates a bidirectional link between DNA methylation, transcriptional regulation and immune signaling. miR-21, miR-126 and miR-29b have each been mechanistically linked to DNA methyltransferase 1 (DNMT1)-associated methylation control in lupus CD4<sup>+</sup> T cells, while genome-wide methylation profiling demonstrated hypomethylation of the miR-17~92 promoter in lupus naive CD4<sup>+</sup> T cells <sup>[7-10]</sup>. This epigenetic-miRNA crosstalk is a recurring theme throughout this review and is revisited mechanistically in Section 3.1 and evidentially in Section 5.3.

This review addresses three questions that we believe are more clinically consequential than compiling further lists of differentially expressed miRNAs: (i) which miRNAs and compartments carry the strongest mechanistic and clinical evidence in 2020-2026; (ii) why ostensibly contradictory results for the same miRNA (particularly miR-146a) keep recurring across studies; and (iii) what analytical and study-design standards would be required before a miRNA signature could credibly influence clinical decisions in SLE. This is a critical narrative rather than a systematic review; the search strategy and its limitations are described in Section 12.

## 2. MicroRNA Dysregulation in Innate Immune Networks

### 2.1. Plasmacytoid and Myeloid Dendritic Cells

Plasmacytoid dendritic cells produce large quantities of type I interferon after sensing nucleic-acid-containing immune complexes through TLR7 and TLR9. The MyD88-IRAK-TRAF6-IRF7 pathway is normally constrained by negative feedback, including miR-146a; reduced miR-146a activity can weaken this feedback and favor sustained interferon signaling <sup>[6,11-14]</sup>. However, miR-146a should not be described as uniformly reduced across every SLE compartment. Whole-blood, PBMC and serum studies can report different directions of change because they sample different mixtures of cells and extracellular material <sup>[12-14]</sup>; this compartment problem is addressed systematically in Section 5.

The Middle Euphrates study by Shlash *et al.* measured serum miR-146a in 45 SLE patients and 45 controls and reported lower serum miR-146a in SLE, with a proposed cutoff of 0.7 yielding a reported sensitivity of 77.8% and specificity of 73.3% <sup>[14]</sup>. These values are clinically interesting but should

be treated as cohort- and assay-specific rather than as a universal diagnostic threshold; the study did not report independent validation, and the modest sample size limits precision around the reported operating characteristics. Its principal value is regional: Middle Eastern biomarker cohorts remain markedly underrepresented in the SLE miRNA literature, and this study helps to close that gap.

### 2.2. Mir-155 and Inflammatory Amplification

miR-155 is a central immunoregulatory miRNA involved in both innate and adaptive immunity. In SLE it can influence suppressor pathways including SOCS1, and a 2024 mechanistic study linked an inflammatory-factor-mediated miR-155/SOCS1 axis to impaired regulatory T-cell (Treg) function <sup>[15,16]</sup>. Because miR-155 is also required for normal host defense against infection, therapeutic inhibition would require careful dose- and tissue-restricted targeting rather than systemic suppression.

### 2.3. Mir-21 And Inflammatory State

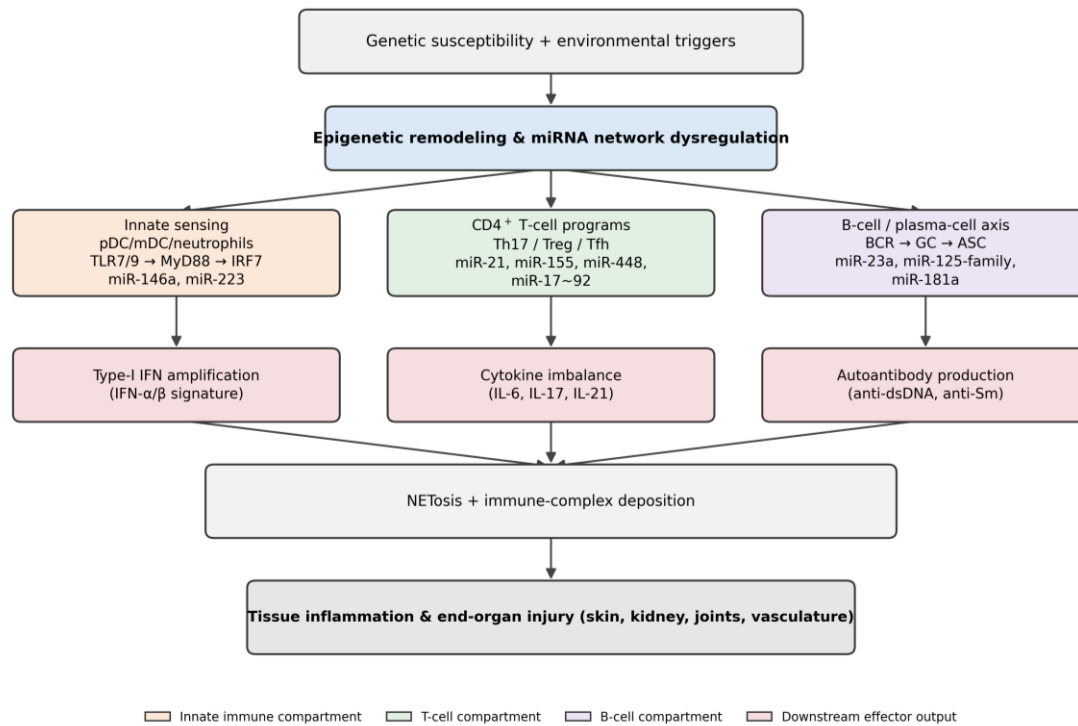
miR-21 is frequently increased in inflammatory and autoimmune states generally. In SLE, elevated miR-21 has been associated with T-cell activation, cytokine networks and disease activity <sup>[13,17,18]</sup>. A 2023 Egyptian study evaluated serum miR-21 and miR-146a together with plasma cell-free DNA, illustrating the potential added value of combining nucleic-acid-based markers into a panel rather than relying on a single analyte <sup>[18]</sup>. miR-21 is nevertheless highly non-specific across inflammatory diseases generally and should not be treated as an SLE-specific biomarker in isolation <sup>[19]</sup>.

### 2.4. Monocytes, Macrophages and Efferocytosis

Macrophages and monocytes link systemic inflammation with tissue injury and are central to the clearance (or failed clearance) of apoptotic debris that drives autoantigen exposure in SLE. miR-150 illustrates the importance of context: renal miR-150 has been associated with fibrosis, whereas experimental miR-150-5p augmentation in lupus-prone mice reduced myeloid dendritic-cell inflammation through the TREM-1 axis <sup>[20,21]</sup>. These apparently opposing observations are not contradictory once tissue compartment and the specific target network are specified, and they illustrate why single-direction summaries of "miR-150 in SLE" are of limited value.

### 2.5. Neutrophils and NETosis

NETosis (neutrophil extracellular trap formation) exposes DNA, histones and neutrophil granule proteins that can become autoantigenic or further stimulate nucleic-acid sensing, creating a feed-forward loop with innate interferon production. Recent work placed miR-223 within a neutrophil-Th17 axis involving PI3K-AKT signaling in SLE, providing a plausible mechanistic bridge linking innate neutrophil activation, miRNA remodeling and downstream adaptive T helper 17 (Th17) inflammation <sup>[22]</sup>.



**Fig 1:** Integrative miRNA-immune network in SLE. Genetic and environmental triggers drive epigenetic remodeling and network-level miRNA dysregulation, which act in parallel across innate sensing, CD4+ T-cell and B-cell compartments. Convergent downstream outputs (type I interferon amplification, cytokine imbalance and autoantibody production) feed into NETosis and immune-complex deposition, culminating in tissue inflammation and end-organ injury.

### 3. Adaptive Immunity: T- and B-Cell Dysregulation

#### 3.1. CD4+ T Cells and DNA Methylation

Lupus CD4+ T cells display abnormal DNA methylation and transcriptional programs. miR-21, miR-126 and miR-29b each provide a mechanistic bridge between post-transcriptional regulation and DNMT1-associated epigenetic control [7-9]. Coit *et al.* demonstrated hypomethylation of the miR-17~92 promoter in naive lupus CD4+ T cells [10], supporting a bidirectional interaction between the lupus epigenome and miRNA expression rather than a one-way effect of methylation on miRNA output alone.

#### 3.2. Th17/Treg Equilibrium

A functional balance between inflammatory Th17 cells and suppressive Tregs is essential for peripheral tolerance. miR-155/SOCS1 and miR-448/SOCS5 are examples of miRNA-centered regulatory axes affecting inflammatory CD4+ T-cell function [13]. Evidence from other autoimmune diseases further supports the relevance of miRNA-mediated regulation of the Th17/IL-17 axis. In a recent Iraqi case-control study of rheumatoid arthritis, miRNA-326 expression was significantly reduced, whereas serum IL-17 was elevated, with a strong inverse correlation between miRNA-326 expression and IL-17 levels (Spearman  $r_s = -0.672$ ,  $P < 0.0001$ ), suggesting that dysregulated miRNA–Th17/IL-17 interactions may represent a broader feature of autoimmune inflammation [24]. These pathways are mechanistically attractive but remain insufficiently validated as human therapeutic targets, and neither axis has yet been tested in a controlled interventional study in SLE patients.

#### 3.3. TFH Cells and B-Cell Help

T follicular helper (Tfh) cells promote B-cell maturation, immunoglobulin class switching and plasma-cell differentiation. Experimental inhibition of miR-21 in lupus-prone mice reduced Tfh-mediated autoimmune responses [25], and the miR-17~92 cluster - already noted for its epigenetic dysregulation in Section 3.1 - also participates directly in T-cell differentiation programs relevant to Tfh biology [10].

#### 3.4. B cells and plasma cells

B cells integrate B-cell receptor (BCR) signals, innate receptor signals, T-cell help and survival factors before differentiating into autoantibody-producing plasma cells. A recent synthesis highlights miR-23a, members of the miR-17~92 cluster, miR-125-family members and miR-181a among the regulators of B-cell development and activation in SLE [26]. A key methodological issue that recurs across this literature is distinguishing a genuine regulatory change within a B-cell subset from a shift in the relative proportions of B-cell subsets (e.g., expansion of plasmablasts) within a bulk sample - a problem addressed further in Section 5.4.

### 4. Lupus Nephritis and End-Organ MicroRNA Signatures

LN is an important test case for precision miRNA medicine because kidney biopsy is invasive and blood biomarkers do not always capture intrarenal activity. Urinary miRNAs and urinary EVs can provide a more anatomically proximate molecular signal [27-31]. A meta-analysis of LN profiling

studies identified recurrent candidates across kidney, blood and urine compartments, including miR-21, miR-150, miR-155 and miR-146a in blood and miR-146a in urine [28].

#### 4.1. Urinary Exosomal Mir-146a

Perez-Hernandez *et al.* studied urinary exosomal miR-146a in 41 SLE patients, including 27 with LN, and correlated the marker with renal biopsy findings. Urinary exosomal miR-146a identified LN with an area under the receiver-operating-characteristic curve (AUC) of 0.82 and was associated with disease activity, proteinuria changes and future flares over 36 months of follow-up [28] - one of the few studies in this field to connect a molecular measurement to both histology and a genuinely longitudinal clinical outcome.

#### 4.2. Urinary Exosomal Profiles and Treatment Response

Garcia-Vives *et al.* profiled urinary exosomal miRNAs in biopsy-proven proliferative LN and found miR-31, miR-107 and miR-135b-5p associated with treatment response; miR-135b showed an AUC of 0.783 for this endpoint [30].

#### 4.3. Mir-195-5p And Cxcl10

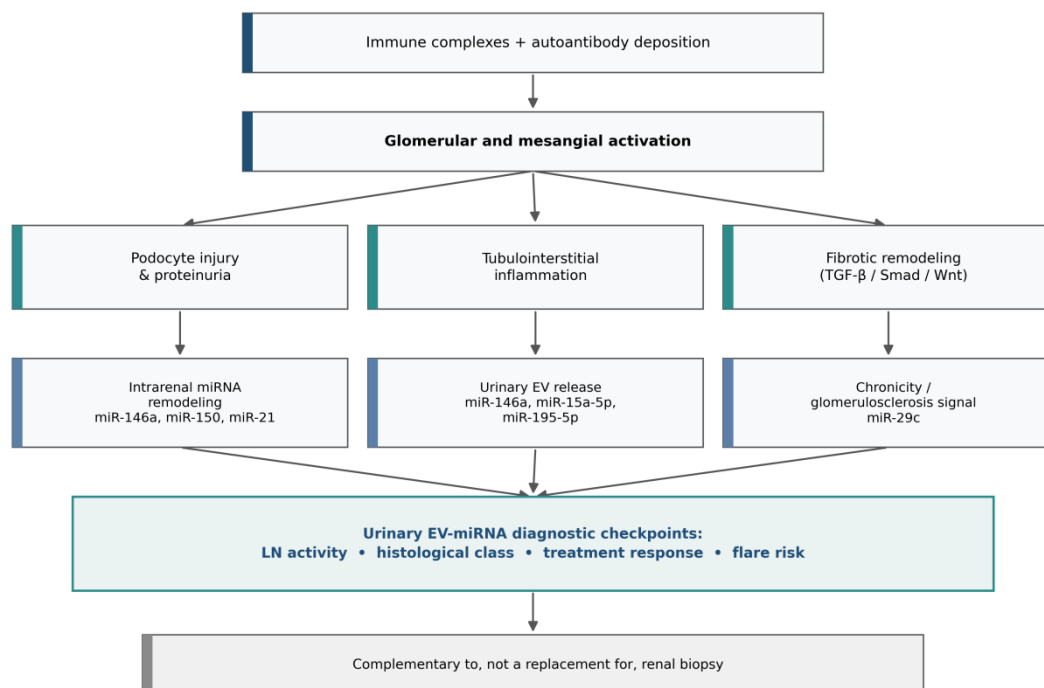
Cheng *et al.* integrated renal miRNA-mRNA co-expression data and validated candidates in urinary exosomes. miR-195-5p, miR-25-3p and miR-429 were reduced in LN, with miR-195-5p showing the strongest diagnostic signal and a plausible mechanistic relationship with the chemokine CXCL10 [31].

#### 4.4. Exosomal Mir-15a-5p And Emerging Renal Panels

A 2025 study directly addressed EV specificity for miR-15a-5p. A three-miRNA plasma-exosomal panel comprising miR-101-3p, miR-144-5p and miR-15a-5p achieved an AUC of 0.964 for LN discrimination in the reported cohort, and miR-15a-5p was independently associated with renal damage and future flares [32]. Serum exosomal miR-497-5p and miR-6515-5p have also been reported as candidate LN biomarkers, with a combined AUC of 0.798 [33]. Broader profiling of urinary EV RNA cargoes beyond miRNA alone is now being explored as a complementary diagnostic and prognostic strategy in LN [56], and this growing body of work has recently been synthesized into comprehensive reviews of urinary exosomes across diagnosis, activity assessment, treatment monitoring and prognosis in LN [57].

#### 4.5. Renal Fibrosis and Chronicity: Mir-29c

miR-29c is relevant to renal fibrosis and chronicity biology: lower urinary exosomal miR-29c correlates with histological chronicity and glomerulosclerosis. This finding's foundational evidence predates the main 2020-2026 window of this review and is therefore identified explicitly as mechanistic background rather than recent validation [55]. Taken together, the LN literature converges on urinary EV-associated miRNAs as the most organ-proximal and clinically promising candidates in this review, but current evidence remains insufficient to replace renal biopsy or established clinical assessment.



**Fig 2:** miRNA-mediated renal injury and urinary extracellular-vesicle diagnostic checkpoints in lupus nephritis. Immune-complex deposition drives glomerular and mesangial activation, which produces three parallel injury programs (podocyte injury/proteinuria, tubulointerstitial inflammation and fibrotic remodeling), each associated with a distinct miRNA signature detectable in intrarenal tissue or urinary extracellular vesicles. These signatures converge on four candidate diagnostic checkpoints that remain complementary to, rather than a replacement for, renal biopsy.

## 5. Disease Heterogeneity and Compartment-Specific Interpretation

SLE heterogeneity is a major barrier to identifying a universal miRNA biomarker. Patients with similar Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores may differ substantially in interferon activity, plasmablast expansion, T-cell dysfunction, renal inflammation, complement consumption and treatment exposure. A bulk blood measurement therefore represents a mixture of genuine biological regulation and changes in cellular composition, and these two contributions are rarely distinguished in the published literature <sup>[1,4,34]</sup>.

### 5.1. Why Mir-146a Results Disagree: A Worked Example

miR-146a is the clearest illustration of this problem and is worth resolving explicitly because it recurs throughout this review. Reduced serum miR-146a in the Middle Euphrates cohort <sup>[14]</sup>, reduced PBMC miR-146a in an independent cohort <sup>[13]</sup>, and increased whole-blood miR-146a reported in earlier work <sup>[12]</sup> should not automatically be regarded as mutually exclusive findings. Whole blood, PBMCs, serum and urinary EVs represent distinct biological compartments with different cellular and molecular origins, and hemolysis, platelet contamination, disease stage, treatment and normalization strategy can further alter the observed profile within any one of them (Section 6). Mechanistically, miR-146a is best interpreted as a feedback regulator whose apparent direction of change depends on compartment and disease context: intracellular miR-146a restrains inflammatory signaling through targets including IRAK1 and TRAF6, whereas urinary/exosomal miR-146a may increase during active renal inflammation, reflecting release from activated or injured renal parenchymal or infiltrating cells rather than a change in the same intracellular regulatory pool measured in blood. The defensible conclusion is that miR-146a is compartment-, cell-state-, treatment- and assay-dependent rather than simply "low" or "high" in SLE, and that the Middle Euphrates serum data <sup>[14]</sup> and the urinary exosomal LN data <sup>[29]</sup> describe different biological signals that happen to share a name.

### 5.2. Total Circulating Mirna Is Not A Single Analyte

"Circulating miRNA" should not be treated as one homogeneous molecular pool. Plasma and serum contain protein-bound miRNAs, EV-associated miRNAs, lipoprotein-associated species, and miRNAs released from damaged or activated blood cells. These fractions can have different cellular origins, kinetics and biological functions, so a total-plasma assay may provide a reproducible biomarker while remaining mechanistically agnostic about its cellular source. EV-focused assays can improve biological specificity, but EV isolation introduces its own recovery and purity variables and should follow MISEV2023 principles

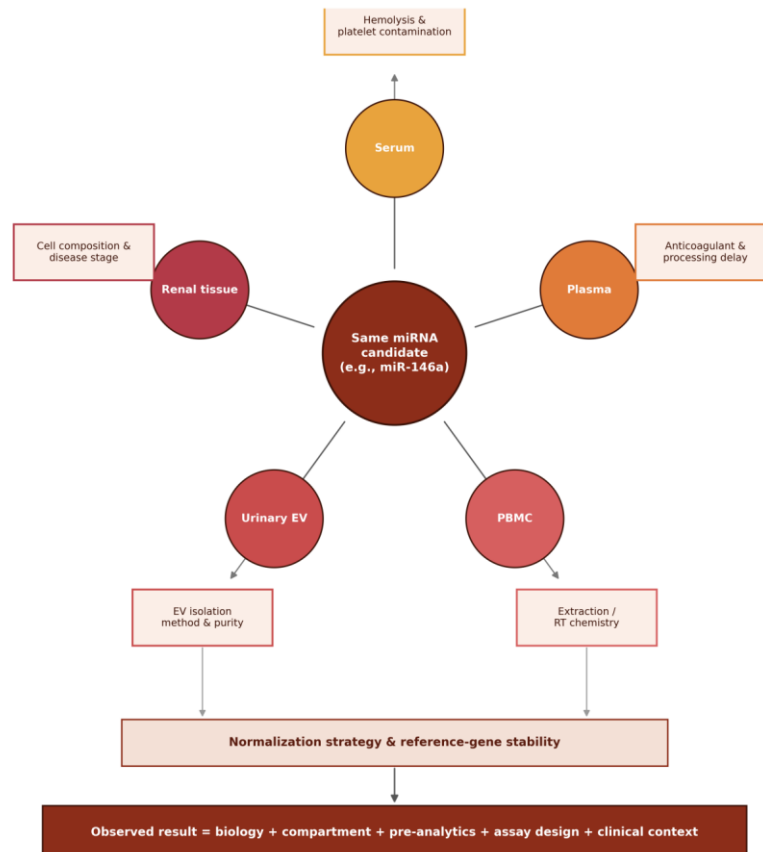
<sup>[51]</sup>. This distinction matters particularly in SLE because platelet activation, hemolysis, leukocyte composition and inflammatory cell death can all alter the extracellular miRNA pool without necessarily reflecting a transcriptional change within a pathogenic immune-cell subset.

### 5.3. Causality Versus Association: How Strong Is The Evidence?

The literature should distinguish differential expression, mechanistic perturbation and demonstrated clinical utility; these are cumulative tiers of evidence rather than interchangeable descriptions of "importance" (see Table 4). A miRNA that differs between SLE patients and controls is not automatically pathogenic. Stronger mechanistic evidence requires miRNA perturbation followed by demonstration of target-gene and phenotype change, ideally with rescue experiments or direct target-site validation. The miR-21/miR-148a-DNMT1 axis provides genuine mechanistic evidence linking miRNA dysregulation to aberrant DNA methylation in lupus CD4+ T cells <sup>[7]</sup>. In contrast, most circulating-miRNA candidates discussed in Sections 2 and 4 remain at the association tier: receiver operating characteristic (ROC) performance in a case-control comparison should not be interpreted as proof of biological causation, and few of the biomarker studies cited in this review include a mechanistic arm.

### 5.4. Single-Cell and Multi-Omic Integration

Bulk PBMC analysis cannot determine whether a miRNA change occurs uniformly across cells or instead reflects a shift in cell-type composition - the same ambiguity noted for B-cell subsets in Section 3.4. Single-cell transcriptomic atlases of SLE and LN have shown that interferon-stimulated states occur across several immune lineages simultaneously and that high disease activity can be concentrated within specific cellular subpopulations rather than distributed evenly <sup>[52-54]</sup>. Conventional single-cell RNA-sequencing, however, measures messenger RNA rather than mature miRNA directly; parallel small-RNA assays or dedicated single-cell miRNA methods are therefore required before a cell-specific miRNA expression claim can be made with confidence. A recent comprehensive synthesis of cellular immune alterations in SLE reinforces the view that multiple, partially overlapping immune endotypes coexist within a single clinical diagnosis <sup>[58]</sup>, underscoring why bulk miRNA measurements averaged across an entire cohort are likely to underperform endotype-stratified analyses. Future SLE molecular atlases should explicitly link miRNA profiles to IFN-high myeloid states, Tfh/Th17 programs, Treg dysfunction, plasmablast expansion and renal inflammatory phenotypes, using matched multi-omic sampling from the same specimens.



**Fig 4:** Why apparently conflicting microRNA biomarker results can arise for the same candidate. The same miRNA (e.g., miR-146a) is measured across different biological compartments (serum, plasma, PBMC, urinary EV, renal tissue), each associated with distinct pre-analytical vulnerabilities. These compartment-specific factors converge on the choice of normalization strategy, so that the final observed result reflects the combined influence of biology, compartment, pre-analytics, assay design and clinical context - not biology alone.

## 6. Pre-Analytical and Analytical Determinants of miRNA Reliability

Pre-analytical variation is a major, underappreciated source of disagreement between circulating-miRNA studies. Specimen matrix, centrifugation protocol, delay before processing, platelet contamination, hemolysis and storage conditions can all alter apparent miRNA abundance independent of any underlying biological difference [35-39].

### 6.1. Hemolysis and Platelet Contamination

Hemolysis is particularly important because erythrocyte-associated miR-451a and miR-16 increase markedly after red-cell rupture. A pre-analytical study found that more than 97% of miR-451a and miR-423-5p in whole blood was localized to red blood cells, and that hemolysis strongly affected their apparent plasma concentrations [36]. miR-451a is therefore useful as a hemolysis indicator but unsafe as a universal normalization control in hemolyzed samples. Platelet depletion should also be documented in every study, because activated platelets release abundant miRNA into plasma independent of the disease process under study [35,37].

### 6.2. RNA Extraction, Reverse Transcription and Qpcr

Phenol/guanidinium extraction, silica columns and magnetic beads can all recover circulating miRNA, but low-input samples require careful control of recovery efficiency. Synthetic spike-in controls can monitor extraction and reverse-transcription performance but do not correct for biological variation between samples. Stem-loop reverse transcription offers mature-miRNA specificity; poly(A)-

tailoring provides flexible universal priming but requires stringent specificity validation. Hydrolysis-probe assays generally improve sequence specificity, whereas SYBR/EvaGreen-based assays require robust melt-curve analysis and additional specificity controls. Digital PCR can provide absolute quantification when small copy-number differences, or reference-gene instability, limit the interpretability of conventional quantitative PCR (qPCR) [45,48].

### 6.3. Normalization

Normalization remains an unresolved methodological problem across this entire field. U6 and other small nuclear RNAs are convenient but may not be stable extracellular reference molecules. miR-16 and miR-451a are themselves influenced by hemolysis (Section 6.1) and are therefore poor universal references. Exogenous cel-miR-39 can monitor technical recovery but does not correct for biological differences between groups. Endogenous reference genes should be empirically validated within the exact specimen type and cohort under study; global-mean normalization approaches are useful mainly in adequately powered discovery datasets with comprehensive miRNA detection [39,45].

### 6.4. What A Clinically Credible Assay Should Demonstrate

Clinical translation requires analytical validation before any claim of diagnostic utility is made. A credible assay should define specimen type, collection tube, processing time,

centrifugation/platelet strategy, hemolysis assessment, extraction method, spike-in strategy, reverse-transcription chemistry, primer/probe sequences, amplification efficiency, dynamic range, limit of detection and limit of quantification. The MIQE 2.0 guidelines strengthen requirements for transparent qPCR reporting, efficiency-aware quantification, and documentation of detection limits and dynamic range

[45,47,48]. For EV-miRNA studies specifically, MISEV2023 additionally requires explicit characterization of the EV preparation and recognition that separation procedures may co-isolate non-vesicular material [51]. These are not merely reporting formalities: together they determine whether an observed difference between groups reflects underlying biology or an analytical artifact of specimen handling.

## 7. Evidence Synthesis Tables

**Table 1:** Selected microRNAs implicated in SLE immune networks

| MicroRNA                 | Expression/context                                                                           | Compartment               | Pathway/target                               | Clinical relevance                            | Refs          |
|--------------------------|----------------------------------------------------------------------------------------------|---------------------------|----------------------------------------------|-----------------------------------------------|---------------|
| miR-146a                 | Context-dependent; often lower in serum/PBMC, higher in urinary EV during renal inflammation | Serum; PBMC; urinary EV   | TRAF6/IRAK1; NF- $\kappa$ B; IFN-I feedbacks | SLE activity; LN; leading biomarker candidate | [11-14,28,31] |
| miR-21                   | Often increased                                                                              | PBMC; serum               | PDCD4; inflammatory/T-cell pathways          | Disease activity; Tfh biology                 | [13,18,24]    |
| miR-155                  | Often increased in inflammatory states                                                       | T cells; myeloid cells    | SOCS1; cytokine signaling                    | Treg dysfunction; therapeutic target          | [15,16]       |
| miR-126                  | Dysregulated                                                                                 | CD4+ T cells; serum       | DNMT1-related epigenetic control             | T-cell activation                             | [7,9]         |
| miR-150                  | Context-dependent (renal vs myeloid)                                                         | Kidney; myeloid cells     | SOCS1; TREM-1                                | Renal fibrosis; mDC inflammation              | [20,21]       |
| miR-223                  | Dysregulated                                                                                 | Neutrophils; immune cells | PI3K-AKT/myeloid programs                    | Th17 expansion                                | [22]          |
| miR-17~92                | Epigenetically hypomethylated                                                                | CD4+ T cells              | T-cell differentiation                       | Lupus epigenetic phenotype                    | [10]          |
| miR-448                  | Increased in SLE CD4+ cells                                                                  | CD4+ T cells              | SOCS5                                        | Inflammatory activation                       | [23]          |
| miR-15a-5p               | Increased in EV fraction in LN                                                               | Plasma EV                 | Renal injury network                         | LN activity/damage/flare risk                 | [31]          |
| miR-195-5p               | Reduced in urinary EVs                                                                       | Urinary EV                | CXCL10-associated                            | LN diagnosis/monitoring                       | [30]          |
| miR-497-5p / miR-6515-5p | Increased in LN                                                                              | Serum EV                  | Inflammation-associated                      | LN discrimination                             | [32]          |

**Table 2:** Reported diagnostic/prognostic performance of candidate microRNA biomarkers

| Candidate                            | Specimen   | Reported performance                                                            | Endpoint                                       | Refs |
|--------------------------------------|------------|---------------------------------------------------------------------------------|------------------------------------------------|------|
| miR-146a                             | Serum      | 77.8% sensitivity; 73.3% specificity at reported cutoff                         | SLE vs control (Middle Euphrates cohort)       | [14] |
| miR-146a                             | Urinary EV | AUC 0.82                                                                        | LN diagnosis; activity; flare prediction       | [28] |
| miR-101-3p + miR-144-5p + miR-15a-5p | Plasma EV  | AUC 0.964                                                                       | LN discrimination                              | [31] |
| miR-497-5p + miR-6515-5p             | Serum EV   | AUC 0.798                                                                       | LN vs SLE without LN                           | [32] |
| miR-135b-5p                          | Urinary EV | AUC 0.783                                                                       | Response to LN therapy                         | [29] |
| Circulating miRNA panels (pooled)    | Blood      | Pooled sensitivity approximately 0.85; specificity approximately 0.83; AUC 0.91 | LN diagnosis (systematic review/meta-analysis) | [39] |

**Table 3:** miRNA-directed therapeutic strategies in preclinical development

| Therapeutic strategy | Target               | Vehicle                                  | Mechanism                                   | Stage/challenge                                   | Refs    |
|----------------------|----------------------|------------------------------------------|---------------------------------------------|---------------------------------------------------|---------|
| miRNA mimic          | miR-146a             | LNP / EV concept                         | Restore anti-inflammatory feedback          | Preclinical; delivery specificity/off-target risk | [40-42] |
| AntagomiR/LNA        | miR-21               | Nucleic-acid delivery                    | Reduce Tfh/inflammatory signaling           | Preclinical (MRL/lpr mice)                        | [24,40] |
| AntagomiR/LNA        | miR-150              | LNA inhibitor                            | Reduce renal fibrosis/inflammation          | Preclinical LN model                              | [20]    |
| Agomir               | miR-150-5p           | Synthetic agomir                         | Suppress mDC TREM-1 signaling               | Preclinical pristane-induced lupus                | [21]    |
| EV delivery          | miR-146a / miR-16-5p | Engineered/adipose-derived stem cell EVs | Immune-cell modulation; restore homeostasis | Experimental                                      | [41,43] |

**Table 4:** Evidence hierarchy for interpreting microRNA claims in SLE

| Evidence tier          | What is demonstrated                                      | SLE miRNA example                           | Translational meaning                           |
|------------------------|-----------------------------------------------------------|---------------------------------------------|-------------------------------------------------|
| 1. Association         | Differential expression in patients vs controls           | Serum/PBMC miR-146a                         | Candidate generation; no causal claim justified |
| 2. Mechanism           | Perturbation plus target/phenotype validation             | miR-21/miR-148a to DNMT1 axis               | Supports biological mechanism                   |
| 3. Analytical validity | QC, efficiency, LOD/LOQ, reproducibility                  | MIQE 2.0-compliant assay                    | Shows the measurement itself is reliable        |
| 4. Clinical validation | Independent/prospective cohorts with predefined endpoints | LN activity/flare signatures                | Required before clinical adoption               |
| 5. Clinical utility    | Improves clinical decisions or outcomes                   | Not yet established for any SLE miRNA assay | Highest translational standard; not yet met     |

## 8. Why Clinical Translation Has Stalled: Six Bottlenecks

### 8.1. Pre-Analytical Variability

Collection tube, processing time, centrifugation protocol, platelet depletion, hemolysis and storage conditions can each independently alter the measured miRNA profile, yet are inconsistently reported across studies [35-38].

### 8.2. Normalization Instability

No single endogenous reference is universally valid across serum, plasma, PBMC and urinary EV assays, and normalization choice can materially change which comparisons reach statistical significance [39,45].

### 8.3. Compartment Mismatch

An extracellular serum signal cannot automatically be interpreted as a direct readout of a particular immune-cell state; the miR-146a example in Section 5.1 illustrates how compartment mismatch alone can generate apparently contradictory literature.

### 8.4. Treatment Confounding

Glucocorticoids, antimalarials, immunosuppressants and biologic agents may each alter immune-cell composition and inflammatory gene programs, yet treatment exposure is inconsistently reported or adjusted for in the biomarker literature reviewed here.

### 8.5. Lack of Prospective Clinical Utility

Many studies stop at case-control ROC analysis; genuine translation requires external validation in an independent cohort and, ultimately, prospective validation against predefined clinical endpoints.

### 8.6. Underdeveloped Clinical Validation and Statistical Design

The field should move beyond case-control ROC curves. Diagnostic studies should use clinically relevant comparator groups (e.g., active LN versus inactive SLE without renal involvement, rather than SLE versus healthy controls), predefined thresholds, blinded testing where feasible, internal validation and independent external cohorts. Prognostic applications require longitudinal sampling, because a marker associated with prevalent disease is not necessarily predictive of a future flare. Candidate models should be evaluated for incremental value over anti-dsDNA, C3/C4, proteinuria, creatinine/eGFR and SLEDAI/British Isles Lupus Assessment Group (BILAG) trajectories, and calibration and decision-curve analysis are appropriate once a miRNA signature is proposed for clinical decision support. A 2025 systematic review and meta-analysis of circulating miRNAs in LN diagnosis reported a pooled sensitivity of 0.85, specificity of 0.83 and AUC of 0.91, while explicitly emphasizing heterogeneity across included studies and the need for prospective multicenter validation [39] - a conclusion this review endorses.

## 9. Toward a Precision-Medicine Framework

A clinically realistic strategy should integrate four layers of information rather than relying on a single miRNA measurement in isolation. Layer 1 is the miRNA signature itself, ideally a compartment-specific, multi-analyte panel rather than a single miRNA. Layer 2 is the immune endotype - for example IFN-high, B-cell/plasmablast-dominant, T-cell/Th17-dominant, or renal-inflammatory - as discussed in

Section 5.4. Layer 3 comprises conventional clinical biomarkers such as anti-dsDNA, C3/C4, creatinine and proteinuria. Layer 4 comprises longitudinal outcomes, including SLEDAI/BILAG trajectory, flare, remission and treatment response. The output of such a model should be probabilistic and phenotype-oriented - for example, an estimated probability of flare within six months within a defined endotype - rather than a binary "SLE positive/negative" classification, which no single miRNA assay is positioned to deliver reliably given the heterogeneity documented throughout this review.

## 10. Therapeutic Opportunities and Challenges

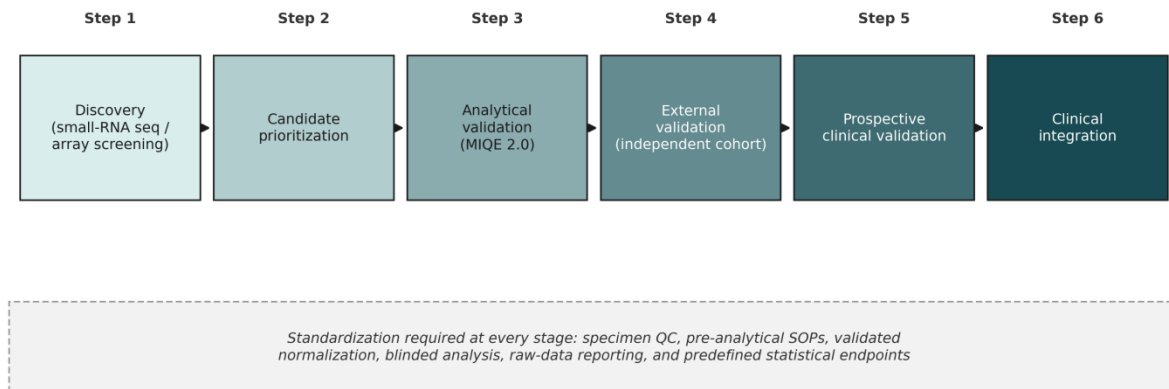
miRNA mimics can theoretically restore deficient regulatory miRNAs, whereas antagomiRs or locked nucleic acid (LNA) inhibitors can suppress pathogenic miRNAs (Table 3). Experimental evidence supports miR-21 inhibition in lupus-prone mice, LNA-mediated miR-150 inhibition in LN models, and miR-150-5p agonism in pristane-induced lupus [20,21,24]. EVs are attractive natural RNA carriers and lipid nanoparticles provide a scalable delivery platform, but tissue targeting, biodistribution, immunogenicity, off-target repression and preservation of host defense remain major obstacles [41-44,51]. A fundamental specificity problem underlies all of these approaches: the same miRNA may have a protective role in one cell type and a pathogenic or compensatory role in another, so systemic delivery risks unintended effects even when the target choice is mechanistically sound. Delivery vehicles must achieve adequate exposure in the intended immune or renal compartment while minimizing hepatic sequestration, innate RNA sensing, unintended target repression and interference with normal host defense. Current EV and nucleic-acid delivery research supports the general feasibility of RNA transport but does not yet establish clinical efficacy for miRNA-based therapy in SLE; miRNA therapeutics accordingly remain experimental in this disease.

## 11. Methodological Standards for Clinical Translation

A translational standard operating procedure for SLE miRNA biomarker studies should specify: specimen type and anticoagulant; time from collection to processing; platelet-control strategy; hemolysis assessment (e.g., spectrophotometric or miR-451a/miR-23a ratio-based); storage temperature and freeze-thaw history; extraction method and kit lot; spike-in control strategy; reverse-transcription chemistry; validated reference-gene strategy specific to the specimen type; technical replicates; no-template and no-reverse-transcriptase controls; assay amplification efficiency; analytical sensitivity (LOD/LOQ); raw quantification-cycle (Cq) values made available for independent reanalysis; and predefined statistical analysis plans, ideally registered before unblinding. MIQE 2.0 provides the relevant framework for transparent qPCR reporting [45,47,48], and EV-focused biomarker studies should additionally follow MISEV2023 principles for EV characterization [51]. Adoption of both frameworks as a condition of publication for SLE miRNA biomarker studies would substantially improve cross-study comparability and materially shorten the path to clinically credible signatures. SLE is best understood as a systems-level disorder rather than a disease driven by a single cytokine or immune-cell population. Genetic susceptibility interacts with environmental triggers and epigenetic remodeling to alter

nucleic-acid sensing, antigen presentation, lymphocyte activation, cytokine production, apoptosis and clearance of cellular debris. Environmental and psychosocial stressors may also interact with metabolic and biological pathways, illustrating how external exposures and physiological stress can contribute to complex, interconnected disease processes [60]. The resulting interferon-rich, immune-complex-laden environment feeds back into transcriptional and post-

transcriptional regulation, creating a self-reinforcing network rather than a linear pathway [1-6,59]. Environmental and behavioral exposures may further interact with physiological and molecular pathways, illustrating the broader systems-level nature of complex disease processes in which biological, environmental, and behavioral factors can converge to influence disease-related outcomes [61].



**Fig 3:** Recommended translational roadmap from microRNA discovery to precision-medicine integration in SLE. Each step (discovery, candidate prioritization, analytical validation, external validation, prospective clinical validation, clinical integration) requires standardized specimen quality control, harmonized pre-analytics, validated normalization, blinded analysis and transparent raw-data/statistical reporting throughout. Most published SLE miRNA biomarker studies to date have not progressed beyond Steps 1-3.

## 12. Limitations of This Review

This is a critical narrative review rather than a systematic review or meta-analysis. PubMed was searched for English-language articles from 2020 to mid-2026 using combinations of “systemic lupus erythematosus,” “lupus nephritis,” “microRNA,” and related terms, supplemented by reference-list hand-searching. Study selection was not conducted by independent reviewers, and formal risk-of-bias tools were not applied. Several cited cohorts are single-center and modestly powered, so reported diagnostic performance values should be regarded as hypothesis-generating. Publication bias likely favors positive associations, and inconsistencies in miRNA nomenclature (e.g., -5p/-3p arms) may contribute to apparent discrepancies across studies.

## 13. Concluding Remarks and Future Directions

The evidence reviewed here supports miRNAs as important network-level regulators that link epigenetic state, innate nucleic-acid sensing, T- and B-cell differentiation, inflammatory feedback and organ injury in SLE - but not as interchangeable, standalone diagnostic biomarkers. miR-146a is the clearest illustration of this principle: the same biologically important miRNA shows different directions and diagnostic performance across serum, whole blood, PBMC and urinary EV studies, and reduced serum or intracellular expression can coexist with increased urinary/exosomal expression during active renal disease because these measurements interrogate different biological compartments (Section 5.1). The Middle Euphrates study by Shlash *et al.* adds valuable regional evidence for serum miR-146a [14], while international LN studies provide stronger organ-proximate evidence for urinary and EV-associated molecular phenotypes [29,31,33].

The field should move beyond compiling further lists of differentially expressed miRNAs toward multicenter,

prospective, compartment-specific signatures built on harmonized pre-analytics, validated normalization, and MIQE 2.0/MISEV2023-compliant reporting (Sections 6, 8 and 11). The most realistic near-term clinical endpoint is a composite molecular score - combining a validated miRNA signature with an immune endotype, conventional clinical biomarkers and longitudinal outcome data (Section 9) - predicting disease activity, organ involvement or treatment response. Such assays should complement, rather than replace, clinical assessment and renal histopathology; for LN specifically, urinary EV-miRNA signatures are the most promising organ-proximal candidates identified in this review, but current evidence remains insufficient to substitute for biopsy or established clinical evaluation.

Future studies should prioritize harmonized standard operating procedures, explicit hemolysis and platelet quality control, validated normalization strategies, MISEV2023-compliant EV characterization, MIQE 2.0-compliant qPCR reporting, and prospective multicenter validation against clinically relevant comparator groups. Therapeutic development should move from proof-of-concept miRNA manipulation toward genuinely cell- and tissue-targeted delivery systems capable of resolving the specificity problem described in Section 10. The most defensible future role for miRNAs in SLE is therefore as components of reproducible, multi-analyte molecular endotypes that explain disease heterogeneity and improve longitudinal risk stratification - not as isolated binary diagnostic labels.

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#### **How to Cite This**

Shlash AAA, AL hadrawi KK, Hussein JM. MicroRNA networks in systemic lupus erythematosus: from compartment-specific biomarkers to precision immune endotypes. *Int J Biol Biomed Res.* 2026;2(5):51-62. doi:10.54660/IJBBR.2026.2.5.51-62.

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