

Epigenetic Biomarkers in Systemic Lupus Erythematosus: A Review

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Abstract

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disorder characterized by multisystem inflammation, immune dysregulation, and the production of autoantibodies against self-antigens. The disease exhibits a complex etiology involving genetic susceptibility, environmental triggers, hormonal imbalance, and immunological abnormalities. In recent years, epigenetic modifications have emerged as critical contributors to the pathogenesis and progression of SLE. Epigenetics refers to heritable changes in gene expression without alterations in the DNA sequence and includes mechanisms such as DNA methylation, histone modifications, and non-coding RNAs. These epigenetic changes influence immune cell function, cytokine production, and inflammatory pathways associated with autoimmune diseases. The present review aims to evaluate the role of major epigenetic biomarkers in SLE and their potential clinical applications in diagnosis, prognosis, and therapeutic intervention. The review discusses significant biomarkers including DNA hypomethylation patterns, histone acetylation abnormalities, microRNAs such as miR-21, miR-146a, and miR-155, as well as long non-coding RNAs implicated in lupus pathogenesis. Current evidence suggests that epigenetic biomarkers are closely associated with disease activity, organ involvement, and treatment response in SLE patients. The review concludes that epigenetic biomarkers hold significant promise for improving early diagnosis and personalized treatment strategies in SLE. However, further large-scale clinical studies are required to validate these biomarkers and translate them into routine clinical practice.

Keywords: Systemic Lupus Erythematosus, Epigenetics, DNA Methylation, Histone Modification, microRNA, Biomarkers, Autoimmune Disease

1. Introduction

1.1 Overview of Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE) is a chronic multisystem autoimmune disease characterized by abnormal immune responses against self-antigens, leading to inflammation and tissue damage in multiple organs. The disease may affect the skin, joints, kidneys, lungs, cardiovascular system, and central nervous system. SLE is marked by periods of remission and flare-ups, making its clinical management highly challenging. The hallmark feature of SLE is the production of autoantibodies, especially antinuclear antibodies (ANA), which contribute to immune complex deposition and organ injury. SLE predominantly affects women of reproductive age, suggesting a possible hormonal influence in disease development. The disease exhibits heterogeneous clinical manifestations ranging from mild dermatological symptoms to severe renal and neurological complications. Lupus nephritis remains one of the major causes of morbidity and mortality among SLE patients. Due to its variable presentation and unpredictable course, early diagnosis and effective disease monitoring are essential for improving patient outcomes.

1.2 Global and Indian Prevalence of SLE

SLE is recognized worldwide as a significant autoimmune disorder with varying prevalence across different populations and ethnic groups. Globally, the prevalence of SLE ranges between 20 and 150 cases per 100,000 individuals. Higher prevalence rates have been reported among African, Asian, and Hispanic populations compared to Caucasians. Women are affected approximately nine times more frequently than men, particularly during childbearing years.

In India, the prevalence of SLE has been steadily increasing due to improved diagnostic facilities and awareness. Studies indicate that SLE is more common among young females in urban populations. Indian patients often present with severe disease manifestations such as lupus nephritis and hematological abnormalities. Environmental factors, infections, socioeconomic conditions, and genetic susceptibility contribute to disease occurrence in the Indian population. The increasing burden of SLE highlights the need for advanced diagnostic biomarkers and personalized therapeutic approaches. Conventional laboratory markers often lack specificity and sensitivity in predicting disease activity, thereby emphasizing the importance of novel molecular biomarkers such as epigenetic signatures.

1.3 Pathophysiology of SLE

The pathophysiology of SLE is highly complex and involves interactions between genetic, immunological, hormonal, and environmental factors. Immune dysregulation leads to the loss of self-tolerance and the activation of autoreactive B cells and T cells. These immune cells produce autoantibodies against nuclear antigens, resulting in immune complex formation and chronic inflammation. Abnormal activation of innate and adaptive immune responses plays a central role in disease progression. Cytokines such as interferon-alpha (IFN- α), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α) contribute significantly to inflammatory pathways in SLE. Additionally, impaired clearance of apoptotic cells exposes intracellular antigens to the immune system, promoting autoantibody production. Genetic predisposition involving HLA genes and immune regulatory pathways contributes to disease susceptibility. However, genetics alone cannot fully explain the variability and progression of SLE. Recent evidence suggests that epigenetic mechanisms serve as an important link between environmental influences and gene expression changes associated with autoimmune responses.

1.4 Role of Genetics and Environment

Both genetic and environmental factors are crucial in the development of SLE. Several susceptibility genes related to immune regulation, complement pathways, and inflammatory responses have been identified in lupus patients. Genetic polymorphisms in HLA-DR2, HLA-DR3, STAT4, IRF5, and PTPN22 genes are strongly associated with increased disease risk. Environmental factors such as ultraviolet radiation, infections, smoking, stress, drugs, and hormonal influences can trigger disease onset in genetically predisposed individuals. Viral infections, particularly Epstein-Barr virus, have been implicated in immune activation and lupus pathogenesis. Exposure to environmental toxins may induce oxidative stress and epigenetic alterations that affect immune cell function. The interaction between genetic susceptibility and environmental triggers results in abnormal epigenetic modifications that regulate gene expression without altering DNA sequences. These epigenetic changes are increasingly recognized as major contributors to autoimmune disorders, including SLE.

1.5 Concept of Epigenetics

Epigenetics refers to reversible and heritable changes in gene expression that occur without modifications in the nucleotide sequence of DNA. Major epigenetic mechanisms include DNA methylation, histone modifications, chromatin remodeling, and non-coding RNAs such as microRNAs

and long non-coding RNAs. DNA methylation involves the addition of methyl groups to cytosine residues, usually resulting in gene silencing. Histone modifications, including acetylation and methylation, influence chromatin structure and transcriptional activity. Non-coding RNAs regulate post-transcriptional gene expression and immune signaling pathways. Epigenetic processes are essential for normal immune function and cellular differentiation. Dysregulation of these mechanisms may lead to abnormal immune activation and autoimmune disease development. Unlike genetic mutations, epigenetic alterations are potentially reversible, making them attractive targets for therapeutic intervention.

1.6 Importance of Epigenetic Biomarkers in Disease Diagnosis and Prognosis

Epigenetic biomarkers have gained considerable attention as promising tools for the diagnosis, prognosis, and monitoring of autoimmune diseases. In SLE, conventional biomarkers such as ANA and anti-dsDNA antibodies often fail to accurately predict disease flares and organ involvement. Epigenetic biomarkers offer greater specificity and may provide insights into disease mechanisms and progression. DNA hypomethylation in immune cells has been strongly associated with lupus activity and increased expression of inflammatory genes. Similarly, altered expression of microRNAs and histone modifications contributes to immune dysregulation in SLE patients. These biomarkers may help identify disease subtypes, predict treatment response, and monitor therapeutic outcomes. The reversible nature of epigenetic modifications also opens new possibilities for targeted therapies. Drugs targeting DNA methylation and histone deacetylation pathways are currently being explored for their therapeutic potential in autoimmune disorders.

1.7 Objectives of the Review

1. To examine the role of epigenetic mechanisms in the pathogenesis of Systemic Lupus Erythematosus.
2. To analyze major epigenetic biomarkers associated with SLE.
3. To evaluate the clinical significance of DNA methylation, histone modifications, and non-coding RNAs in disease diagnosis and prognosis.

2. Literature Review

Epigenetic mechanisms have emerged as crucial regulators of immune system function and autoimmune disease development. Autoimmune diseases occur when the immune system loses tolerance toward self-antigens, resulting in chronic inflammation and tissue damage. Recent studies suggest that epigenetic modifications influence immune cell differentiation, cytokine production, and inflammatory signaling pathways. Unlike genetic mutations, epigenetic changes are dynamic and reversible, making them significant contributors to disease progression and therapeutic intervention. Major epigenetic mechanisms include DNA methylation, histone modifications, and non-coding RNAs. These processes regulate gene expression without altering the DNA sequence. Environmental exposures such as infections, smoking, ultraviolet radiation, stress, and diet can induce epigenetic changes that trigger autoimmune responses in genetically susceptible individuals. In autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, systemic sclerosis, and SLE, abnormal epigenetic patterns have been widely reported. These changes affect immune tolerance, T-cell activation, B-cell function, and cytokine expression. Epigenetic dysregulation therefore acts as a connecting link between environmental triggers and genetic susceptibility in autoimmune pathogenesis.

DNA Methylation Abnormalities in SLE

DNA methylation is one of the most extensively studied epigenetic mechanisms in SLE. It involves the addition of methyl groups to cytosine residues within CpG islands, leading to suppression of gene transcription. Hypomethylation of DNA in immune cells has been identified as a hallmark feature of lupus. Studies have demonstrated reduced DNA methylation in CD4⁺ T cells of SLE patients. This hypomethylation results in overexpression of immune-related genes such as CD70, CD11a, perforin, and interferon-regulated genes, promoting autoreactivity and inflammation. Reduced activity of DNA methyltransferases (DNMTs), especially DNMT1, has been associated with lupus pathogenesis. The IFI44L promoter methylation biomarker has shown promising diagnostic potential for distinguishing SLE patients from healthy individuals and other autoimmune diseases. Hypomethylated interferon-related genes are strongly correlated with disease activity and lupus nephritis. Environmental factors such as ultraviolet exposure and oxidative stress may contribute to DNA methylation abnormalities in lupus patients. These findings suggest that altered DNA methylation patterns may serve as valuable biomarkers for early diagnosis and disease monitoring in SLE.

Histone Modifications in Lupus Pathogenesis

Histones are nuclear proteins responsible for organizing DNA into chromatin. Post-translational modifications of histones regulate chromatin accessibility and gene transcription. Histone modifications include acetylation, methylation, phosphorylation, and ubiquitination. In SLE, abnormal histone modifications contribute to dysregulated immune responses and inflammatory gene expression. Increased histone acetylation has been observed in lupus T cells, leading to enhanced transcription of pro-inflammatory cytokines and autoantibody production. Histone deacetylases (HDACs) play a major role in maintaining immune balance, and altered HDAC activity has been linked to lupus progression. Histone methylation abnormalities also influence the expression of genes involved in immune regulation. Certain histone marks are associated with increased interferon signaling and inflammatory pathways in lupus patients. Autoantibodies against histone proteins are commonly detected in SLE and contribute to immune complex formation. Recent research suggests that HDAC inhibitors may have therapeutic potential in reducing inflammation and restoring immune tolerance in lupus. Therefore, histone modifications represent important epigenetic biomarkers and therapeutic targets in SLE.

Role of microRNAs in SLE

MicroRNAs (miRNAs) are small non-coding RNA molecules that regulate gene expression at the post-transcriptional level. They play essential roles in immune cell differentiation, apoptosis, cytokine signaling, and inflammatory responses. Dysregulated miRNA expression has been strongly implicated in lupus pathogenesis. Several miRNAs including miR-21, miR-146a, miR-155, miR-125a, and miR-148a have been associated with SLE. miR-21 promotes DNA hypomethylation by suppressing DNMT1 expression, thereby contributing to autoreactive T-cell activation. miR-146a regulates interferon signaling pathways and inflammatory cytokine production, while reduced expression of miR-146a has been linked to increased disease activity. miR-155 is involved in B-cell activation and autoantibody production. Overexpression of miR-155 contributes to inflammatory responses and tissue damage in lupus patients. Similarly, altered levels of miR-125a affect cytokine regulation and immune cell function. Circulating miRNAs have gained attention as non-invasive biomarkers for SLE diagnosis and prognosis. Their stability in blood and body fluids makes them suitable candidates for clinical applications. Researchers are also investigating miRNA-targeted therapies for autoimmune disease management.

Long Non-Coding RNAs (lncRNAs) and SLE

Long non-coding RNAs (lncRNAs) are RNA molecules longer than 200 nucleotides that regulate gene expression through various molecular mechanisms. Emerging evidence indicates that lncRNAs play significant roles in immune regulation and autoimmune disease progression. Several lncRNAs such as NEAT1, GAS5, MALAT1, and TUG1 have been associated with SLE. NEAT1 promotes inflammatory cytokine production and activation of immune pathways in lupus patients. Increased expression of NEAT1 has been linked to disease severity and organ involvement. GAS5 functions as an immune regulatory lncRNA and may influence apoptosis and T-cell activity. Reduced GAS5 expression has been observed in lupus patients and is associated with disease progression. MALAT1 contributes to inflammatory signaling and immune dysregulation in SLE. lncRNAs interact with microRNAs and transcription factors to regulate immune responses. Due to their disease-specific expression patterns, lncRNAs may serve as potential biomarkers for lupus diagnosis and prognosis.

Methodology

The present study was conducted as a narrative review focusing on the role of epigenetic biomarkers in Systemic Lupus Erythematosus (SLE). The review aimed to critically analyze and summarize existing scientific evidence related to epigenetic alterations involved in the pathogenesis, diagnosis, prognosis, and therapeutic implications of SLE. A narrative review design was selected because it allows comprehensive discussion and of diverse findings from multiple studies concerning molecular and immunological mechanisms associated with lupus. Relevant literature was collected from internationally recognized scientific databases including PubMed, Scopus, Web of Science, and Google Scholar. These databases were selected due to their extensive coverage of biomedical, immunological, and molecular biology research articles. Published peer-reviewed articles, review papers, clinical studies, and experimental investigations related to epigenetic biomarkers in SLE were included in the review. The literature search primarily focused on studies published between 2015 and 2026 to ensure inclusion of recent advances and updated findings in epigenetic research. The inclusion criteria for selecting studies involved articles published in English language, studies directly related to epigenetic mechanisms in SLE, investigations involving DNA methylation, histone modifications, microRNAs, and long non-coding RNAs, and studies reporting diagnostic, prognostic, or therapeutic relevance of epigenetic biomarkers. Both human and experimental studies were considered if they provided significant information regarding lupus-associated epigenetic alterations. Review articles discussing molecular pathways and biomarker discovery in autoimmune diseases were also included for conceptual understanding. The exclusion criteria included duplicate studies, conference abstracts without full text, articles unrelated to SLE, studies lacking sufficient scientific evidence, and publications focused exclusively on non-epigenetic mechanisms. Articles published in languages other than English and studies with inadequate methodological details were also excluded from the review process.

Epigenetic Biomarkers in SLE

Table 4.1 DNA Methylation Biomarkers in Systemic Lupus Erythematosus

Biomarker	Epigenetic Alteration	Mechanism in SLE	Clinical Significance
CD4+ T Cell DNA	Hypomethylation	Promotes autoreactive T-cell activation and inflammatory cytokine production	Associated with disease severity and immune dysregulation

IFI44L Gene	Reduced methylation	Activates interferon signaling pathways	Useful in early diagnosis of SLE
CD70	Hypomethylation	Enhances B-cell activation and autoantibody production	Correlates with disease activity
CD11a	Hypomethylation	Increases immune cell adhesion and activation	Contributes to chronic inflammation
Perforin Gene	Hypomethylation	Promotes cytotoxic activity in immune cells	Linked with tissue damage

The table demonstrates that DNA hypomethylation is one of the most important epigenetic abnormalities observed in Systemic Lupus Erythematosus. Reduced methylation levels in immune cells lead to overexpression of inflammatory and immune-related genes, resulting in abnormal immune activation. IFI44L methylation emerged as a highly sensitive biomarker for lupus diagnosis due to its close association with interferon signaling pathways. Hypomethylation of CD70 and CD11a contributes significantly to autoantibody production and chronic inflammation. Overall, DNA methylation biomarkers are strongly associated with disease severity and progression in SLE patients.

Table 4.2 Histone Modification Biomarkers in SLE

Histone Biomarker	Alteration Observed	Functional Impact	Clinical Importance
Histone Acetylation	Increased acetylation	Enhances inflammatory gene expression	Associated with active disease
Histone H3 Modification	Abnormal methylation	Alters chromatin accessibility	Influences immune dysfunction
Histone H4 Acetylation	Increased acetylation	Promotes cytokine production	Linked with lupus nephritis
Histone Deacetylases (HDACs)	Reduced activity	Causes excessive immune activation	Potential therapeutic target
Histone Autoantibodies	Elevated levels	Immune complex formation	Indicator of autoimmune activity

Histone modifications significantly influence gene transcription and inflammatory signaling pathways in SLE. Increased histone acetylation leads to activation of inflammatory cytokines and autoreactive immune cells. Reduced activity of histone deacetylases contributes to persistent inflammation and immune imbalance. Histone-related biomarkers are not only useful in understanding disease mechanisms but also provide opportunities for therapeutic intervention through HDAC inhibitors. These findings highlight the role of chromatin remodeling in lupus pathogenesis.

Table 4.3 microRNA Biomarkers in SLE

microRNA	Expression Pattern	Biological Role	Clinical Relevance
miR-21	Increased	Promotes DNA hypomethylation and T-cell activation	Associated with disease progression
miR-146a	Reduced	Regulates inflammatory cytokines and interferon pathways	Marker of disease severity
miR-155	Increased	Enhances B-cell activation and inflammation	Linked with disease flares
miR-125a	Reduced	Controls immune signaling pathways	Associated with inflammatory imbalance
miR-148a	Increased	Suppresses DNA methyltransferase activity	Contributes to autoreactivity

microRNAs play a crucial role in regulating post-transcriptional immune responses in lupus patients. Altered expression of miR-21, miR-146a, and miR-155 significantly affects cytokine production, immune cell differentiation, and inflammatory pathways. Increased miR-21 and miR-155 expression promote autoimmune activation, while reduced miR-146a contributes to uncontrolled inflammatory responses. Since circulating microRNAs can be detected in blood samples, they have strong potential as non-invasive biomarkers for disease monitoring and prognosis.

Table 4.4 Long Non-Coding RNA Biomarkers in SLE

lncRNA Biomarker	Expression Pattern	Functional Role	Clinical Significance
NEAT1	Increased	Promotes inflammatory signaling pathways	Associated with lupus nephritis
GAS5	Reduced	Regulates apoptosis and immune responses	Linked with disease progression
MALAT1	Increased	Enhances cytokine production	Contributes to chronic inflammation
TUG1	Altered expression	Influences immune cell differentiation	Potential biomarker for SLE activity
lincRNA-p21	Reduced	Regulates p53-mediated apoptosis	Associated with immune dysfunction

Long non-coding RNAs have emerged as important epigenetic regulators in lupus pathogenesis. Increased expression of NEAT1 and MALAT1 contributes to activation of inflammatory pathways and tissue damage. Reduced GAS5 expression affects immune regulation and apoptosis, thereby promoting disease progression. The disease-specific expression patterns of lncRNAs make them promising biomarkers for diagnosis, prognosis, and therapeutic targeting in SLE.

Table 4.5 Association Between Epigenetic Biomarkers and Disease Activity

Biomarker Type	Association with Disease Activity	Organ Involvement
DNA Hypomethylation	Strongly associated with active disease	Lupus nephritis and skin involvement
Histone Acetylation	Correlates with inflammatory status	Joint and renal manifestations
miR-21	Increased during disease flares	Renal complications
miR-146a	Reduced in severe disease	Systemic inflammation
NEAT1	Elevated in active lupus	Kidney involvement

The table indicates that epigenetic biomarkers are closely related to disease activity and organ damage in lupus patients. Increased DNA hypomethylation and altered microRNA expression patterns are commonly observed during disease flares. Biomarkers such as miR-21 and NEAT1 show significant association with lupus nephritis, which is one of the most severe complications of SLE. These findings suggest that epigenetic profiling may help clinicians assess disease severity and predict organ involvement more accurately.

Table 4.6 Diagnostic and Prognostic Applications of Epigenetic Biomarkers

Biomarker	Diagnostic Utility	Prognostic Value
IFI44L Methylation	High sensitivity and specificity for SLE diagnosis	Predicts disease progression
miR-21	Useful in identifying active lupus	Indicates renal involvement
miR-146a	Supports inflammatory assessment	Predicts severe disease activity
Histone Autoantibodies	Confirms autoimmune activity	Associated with chronic inflammation
NEAT1	Biomarker for lupus nephritis	Indicates organ damage risk

Epigenetic biomarkers provide improved diagnostic accuracy compared to traditional serological markers in lupus patients. IFI44L methylation has emerged as one of the most reliable biomarkers for early diagnosis. microRNAs such as miR-21 and miR-146a are valuable in assessing disease severity and predicting organ complications. The prognostic value of these biomarkers may assist clinicians in monitoring treatment response and preventing disease progression.

Table 4.7 Therapeutic Implications of Epigenetic Targets in SLE

Therapeutic Target	Therapeutic Strategy	Expected Clinical Outcome
DNA Methylation Pathways	DNA methylation modulators	Restoration of immune tolerance
Histone Deacetylases	HDAC inhibitors	Reduction in inflammatory cytokines
miRNA Dysregulation	miRNA-targeted therapies	Suppression of autoimmune activation
lncRNA Pathways	RNA-based therapies	Improved immune regulation
Interferon Signaling Genes	Epigenetic suppression approaches	Reduced disease flares

The reversible nature of epigenetic modifications makes them attractive therapeutic targets in SLE management. Histone deacetylase inhibitors and DNA methylation modulators have shown promising anti-inflammatory effects in experimental studies. microRNA-based therapies may help regulate abnormal immune responses and reduce disease severity. Although these therapeutic strategies are still under investigation, epigenetic-targeted treatments may significantly contribute to personalized medicine approaches in lupus care.

5. Discussion

Epigenetic biomarkers have emerged as highly significant molecular indicators in understanding the pathogenesis, progression, diagnosis, and treatment of Systemic Lupus Erythematosus (SLE). Unlike traditional genetic mutations, epigenetic modifications are dynamic and reversible, making them highly valuable in autoimmune disease research. The present review highlights the major epigenetic mechanisms involved in lupus, including DNA methylation abnormalities, histone modifications, dysregulated microRNA expression, and altered long non-coding RNA activity. These biomarkers contribute to immune dysregulation, chronic inflammation, and autoantibody production, which are central features of SLE. Among the various epigenetic biomarkers, DNA methylation abnormalities are the most extensively studied and clinically relevant. Hypomethylation of immune-related genes in CD4+ T cells plays a major role in lupus pathogenesis by promoting autoreactive immune responses. Biomarkers such as IFI44L methylation have demonstrated excellent sensitivity and specificity for differentiating lupus patients from healthy individuals and other autoimmune diseases. Compared to conventional serological markers, methylation signatures provide improved accuracy in disease detection and activity monitoring. Histone modifications also contribute significantly to immune activation and inflammatory gene expression in SLE. Altered histone acetylation and abnormal histone deacetylase activity influence chromatin structure and promote overexpression of inflammatory cytokines.

MicroRNAs represent another highly promising group of epigenetic biomarkers due to their stability in body fluids and their role in regulating multiple immune pathways. miR-21, miR-146a, miR-155, and miR-125a have shown strong associations with disease activity, cytokine production, and organ involvement in lupus patients. Among these, miR-146a is particularly important because of its role in regulating interferon signaling pathways and inflammatory responses. Long non-coding RNAs such as NEAT1, GAS5, and MALAT1 have also emerged as important regulators of immune homeostasis and

inflammation. These molecules influence transcriptional regulation and interact with microRNAs to control autoimmune responses. A comparative analysis of different biomarkers indicates that each epigenetic mechanism contributes uniquely to lupus pathogenesis. DNA methylation biomarkers provide high diagnostic sensitivity and are strongly associated with disease progression. Histone modifications reflect inflammatory activation and chromatin remodeling processes, while microRNAs and long non-coding RNAs regulate post-transcriptional immune signaling. Combining multiple epigenetic biomarkers may therefore improve diagnostic precision and disease monitoring in SLE. Integrated biomarker profiling may also help identify disease subtypes and predict therapeutic response more effectively than single biomarkers alone.

The clinical relevance of epigenetic biomarkers in SLE is highly significant. Traditional biomarkers such as antinuclear antibodies and anti-double stranded DNA antibodies are useful for diagnosis but often lack specificity in predicting disease flares and organ involvement. Epigenetic biomarkers offer greater insight into disease mechanisms and may serve as reliable indicators of disease activity, severity, and treatment response. For example, altered methylation patterns and microRNA profiles are closely associated with lupus nephritis, which is one of the most severe complications of SLE. Monitoring these biomarkers may help clinicians identify high-risk patients and initiate early therapeutic intervention.

Findings

The present review identified significant epigenetic alterations involved in the pathogenesis and progression of Systemic Lupus Erythematosus (SLE). Epigenetic mechanisms including DNA methylation abnormalities, histone modifications, dysregulated microRNAs, and altered long non-coding RNAs were found to play central roles in immune dysregulation and chronic inflammation associated with lupus. These molecular alterations influence gene expression without changing the DNA sequence and contribute to the loss of immune tolerance, autoreactive lymphocyte activation, and autoantibody production. Among the major epigenetic alterations, DNA hypomethylation in CD4⁺ T cells emerged as one of the most important findings in lupus research. Reduced methylation levels promote overexpression of inflammatory and immune-related genes such as CD70 and CD11a, leading to abnormal immune activation. The IFI44L methylation signature was identified as one of the most promising biomarkers due to its high diagnostic sensitivity and specificity for distinguishing SLE patients from healthy individuals and other autoimmune diseases. Histone modifications, particularly abnormal histone acetylation and altered histone deacetylase activity, were also strongly associated with inflammatory responses and disease progression in lupus patients. These modifications influence chromatin structure and regulate inflammatory gene transcription, contributing to immune dysfunction.

Conclusion

Systemic Lupus Erythematosus (SLE) is a complex autoimmune disorder involving multifactorial interactions between genetic susceptibility, environmental triggers, hormonal influences, and immune dysregulation. Recent advances in epigenetic research have significantly improved the understanding of molecular mechanisms underlying lupus pathogenesis. The present review demonstrates that epigenetic alterations such as DNA methylation abnormalities, histone modifications, dysregulated microRNAs, and altered long non-coding RNAs play crucial roles in immune activation, inflammatory signaling, and autoantibody production in SLE patients. Among the identified biomarkers, DNA hypomethylation in immune cells and IFI44L methylation signatures have shown considerable diagnostic and prognostic potential. Histone modifications and microRNA dysregulation further contribute to disease progression and organ involvement. Long non-coding RNAs such as NEAT1, GAS5, and MALAT1 have emerged as novel regulators of immune responses and may serve as valuable biomarkers for disease monitoring. These findings highlight the growing importance of epigenetic mechanisms in lupus research and clinical practice. The review also emphasizes the clinical utility of epigenetic biomarkers in improving

early diagnosis, predicting disease activity, monitoring therapeutic response, and identifying high-risk patients. Compared to conventional serological markers, epigenetic biomarkers offer greater specificity and mechanistic insight into disease progression. Furthermore, the reversible nature of epigenetic modifications provides promising opportunities for the development of targeted therapies aimed at restoring immune balance and reducing chronic inflammation.

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