Volume 3 Issue 7
www.westlandpublishers.com

ISSN: 3066-3822

WestLand Publishers

Digital Journal of Science (DJS)

Mini Review

Systemic Lupus Erythematosu (SLE)

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Received Date: 26 August, 2026 ; **Published Date:** 09 September, 2026

Keywords:
Systemic lupus erythematosus; transcriptomics; gene expression profiling; biomarkers; interferon signature; single-cell RNA sequencing; precision medicine; machine learning

Citation:
Oktay E* (2026) Systemic Lupus Erythematosu (SLE). Digital J Sci 3(7): 179.

DOI: 10.63592/DJS/179

Abstract

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease characterized by remarkable clinical heterogeneity and unpredictable disease course. Current diagnostic frameworks rely on clinical criteria and serological markers, which often fail to capture early disease, monitor subclinical activity, or predict treatment response. Transcriptomics the genome-wide measurement of RNA transcripts, has emerged as a transformative tool for dissecting the molecular complexity of SLE. Blood and tissue transcriptomic profiling has revealed a core interferon (IFN) signature, neutrophil and plasmablast modules, and metabolic dysregulation that correlate with disease activity and organ involvement. Single-cell RNA sequencing further resolves cell-type-specific contributions, refining our understanding of pathogenesis. In diagnostics, transcriptomic panels and machine-learning classifiers can distinguish SLE from other rheumatic diseases with high accuracy, while longitudinal transcriptomic monitoring improves flare prediction and renal outcome stratification. Therapeutically, molecular signatures are now guiding the use of targeted biologics such as anifrolumab (anti-IFN receptor) and belimumab (anti-BAFF), with emerging data supporting transcriptome-based patient selection. Despite challenges in standardization, cost, and translation, integration of transcriptomics with multi-omics and artificial intelligence promises a new era of precision medicine in SLE. This presentation reviews current transcriptomic insights, their clinical applications, and the road ahead for routine implementation.

Introduction

Systemic lupus erythematosus (SLE) affects approximately 20–150 per 100,000 individuals worldwide, predominantly women of childbearing age. The disease can involve virtually any organ, and its course fluctuates between flares and remission, making clinical management challenging. The 2019 EULAR/ACR classification criteria, while improving specificity, rely heavily on clinical manifestations and autoantibody profiles, which may manifest late or lack sensitivity for early or atypical disease. Consequently, diagnostic delay averages several years, and current laboratory tests (anti-dsDNA, complement levels) correlate imperfectly with disease activity. Furthermore, treatment decisions remain mostly empirical: broad-spectrum immunosuppression is used with varied efficacy and significant toxicity. A molecular understanding that complements clinical assessment is urgently needed. Transcriptomics, the study of the complete set of RNA transcripts, has provided a systems-level view of SLE pathogenesis. Over the past two decades, microarray and RNA-sequencing (RNA-seq) analyses of peripheral blood, isolated cell populations, and tissue biopsies have uncovered a

wealth of differentially expressed genes and co-expressed modules. These transcriptomic signatures reflect the coordinated activity of immune pathways and can serve as diagnostic biomarkers, prognostic tools, and pharmacodynamic markers to guide therapy. The advent of single-cell RNA-seq (scRNA-seq) has further dissected cellular heterogeneity, revealing that seemingly uniform clinical phenotypes can harbor distinct molecular cell states. With the growing availability of large-scale transcriptomic datasets and machine-learning algorithms, the vision of transcriptome-guided precision medicine in SLE is becoming tangible. This presentation provides an overview of current transcriptomic methodologies, their diagnostic and therapeutic applications in SLE, and the main hurdles to clinical adoption [1].

Discussion

Transcriptomic technologies: from bulk to single cells

The landscape of transcriptomic profiling in SLE has evolved rapidly. Early pioneering studies used microarray platforms to profile peripheral blood mononuclear cells (PBMCs) or whole blood, yielding thousands of gene measurements at relatively low cost. Microarrays identified the dominant interferon (IFN)-α-induced gene signature as a hallmark of SLE, along with signatures of granulopoiesis, plasmablasts, and lymphopenia. RNA-seq later supplanted microarrays by providing unbiased coverage of the transcriptome, detection of alternative splicing events, non-coding RNAs, and low-abundance transcripts. RNA-seq also allows allele-specific expression analysis, relevant for understanding genetic risk variants. More recently, scRNA-seq has enabled profiling of individual immune cells, revealing that the bulk IFN signature derives from specific cell types, such as classical monocytes and plasmacytoid dendritic cells, and not others. Mass cytometry (CyTOF) combined with RNA-seq (CITE-seq) adds surface protein information, linking transcriptomes to immunophenotypes. Spatial transcriptomics is beginning to map gene expression in tissue sections, promising insights into kidney, skin, and central nervous system lupus. Each technology has trade-offs in throughput, cost, and resolution, but collectively they have built a detailed molecular atlas of SLE [2].

Transcriptomic Signatures in SLE Diagnosis

The blood transcriptome of SLE patients is dominated by a type I interferon (IFN) gene signature, detectable in approximately 60–80% of adults and up to 90% of children. The signature includes genes such as IFIT1, MX1, ISG15, OAS1, and IFI44L, reflecting activation of the IFN-α/β receptor pathway. Although not perfectly sensitive, this signature has high specificity for SLE compared with healthy controls and has been proposed as a diagnostic biomarker. However, the IFN signature is also present in other immune-mediated diseases (e.g., dermatomyositis, systemic sclerosis, primary Sjögren's syndrome), so the diagnosis cannot rely on it alone. Researchers have thus developed multi-modular signatures that capture additional pathways aberrant in SLE. The landmark Chaussabel and Pascual groups described a modular transcriptional framework consisting of dozens of co-expressed gene clusters, including modules for inflammation, plasmablasts, neutrophils, myeloid lineage, B cells, T cells, erythropoiesis, and the cell cycle. By quantifying these modules, a composite score can discriminate SLE from healthy individuals and from other diseases with high accuracy. For instance, the modular combination of IFN, plasmablast, neutrophil, and B-cell modules reached an area under the curve (AUC) >0.95 in some cohorts [3]. Machine learning has further refined diagnostic classifiers. A recent study used whole-blood RNA-seq data from over 3,000 samples (SLE and other rheumatic diseases) to train a random forest classifier using 25 gene expression ratios. This test, now commercialized as a CLIA-validated molecular diagnostic, distinguishes SLE from non-SLE connective tissue diseases with excellent performance (AUC ~0.90) and performs well even in patients on immunosuppressive therapy. Another classifier, based on a 14-gene panel plus anti-dsDNA, achieved comparable discriminatory power. These molecular tests can potentially shorten the diagnostic delay in ambiguous cases [2, 3]. Transcriptomics of organ-specific tissue – particularly kidney biopsies – provides complementary information. In Lupus Nephritis (LN), intrarenal transcriptomics better reflects local inflammation and damage than blood. Tubulointerstitial gene expression of cytokines, matrix metalloproteinases, and fibrosis-related genes correlates with histologic activity and chronicity indices. A landmark study by the Accelerating Medicines Partnership (AMP) in SLE used scRNA-seq on kidney biopsies to reveal that distinct immune infiltrates (e.g., myeloid cells, T cells, B cells, and plasma cells) correlate with different LN histologic classes and prognosis. A molecular classification of LN based on tubular and glomerular transcriptomics is merging with histopathology to refine therapeutic decisions [3].

Prognostic Value and Disease Monitoring

Beyond diagnosis, transcriptomic signatures hold promise for predicting flares, organ damage, and treatment outcomes. The IFN signature, particularly when sustained over time, correlates with higher disease activity and an increased risk of future severe flares. A high neutrophil

module score and elevated granulopoiesis signature at baseline predicted renal flare in predominantly African American cohorts, independent of anti-dsDNA and complement. Conversely, a high plasmablast signature was associated with constitutional and mucocutaneous flares. In a prospective longitudinal study of SLE patients, shifts in blood transcriptomic modules preceded clinical flare onset by several weeks, suggesting a potential window for preventive intervention [3, 4]. In lupus nephritis, the renal transcriptomic profile provides prognostic granularity beyond standard proteinuria and serology. Tubulointerstitial expression of genes related to fibrosis (e.g., COL1A1, TGFB1) at the time of biopsy predicted progressive renal function decline, even in patients with moderate histologic activity. The previously mentioned AMP network identified a "fibrotic" molecular signature that correlated with poor renal outcomes, and an "inflammatory" signature that responded better to standard immunosuppression. Integrating blood and urine transcriptomics may improve non-invasive monitoring. Urinary messenger RNA and microRNA profiles, particularly those of podocyte damage (nephrin, podocin) and tubular injury (NGAL, KIM-1), correlate with histologic activity and predict treatment response. Although not yet used in routine care, multiplex urinary transcriptomic panels are being evaluated in clinical trials. Transcriptomic monitoring is also valuable for assessing subclinical disease in patients who appear clinically quiescent. Serologically active but clinically quiescent (SACQ) patients pose a dilemma: they have elevated autoantibodies but no symptoms. Blood transcriptomics in SACQ individuals can reveal ongoing IFN activation and plasmablast expansion, identifying those at risk of imminently developing clinical manifestations, thereby aiding in preventive therapy decisions [4, 5].

Transcriptomics-Guided Treatment Strategies

The ultimate goal of transcriptomic profiling is to inform therapeutic choices, moving from trial-and-error to targeted precision medicine. The clearest success story is the development of anifrolumab, a monoclonal antibody blocking the type I IFN receptor. Approval was based on phase III trials demonstrating efficacy in reducing overall disease activity, particularly in patients with a high IFN gene signature at baseline. Pre-specified transcriptomic analysis showed that anifrolumab neutralized the IFN signature across a broad panel of 21 genes, and patients with the highest signature experienced the greatest clinical benefit. This pharmacodynamic marker is now routinely measured in trials to confirm target engagement and to enrich the study population [5]. B-cell targeted therapies provide another illustration. Belimumab, a BAFF inhibitor, has proven efficacy in SLE, yet response is variable. Baseline transcriptomic profiles enriched for B-cell and plasmablast modules, as well as high expression of BAFF-related survival genes, predict better clinical response to belimumab. Similarly, rituximab, though failing in randomized controlled trials, shows real-world benefit in patients with high B-cell–predominant gene expression, especially those with active proliferative LN. The BEAT-LUPUS and RINGO trials are incorporating molecular signatures to prospectively select patients for B-cell depletion [4, 5].

Transcriptomics is also accelerating new target discovery. Whole-blood RNA-seq in large, multi-ancestral SLE cohorts has revealed upregulation of oxidative phosphorylation, mTORC1 signaling, and NETosis-related genes. Targeting mTOR with sirolimus in a subset of SLE patients showed clinical improvement, accompanied by normalization of T-cell transcriptomic profiles. Inhibition of the JAK–STAT pathway, downstream of many cytokine receptors, is being tested in SLE, and transcriptomic readouts of JAK activation (e.g., phosphorylated STAT1 signatures) are used as biomarkers of target engagement [5]. Single-cell transcriptomics has uncovered pathogenic cell states that can be therapeutically exploited. For instance, scRNA-seq of LN kidneys identified a population of infiltrating CD4+ T follicular helper-like cells with high BCL-6 expression that orchestrate local B-cell responses, suggesting that targeting follicular helper T cells or their interactions might be beneficial. Similarly, a population of CD16+ cytotoxic T cells with a senescent profile was expanded in SLE and correlated with vascular damage; senolytics could be considered in the future. Pharmacogenomic transcriptomics the study of gene expression predictors of drug toxicity – is nascent but important. For example, genetic variants in thiopurine methyltransferase (TPMT) are already used to adjust azathioprine dose; transcriptomic correlates of TPMT activity and metabolites could further refine dosing, especially in diverse populations [5, 6].

Challenges and Future Directions

Despite remarkable progress, several barriers hinder routine implementation of transcriptomics in SLE management. First, standardization is lacking: sample collection (whole blood, PBMCs, PAXgene tubes), RNA isolation, library preparation, sequencing depth, and bioinformatic pipelines vary across studies. Cross-institutional variability limits the generalizability of signatures. International consortia such as PRECISESADS and the AMP network are addressing this by harmonizing protocols and creating reference databases [7].

Second, the transcriptome is dynamic. A single snapshot may not capture the evolving nature of SLE. Dense, longitudinal sampling combined with wearable technology and e-health platforms could enable real-time molecular monitoring, but the cost and logistics are currently prohibitive for most settings.

Third, most transcriptomic studies have been performed in patients of European ancestry, yet SLE is more severe in African, Hispanic, and Asian populations. Ancestry-specific transcriptomic signatures exist; for example, the IFN signature is less pronounced in African-American patients, whereas neutrophil modules are more prominent. Future panels must be validated in multi-ethnic, real-world cohorts [6, 7].

Fourth, translating large-scale transcriptomic data to an individual-patient decision requires clinical decision support tools. Machine-learning models must be interpretable, seamlessly integrated into electronic health records, and endorsed by clinical guidelines. Regulatory frameworks for molecular diagnostic tests and therapeutic companion diagnostics are evolving but currently vary across jurisdictions [7]. The future will likely involve integration of transcriptomics with other omics layers – genomics (risk alleles, HLA types), epigenomics (DNA methylation, chromatin accessibility), proteomics (serum cytokines, autoantibody profiles), and metabolomics. Multi-omic integration can refine patient stratification further. For example, a recent multi-omic clustering of SLE patients identified distinct molecular subtypes that cut across traditional organ-based classifications: one subtype featured high IFN, another had neutrophil extracellular trap (NET) activation and cardiometabolic risk, and a third had T-cell exhaustion. These subtypes respond differently to standard care and might dictate personalized therapy.

Finally, artificial intelligence and deep-learning algorithms are being trained on massive transcriptomic datasets to predict flares, organ damage, and treatment responses. Such models, if embedded in point-of-care devices or cloud-based platforms, could empower clinicians to make data-driven decisions at the bedside [6, 7].

Conclusion

Transcriptomics has revolutionized our understanding of SLE as a molecularly heterogeneous disease. Blood and tissue transcriptomic signatures not only confirm the central role of type I interferon but also illuminate neutrophil, B-cell, T-cell, and metabolic pathways that contribute to organ damage. These molecular insights have led to the development of diagnostic classifiers that improve early and accurate diagnosis and have provided prognostic biomarkers for flare and renal outcome prediction. Most impactfully, transcriptomic profiling now guides the use of targeted biologics such as anifrolumab and belimumab, and it informs the repurposing of agents like mTOR inhibitors. While challenges of standardization, cost, and diverse population validity remain, ongoing international collaboration and technological advances are bringing transcriptomic tools closer to routine clinical practice. The next decade promises a shift from empirical immunosuppression to precision medicine in SLE, where treatment will be tailored to an individual's molecular fingerprint, ultimately improving outcomes and reducing toxicity [4,6,8,9].

Acknowledgements: I would like to thank Tuğçe OKTAY GÜNEŞ, General Manager and Electrical-Electronics Engineer of TOG ENGINEERING, for her financial support and contributions.

Financial Support and Sponsorship: None

Conflict of Interest: The author declares no conflict of interest.

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