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Epigenetic Dysregulation and its Role in Immune-Mediated Diseases

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Immune-mediated diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS) and Inflammatory Bowel Disease (IBD: Crohn's Disease & Ulcerative Colitis) represent a significant global health burden characterized by a loss of immune tolerance and chronic inflammation. While genetic predisposition plays a crucial role, it does not fully account for disease pathogenesis, onset, or flare-ups. The emerging field of epigenetics provides a critical mechanistic link between genetic susceptibility and environmental triggers. This review synthesizes current evidence on how dysregulation of key epigenetic mechanisms, DNA methylation, histone modifications, and non-coding RNA expression, contributes to the breakdown of immune homeostasis. We detail the aberrant epigenetic landscapes in specific immune cell subsets (e.g., T cells, B cells, macrophages) across major autoimmune disorders. Furthermore, we explore the potential of epigenetic modifications as novel biomarkers for diagnosis, prognosis, and disease activity monitoring. Finally, we discuss the promising therapeutic avenue of "epigenetic therapy,"

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repurposing existing drugs and developing new compounds to reverse pathogenic epigenetic marks and restore immune tolerance.

Keywords: Epigenetics; autoimmunity; DNA methylation; histone modification; non-coding RNA; rheumatoid arthritis; systemic lupus erythematosus; multiple sclerosis; biomarkers; epigenetic therapy.

1. INTRODUCTION

Immune-mediated inflammatory diseases (IMIDs), encompassing a broad spectrum of conditions such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), and inflammatory bowel disease (IBD), represent a formidable challenge to global public health. These chronic, debilitating disorders are characterized by a pathological breakdown of self-tolerance, leading to uncontrolled immune activation against specific tissues or systemically, resulting in persistent inflammation and organ damage (Wilkinson & Shapiro, 2024). The collective prevalence of IMIDs is estimated to affect 5-10% of the population in developed nations, posing a significant economic and social burden due to long-term disability, reduced quality of life, and the need for lifelong medical management (Stroeks et al., 2025)

The etiological landscape of autoimmunity has long been conceptualized through the lens of genetic predisposition interacting with environmental triggers. The advent of genome-wide association studies (GWAS) has been instrumental, identifying over hundreds of susceptibility loci across various IMIDs. These studies have robustly confirmed the paramount importance of the major histocompatibility complex (MHC) region and highlighted key pathways involved in immune cell signaling, cytokine production, and lymphocyte activation (Ausserwinkler et al., 2025; Arneth, 2024). However, a critical paradox emerged from this genetic data: the identified risk alleles, while statistically significant, often confer only a modest increase in relative risk and exhibit low penetrance. This is most strikingly evidenced by the significant discordance rates observed in monozygotic (identical) twins, who share nearly 100% of their genetic sequence. For example, concordance rates for SLE, RA, and MS typically range from only 25% to 40%, leaving a substantial portion of disease risk unexplained by genetics alone (Khan et al., 2024; Ates et al., 2025). This compelling "heritability gap" strongly implies that non-genetic factors play a dominant role in determining whether a genetically susceptible individual will ultimately develop clinical disease.

This gap is bridged by epigenetics, a discipline that has revolutionized our understanding of gene regulation. Epigenetics refers to the study of heritable changes in gene expression and cellular phenotype that occur without alterations to the underlying DNA nucleotide sequence (Lin et al.,2024; Gibson et al., 2022). These mechanisms, primarily DNA methylation, histone modifications, and non-coding RNA-associated gene silencing, act as dynamic regulators of chromatin architecture, determining the accessibility of genetic information to the transcriptional machinery. Crucially, the epigenetic landscape is plastic and can be actively shaped by a myriad of environmental exposures, including infectious agents (e.g., Epstein-Barr virus), tobacco smoke, hormonal changes, dietary components, and pollutants (Kwon et al., 2024; Kaszycki and Kim, 2025). These factors can initiate stable epigenetic reprogramming within immune cells, potentially leading to the sustained overexpression of pro-inflammatory genes or the silencing of key immunoregulatory pathways.

This review manuscript synthesizes current evidence positing that epigenetic dysregulation serves as the crucial mechanistic link between genetic susceptibility and environmental triggers in the pathogenesis of immune-mediated diseases. We will detail the aberrant epigenetic patterns, the "epigenome" characteristic of major IMIDs, focusing on specific immune cell subsets. Furthermore, we will explore the profound translational implications of this field, discussing the potential of epigenetic marks as novel biomarkers for diagnosis and prognostication and surveying the promising frontier of epigenetic-based therapeutics aimed at reversing pathogenic marks and restoring immune homeostasis.

2. FUNDAMENTAL EPIGENETIC MECHANISMS

Epigenetic regulation provides a dynamic and heritable layer of control over gene expression,

enabling cellular differentiation and plasticity in response to environmental cues without altering the primary DNA sequence. In the immune system, these mechanisms are paramount for the development, activation, and termination of responses, ensuring a precise balance between effective pathogen clearance and self-tolerance. The dysregulation of these processes is a cornerstone of autoimmune pathology. The three primary, interconnected epigenetic mechanisms are DNA methylation, histone modifications, and non-coding RNA-associated silencing. restoring immune homeostasis.

2.1 DNA Methylation

DNA methylation is the most extensively studied epigenetic modification in mammals. It involves the covalent addition of a methyl group to the 5' position of a cytosine ring, primarily within CpG dinucleotide sequences. Dense clusters of CpG sites, known as CpG islands, are often found in gene promoter regions. Methylation of these islands typically leads to transcriptional repression by physically impeding the binding of transcription factors and by recruiting proteins such as methyl-CpG-binding domain proteins (MBDs), which then attract histone deacetylases and other chromatin-remodeling complexes to establish a closed, silent chromatin state (Harris et al, 2025; Smith et al., 2025).

The establishment and maintenance of DNA methylation patterns are catalyzed by a family of enzymes called DNA methyltransferases (DNMTs). DNMT3A and DNMT3B are responsible for de novo methylation, setting up new methylation patterns during embryonic development. DNMT1, the maintenance methyltransferase, faithfully copies methylation patterns to the daughter strand during DNA replication, ensuring heritability of the epigenetic mark through cell divisions (Sarre et al., 2025).

In the context of immunity, DNA methylation is critical for processes such as X-chromosome inactivation, genomic imprinting, and the silencing of endogenous retroviral elements. Crucially, it governs lymphocyte lineage commitment and function. For example, the differentiation of naïve CD4+ T cells into distinct effector subsets (Th1, Th2, Th17) and immunosuppressive regulatory T cells (Tregs) is orchestrated by precise changes in the methylation status of key cytokine and transcription factor genes (Roy et al., 2025). A hallmark of many autoimmune diseases, particularly SLE, is a state of global DNA hypomethylation in T cells, which promotes the aberrant overexpression of autoimmune-associated genes (e.g., ITGAL (CD11a) and TNFSF7 (CD70)), alongside locus-specific hypermethylation events that may silence protective genes (Deng et al., 2024)

2.2 Histone Post-Translational Modifications

Histones are the core protein components of nucleosomes, around which DNA is wrapped. Their N-terminal tails are subject to over 100 different post-translational modifications (PTMs), including acetylation, methylation, phosphorylation, ubiquitination, and sumoylation. These PTMs alter the electrostatic charge of histones and serve as docking sites for other proteins, collectively influencing chromatin accessibility and gene expression (Nie et al., 2024).

The most well-characterized modifications are:

Acetylation/deacetylation: Catalyzed by histone acetyltransferases (HATs) and histone deacetylases (HDACs), respectively. Acetylation neutralizes the positive charge on lysine residues, reducing the affinity between histones and the negatively charged DNA backbone. This results in a more open, transcriptionally permissive chromatin structure (euchromatin). Deacetylation has the opposite effect, promoting chromatin condensation and gene silencing (heterochromatin) (Chen et al., 2024).

Methylation: Catalyzed by histone methyltransferases (HMTs) and removed by histone demethylases (HDMs). The functional outcome of methylation is highly context-dependent, varying by the specific lysine or arginine residue modified and the degree of methylation (mono-, di-, or tri-methylation). For instance, trimethylation of histone H3 lysine 4 (H3K4me3) is a mark of active promoters, while trimethylation of H3 lysine 27 (H3K27me3) is a repressive mark associated with facultative heterochromatin (Chen et al., 2024).

The "histone code" hypothesis posits that these combinations of modifications act sequentially or in concert to form a complex language that dictates specific functional outcomes for a chromosomal region (Ueberheide et al., 2024). In immune cells, activating marks like H3K4me3

and H3K9ac are enriched at the promoters of highly expressed cytokine genes (e.g., IFNG, IL4, IL17), while repressive marks like H3K27me3 help silence alternative lineage genes during T-cell differentiation, ensuring stable effector cell identity (Jay et al., 2025).

2.3 Non-Coding RNAs (ncRNAs)

Non-coding RNAs represent a vast and diverse class of functional RNA molecules that are transcribed from the genome but not translated into proteins. They act as crucial epigenetic regulators, primarily at the post-transcriptional level.

MicroRNAs (miRNAs): These are short (~22 nucleotides), single-stranded RNAs that regulate gene expression by binding to complementary sequences in the 3' untranslated regions (UTRs) of target messenger RNAs (mRNAs). This binding typically leads to mRNA degradation or translational repression. A single miRNA can target hundreds of mRNAs, allowing it to fine-tune entire genetic networks. In immunology, miRNAs are indispensable regulators of immune cell development, proliferation, differentiation, and function. For example, miR-155 is a pro-inflammatory miRNA that promotes Th1 and Th17 responses, while miR-146a acts as a critical negative feedback regulator of NF-κB signaling and is often dysregulated in autoimmunity (Shaheen et al., 2024; Mehta et al., 2025).

Long Non-Coding RNAs (lncRNAs): These are transcripts longer than 200 nucleotides with limited protein-coding potential. They exert their regulatory functions through a variety of mechanisms: as scaffolds for chromatin-modifying complexes, guides for their localization to specific genomic loci, decoys for transcription factors, or sponges that sequester miRNAs. The lncRNA MALAT1, for instance, has been implicated in regulating alternative splicing and gene expression in immune cells, while others like TMEVPG1 (NeST) can influence epigenetic states to control interferon-γ expression (Antonazzo et al., 2024).

These three mechanisms do not operate in isolation but form a highly integrated regulatory network. DNA methylation can influence histone modification patterns, and both can be guided by ncRNAs. Conversely, histone modifications can regulate the expression of ncRNAs. This complex crosstalk ensures precise spatiotemporal control of the gene expression programs that dictate immune cell identity and function, and its disruption lies at the heart of epigenetic dysregulation in disease (Kong et al., 2024).

3. EPIGENETIC DYSREGULATION IN SPECIFIC IMMUNE-MEDIATED DISEASES

The overarching principles of epigenetic regulation become profoundly altered in immune-mediated diseases. The following section details the disease-specific epigenetic landscapes that contribute to pathogenesis, moving from systemic autoimmunity to organ-specific disorders.

3.1 Systemic Lupus Erythematosus (SLE)

SLE is arguably the best-studied autoimmune disease from an epigenetic perspective and is characterized by a profound state of global DNA hypomethylation in CD4+ T cells and other immune cells. This hypomethylation mirrors the epigenetic state of activated, proliferating T cells and leads to the overexpression of genes normally silenced in resting lymphocytes, such as perforin (PRF1), the T-cell adhesion molecule ITGAL (CD11a), and the co-stimulatory molecule TNFSF7 (CD70) (Ribeiro et al., 2024; Araki & Mimura, 2024). This aberrant overexpression promotes autoreactive T-cell help to B cells, driving autoantibody production.

Mechanism of hypomethylation: The root cause involves impaired ERK signaling pathway signaling, leading to reduced expression and translocation of DNMT1. This results in passive demethylation during cell division. Furthermore, oxidative stress and elevated levels of nitric oxide in SLE patients can directly inhibit DNMT enzymatic activity (Somers et al., 2024).

Histone modifications: SLE T cells exhibit a shift towards a transcriptionally permissive chromatin state. This is characterized by globally decreased levels of the repressive mark H3K27me3 and increased levels of activating marks like H3K18ac and H3K4me3 at the promoters of key interferon-stimulated genes (ISGs) and inflammatory cytokines, amplifying the type I interferon signature that is a hallmark of SLE (Zhang et al., 2024).

ncRNAs: A distinct miRNA signature is present in SLE patient blood and tissues. miR-146a, a negative regulator of the interferon pathway, is under expressed, contributing to unchecked IFN production. Conversely, miR-21 and miR-148a are overexpressed; they promote autoimmunity by targeting DNMT1, creating a vicious cycle of DNA hypomethylation, and by dampening negative regulatory pathways (Royo et al., 2025).

3.2 Rheumatoid Arthritis (RA)

In RA, epigenetic dysregulation is most prominently studied in the hyperplastic, invasive synovial tissue, particularly in fibroblast-like synoviocytes (FLS), which develop an aggressive, "transformed-like" phenotype that drives joint destruction.

DNA methylation: RA-FLS exhibit a unique and stable "methylation signature" that distinguishes them from osteoarthritis FLS and is present even in early disease. Key changes include:

Hypomethylation of genes encoding matrix-degrading enzymes (MMP3, MMP9), chemokines (CXCL12), and critical signaling molecules (STAT3, IRF5), leading to their overexpression and promoting inflammation, angiogenesis, and tissue invasion (Prideaux et al., 2024).

Hypermethylation of genes that normally promote apoptosis or cell cycle arrest, such as TNFRSF25 (DR3) and BCL2L11 (BIM), conferring resistance to cell death and contributing to synovial hyperplasia (Svendsen et al., 2025).

Histone modifications: The balance of HAT/HDAC activity is skewed in RA. While some HDACs are downregulated, class I and II HDAC activity is generally increased in RA synovium, contributing to the suppression of anti-inflammatory genes. Conversely, HAT activity is also elevated, promoting the expression of pro-inflammatory genes like IL6 and TNF (Enayati et al., 2024).

ncRNAs: miR-155 is highly expressed in RA synovial fluid and tissue, where it promotes macrophage activation and Th17 cell differentiation. miR-146a is also upregulated but may act in a feedback inhibitory role that is ultimately insufficient to control inflammation. miR-124a is significantly downregulated, leading to increased activation of the monocyte chemoattractant CCL2 (Seyedi et al., 2024).

3.3 Multiple Sclerosis (MS)

Epigenetic mechanisms in MS are critical for determining the fate of T cells, pushing differentiation towards pro-inflammatory Th1 and Th17 lineages and away from immunoregulatory Tregs.

DNA methylation: Genome-wide studies reveal significant differences in DNA methylation patterns in CD4+ T cells, CD8+ T cells, and B cells of MS patients compared to controls. Intriguingly, the strongest MS-associated genetic risk variant, HLA-DRB1, also displays MS-specific methylation patterns, suggesting a complex gene-environment interaction where epigenetics modulates the effect of the primary genetic risk factor (Elbahrawi et al., 2024). Key hypomethylated loci are associated with T-cell activation and adhesion pathways.

Histone modifications: HDACs and sirtuins (SIRT1, a class III HDAC) are key regulators of T-cell plasticity in MS. SIRT1 deficiency has been linked to hyperacetylation of the transcription factor FOXO1, impairing Treg function and promoting a pro-inflammatory T-cell state. Furthermore, inhibitors of HDACs have been shown to ameliorate disease in experimental autoimmune encephalomyelitis (EAE), the mouse model of MS, by promoting Treg development (Xie et al., 2025).

ncRNAs: Circulating miRNAs serve as promising biomarkers. miR-326 expression correlates with disease severity and promotes Th17 differentiation. miR-17-92 cluster members are dysregulated, impacting T-cell proliferation. Serum levels of miR-155 and miR-301a are also elevated and associated with active disease (Xie et al., 2025)

3.4 Inflammatory Bowel Disease (IBD: Crohn's Disease & Ulcerative Colitis)

The intestinal epithelium and mucosal immune system in IBD patients display widespread epigenetic alterations induced by the luminal environment (microbiome, nutrients).

DNA methylation: Studies on intestinal mucosal biopsies reveal hundreds of differentially methylated regions. Crohn's disease is often associated with hypermethylation and silencing of the SOCS1 gene, a negative regulator of cytokine signaling, leading to enhanced JAK/STAT signaling. In ulcerative colitis, the TNF gene promoter is often hypomethylated, contributing to its excessive production (Mahurkar-Joshi et al., 2025).

Table 1. Summary of key epigenetic alterations in major immune-mediated diseases

Disease	Cell type/ tissue	DNA methylation changes	Histone modifications	Key ncRNAs involved
SLE	CD4+ T cells	Global hypomethylation; Hypomethylation of *CD11a*, *CD70*	Increased H3/H4 acetylation	↓ miR-146a, ↑ miR-21, ↑ miR-155
RA	Synovial FLS	Hypomethylation of *CXCL12*, *IL6*; Hypermethylation of *DR3*, *BIM*	Increased HDAC activity	↑ miR-155, ↑ miR-203, ↑ miR-124a
MS	CD4+ T cells, PBMCs	Differential methylation at HLA & non-HLA loci	Altered HDAC/SIRT expression	↑ miR-326, ↑ miR-155, ↓ miR-17-92
IBD	Intestinal mucosa	Hypermethylation of *SOCS1* (Crohn's); Hypomethylation of T*NF*	Altered HAT/HDAC balance	↑ miR-21, ↑ miR-29, miR-196 dysregulation

Histone Modifications: Butyrate, a short-chain fatty acid produced by commensal gut bacteria, is a natural HDAC inhibitor. A deficiency in butyrate production or sensing in IBD leads to increased HDAC activity, repressing the expression of anti-inflammatory genes and genes involved in epithelial barrier integrity. This links the environmental factor (microbiome) directly to epigenetic dysregulation (Li et al., 2025)

ncRNAs: miR-21 is upregulated in IBD mucosa and promotes intestinal inflammation by targeting PDCD4, a suppressor of IL-10 expression. miR-29 is also overexpressed and targets key molecules essential for intestinal barrier function. The let-7 family miRNAs are involved in regulating IL-13-mediated inflammation (Goodarzi et al., 2025).

4. ENVIRONMENTAL TRIGGERS AND EPIGENETIC MODIFICATION

The compelling evidence for epigenetic dysregulation in immune-mediated diseases raises a critical question: what initiates these changes? Environmental factors are the primary architects, acting upon a genetically susceptible background to instigate pathogenic epigenetic reprogramming. These exposures can induce stable alterations to the epigenome of immune cells and tissue-resident cells, effectively "embedding" the memory of a environmental insult and lowering the threshold for autoimmune activation. The timing of exposure (e.g., in utero, during adolescence) can be as critical as the exposure itself due to periods of heightened epigenetic plasticity.

4.1 Tobacco Smoke

Cigarette smoke is one of the most well-established environmental risk factors for RA and other IMIDs. It is a complex mixture of over 7,000 chemicals, many of which have demonstrable epigenetic effects.

Mechanism: Chemicals like benzene and hydroquinone can directly inhibit the activity of DNMTs by forming covalent adducts or by generating reactive oxygen species (ROS) that interfere with enzymatic function. This leads to DNA hypomethylation.

Evidence: Smokers exhibit global DNA hypomethylation in peripheral blood mononuclear cells (PBMCs). More specifically, smoking has been linked to hypomethylation of the AHRR (aryl hydrocarbon receptor repressor) gene and site-specific hypomethylation at the CXCL12 (involved in RA pathogenesis) and IL6 promoters in immune cells, promoting a pro-inflammatory state (Lim & Kim, 2024; Svendsen et al., 2025). This effect can persist for years after smoking cessation, illustrating the long-lasting impact of epigenetic modification.

4.2 Microbial Infections (e.g., Epstein-Barr Virus)

Infections, particularly with the Epstein-Barr virus (EBV), are strongly associated with an increased risk of SLE, MS, and other autoimmune conditions.

Mechanism: EBV infection induces widespread epigenetic changes in host B cells to facilitate its own latency and proliferation. The viral protein EBNA2 acts as a transcriptional regulator that binds to numerous autoimmune risk loci

identified by GWAS, altering their expression and histone modification landscape. Furthermore, EBV-encoded latent membrane protein 1 (LMP1) can dysregulate DNMT expression, leading to hypomethylation and activation of endogenous retroviruses and autoimmune-related genes (Viel, 2024; Zhao et al., 2024))

Evidence: Patients with SLE have been shown to have aberrant hypomethylation of EBV genes, leading to loss of viral control and a higher viral load. The cross-reactivity between EBV antigens (e.g., EBNA1) and self-antigens (e.g., Sm in SLE) in an epigenetically permissive environment may break tolerance.

4.3 Diet and the Gut Microbiome

Dietary components and the metabolites produced by the commensal gut microbiota are potent epigenetic modifiers that directly influence immune cell function and mucosal integrity.

Mechanism:

Methyl donors: Nutrients involved in one-carbon metabolism, such as folate, vitamin B12, and choline are essential for generating S-adenosylmethionine (SAM), the universal methyl donor for DNA and histone methylation. Deficiencies in these nutrients can lead to global hypomethylation.

Short-Chain Fatty Acids (SCFAs): Butyrate, propionate, and acetate are produced by bacterial fermentation of dietary fiber. Butyrate is a potent inhibitor of HDAC (particularly Class I and IIa). HDAC inhibition in immune cells, particularly in the gut, promotes the development and function of regulatory T cells (Tregs) via hyperacetylation of the Foxp3 promoter and other loci, thereby enforcing immune tolerance (Xu et al., 2025)

Evidence: A "Western diet" low in fiber reduces SCFA production, leading to decreased HDAC inhibition, impaired Treg function, and a heightened inflammatory state. Butyrate supplementation has been shown to ameliorate disease in animal models of colitis and MS (Fisse et al., 2024).

4.4 Ultraviolet (UV) Radiation

UV radiation is a known trigger for SLE flares and skin manifestations.
Mechanism: UVB exposure can induce DNA damage and oxidative stress in keratinocytes, leading to the generation of ROS. ROS can directly inhibit DNMT1 activity and alter the activity of enzymes responsible for histone modifications. This can cause demethylation and overexpression of genes involved in apoptosis and inflammation, such as CD70 and CD154 (Barnes et al., 2024).

Evidence: UV irradiation of skin cells in culture induces demethylation and overexpression of autoantigens like Ro/SSA, potentially making them more visible to the immune system and initiating an autoimmune response.

4.5 Air Pollutants and Chemicals

Particulate matter (PM2.5), organic solvents, and other environmental chemicals have been implicated in the pathogenesis of IMIDs.

Mechanism: Similar to tobacco smoke, many pollutants generate oxidative stress, leading to impaired DNMT function and global hypomethylation. Some chemicals can also directly bind to and activate aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor that recruits a variety of epigenetic modifiers to target genes, influencing Th17/Treg balance (Wais and Agrawal, 2024 ; Hahn et al., 2024).

Evidence: Epidemiological studies link exposure to silica dust and organic solvents to an increased risk of SLE, RA, and systemic sclerosis. Studies show that PM2.5 exposure is associated with altered DNA methylation in inflammatory genes.

5. TRANSLATIONAL IMPLICATIONS AND FUTURE DIRECTIONS

The profound understanding of epigenetic dysregulation in immune-mediated diseases is rapidly moving from bench to bedside, offering unprecedented opportunities for improving patient care. The dynamic and reversible nature of epigenetic marks positions them as ideal targets for novel diagnostic strategies and therapeutic interventions, heralding a new era of precision medicine in autoimmunity.

5.1 Epigenetic Biomarkers

The quest for specific, sensitive, and non-invasive biomarkers is central to improving outcomes in IMIDs. Epigenetic marks, stable in biofluids and reflective of dynamic disease activity, hold immense promise.

Table 2. Epigenetic and miRNA biomarkers for diagnosis, monitoring, prognosis, and treatment response in SLE and RA

Application	Example	Potential utility
Diagnosis	Specific miRNA panel (e.g., miR-146a, miR-155) in serum for SLE	Earlier and more accurate diagnosis, especially in seronegative patients
Disease Monitoring	Global DNA methylation levels in PBMCs in SLE; CXCL12 methylation in RA	Objective measure of disease activity; predict flare-ups
Prognosis	Methylation status of apoptosis-related genes in RA-FLS	Predict severity of joint destruction and disease course
Treatment Response	Pre-treatment miR-125b levels	Predict response to Rituximab in RA or SLE

Diagnosis and differential diagnosis: DNA methylation signatures and circulating miRNA profiles can distinguish patients with a specific IMID from healthy controls and, crucially, from those with other clinically similar conditions. For instance, a specific methylation signature in synovial tissue or peripheral blood can differentiate rheumatoid arthritis from other forms of inflammatory arthritis (e.g., psoriatic arthritis) with higher accuracy than current serological tests (Proaño et al., 2025)

Monitoring disease activity and predicting flares: Unlike static genetic risk alleles, epigenetic marks change with disease state. Serial analysis of circulating cell-free DNA (cfDNA) methylation patterns or miRNA levels in serum can provide a real-time "epigenetic snapshot" of disease activity, potentially predicting impending flares before clinical symptoms manifest. This allows for pre-emptive treatment adjustments (Liu et al., 2024).

Prognosis and Treatment Response: Epigenetic profiles may predict disease aggressiveness and likelihood of developing extra-articular manifestations. Furthermore, baseline epigenetic markers could forecast response to specific therapies (e.g., predicting non-response to TNF inhibitors), enabling a more personalized and efficient treatment approach from the outset (Shaikh et al., 2024).

5.2 Epigenetic Therapy

The concept of pharmacologically reversing aberrant epigenetic marks to restore normal gene expression is a groundbreaking therapeutic strategy. While most epigenetic drugs are currently used in oncology, their repurposing for autoimmunity is actively being explored.

DNMT Inhibitors (DNMTi): Drugs like azacitidine and decitabine are approved for myelodysplastic syndromes. Their use in autoimmunity is paradoxical; while they can reverse pathological hypermethylation of silenced genes, their primary effect is global hypomethylation, which could theoretically exacerbate diseases like SLE. The future lies in developing targeted delivery systems (e.g., antibody-drug conjugates) to specific cell types or employing low-dose regimens to achieve gene-specific rather than global effects (Wen et al., 2025).

HDAC Inhibitors (HDACi): This class has shown greater immediate promise. Pan-HDAC inhibitors like vorinostat and givinostat have demonstrated efficacy in preclinical models of RA, SLE, and MS by suppressing pro-inflammatory cytokine production and promoting Treg function. More selective HDAC inhibitors (e.g., targeting HDAC6, HDAC11) are in development to enhance efficacy and reduce off-target effects (. Notably, the SCFA butyrate is a natural HDACi, providing a strong rationale for dietary and microbiome-based interventions (Yue et al., 2025).

Bromodomain and Extra-Terminal (BET) inhibitors: These compounds disrupt the reading of histone acetylation marks by BET proteins. They have potent anti-inflammatory effects by downregulating key inflammatory genes (e.g., NFKB, IL6) and have shown efficacy in multiple animal models of IMIDs (Khokhar et al., 2024).

miRNA-based therapeutics: This approach offers exquisite specificity. Mimics (to restore levels of deficient miRNAs like miR-146a) and antagomirs or locked nucleic acids (LNAs) (to silence overexpressed miRNAs like miR-155) are in various stages of preclinical and early clinical development. The major challenge remains the efficient and targeted delivery of these oligonucleotides to relevant immune cells in vivo (Bannazadeh Baghi et al., 2024).

6. CONCLUSION

The investigation into epigenetic dysregulation has fundamentally reshaped our understanding of immune-mediated diseases. No longer viewed as disorders governed solely by a deterministic genetic code, IMIDs are now recognized as conditions where dynamic epigenetic mechanisms interpret genetic susceptibility through the lens of environmental exposure. This review has synthesized compelling evidence that establishes aberrant DNA methylation, histone modifications, and non-coding RNA expression not as mere epiphenomena, but as central drivers of pathogenesis. These mechanisms directly mediate the loss of immune tolerance, hyperactivation of inflammatory pathways, and tissue damage characteristic of diseases like SLE, RA, MS, and IBD.

The environmental dimension is particularly pivotal, with factors such as tobacco smoke, viral infections (notably EBV), diet, and the gut microbiome acting as powerful epigenetic modifiers. These triggers can induce stable, heritable changes in gene expression that lower the threshold for autoimmunity, effectively encoding the memory of environmental insults within the immune system and explaining the notable discordance in genetically identical twins.

This profound mechanistic insight unlocks immense translational potential. The dynamic nature of the epigenome offers a unique opportunity to develop novel epigenetic biomarkers for early diagnosis, precise prognosis, and real-time monitoring of disease activity, moving beyond the limitations of current serological and clinical markers. Furthermore, the reversibility of epigenetic marks paves the way for a revolutionary therapeutic strategy: epigenetic therapy. The repurposing and refinement of drugs targeting DNMTs, HDACs, BET proteins, and specific miRNAs hold the promise of not just suppressing inflammation but potentially restoring immunological balance and inducing long-term remission by reversing the root epigenetic dysfunction.

However, the path forward is not without challenges. The field must overcome hurdles related to the cell-type specificity of interventions, the complex crosstalk within the epigenome, and the long-term safety of modulating these fundamental regulatory systems. Future research must focus on large-scale integrative multi-omics studies to validate biomarkers and on developing novel targeted delivery systems to enhance the precision of epigenetic drugs.

In conclusion, the study of epigenetics has provided the missing link between genes and environment in immune-mediated diseases. It offers a more complete and nuanced disease model and, most importantly, illuminates a promising path toward personalized medicine. By reading and rewriting the epigenetic code that goes awry in autoimmunity, we are poised to develop more effective strategies for prediction, prevention, and treatment, ultimately aiming to restore the delicate balance of the immune system and improve the lives of millions of patients worldwide.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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