Epigenetic dysregulation of B-cells in autoimmune diseases and lymphomas (Review)

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Abstract. B-lymphocytes (B-cells) develop from hematopoietic stem cells in the bone marrow or fetal liver and differentiate into antibody-secreting cells and memory B-cells upon encountering antigens in peripheral lymphoid organs. Throughout this process, the expression of lineage-associated genes is upregulated, whereas that of lineage-inappropriate genes is repressed, thereby directing commitment to a specific B-cell fate. Epigenetic regulatory mechanisms, including DNA methylation, post-translational histone modifications and non-coding RNAs, regulate gene transcription and play crucial roles in B-cell development and differentiation. The dysregulation of these epigenetic processes may contribute to the pathogenesis of autoimmune diseases and B-cell malignancies. Recent advances in high-throughput techniques, including single-cell RNA sequencing, chromatin immunoprecipitation-sequencing and whole-genome bisulfite sequencing, have significantly enhanced the understanding of epigenetic dysregulation in these disorders. The present review summarizes recent advances in the understanding of dysregulated epigenetic mechanisms underlying B-cell-mediated autoimmune diseases (such as systemic lupus erythematosus, rheumatoid arthritis, primary Sjögren's syndrome, multiple sclerosis and type 1 diabetes mellitus) and lymphomas (such as diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, Burkitt lymphoma and marginal zone lymphoma), and highlights emerging diagnostic biomarkers and therapeutic strategies.

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Abbreviations: B-NHL, B-cell non-Hodgkin lymphoma; BL, Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; EMZL, extranodal marginal zone lymphoma; FL, follicular lymphoma; GC, germinal center; HATs, histone acetyltransferases; HMTs, histone methyltransferases; HDACs, histone deacetylases; KDMs, histone demethylases; lncRNAs, long non-coding RNAs; miRNA/miR, microRNA; MCL, mantle cell lymphoma; MS, multiple sclerosis; MZL, marginal zone lymphoma; NMZL, nodal marginal zone lymphoma; pSS, primary Sjögren's syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T1DM, type 1 diabetes mellitus

Key words: B-cells, epigenetic dysregulation, autoimmune disease, lymphoma

Contents

1. Introduction

B-cells develop from hematopoietic stem cells (HSCs) in the bone marrow (BM) of adult mammals or in the fetal liver during embryogenesis (1). The sequential and coordinated expression of lineage-specifying transcription factors, including E2A, PU.1, Ikaros and EBF1, drives HSCs into early lymphoid progenitors (ELPs), which activate lymphoid-restricted gene programs indicative of B-cell potential (2). ELPs, characterized by interleukin (IL)-7 receptor (IL-7R, CD127) negativity, subsequently differentiate into common lymphoid progenitors

(CLPs) in the BM. CLPs serve as immediate precursors not only for B-cells, but also for T-cells, natural killer cells and dendritic cells (3). B-cell maturation proceeds through discrete stages, including pro-B, pre-B, immature B and mature B-cells, under the coordinated control of transcription factors (including E2A, Pax5, PU.1, Ikaros, EBF1, Sox4, IRF4 and IRF8) and cytokines such as IL-7 (1). During these stages, developing B-cells undergo tightly ordered V(D)J recombination events to assemble a functional, non-autoreactive heterodimeric B-cell receptor (BCR), thereby equipping them for antigen recognition and adaptive immune responses. Once they migrate to secondary lymphoid organs, mature B-cells can be activated via T-cell-dependent (TD) or T-cell-independent (TI) pathways and differentiate into antibody-secreting plasma cells (PCs) and long-lived memory B-cells (MBCs) (4).

In contrast to genetic mechanisms, epigenetic mechanisms regulate gene expression without altering the DNA sequence, thereby modulating cellular metabolism and function (5). Emerging evidence indicates that epigenetic regulation plays a crucial role in establishing B-cell lineage identity and effector functions. The dysregulation of DNA methylation, histone modifications and the altered expression of long non-coding RNAs (lncRNAs) and microRNAs (miRNAs/miRs) can impair B-cell tolerance and contribute to the pathogenesis of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and mantle cell lymphoma (MCL) (6-8). Dissecting the specific epigenetic perturbations that drive these pathologies may reveal novel biomarkers and therapeutic targets. Indeed, clinical and preclinical studies of autoimmune disorders and B-cell malignancies have shown that agents capable of reversing aberrant epigenetic states, such as histone deacetylase and DNA methyltransferase inhibitors, hold significant therapeutic potential (7,9). A comprehensive understanding of epigenetic dysregulation in disease is crucial for elucidating pathogenic mechanisms and designing targeted epigenetic therapies. The present review aimed to provide an overview of current insights into the epigenetic regulation of B-cell development and the consequences of its dysregulation in autoimmune diseases and B-cell lymphomas.

2. Major epigenetic modifications

Eukaryotic DNA is organized into chromatin, with the nucleosome as the fundamental repeating unit, consisting of ~147 base pairs of DNA wrapped around an octamer of core histones (10). Nucleosomes are further compacted and folded to form higher-order chromatin structures. Dynamic changes in chromatin structure play a crucial role in gene transcription. Generally, the chromatin in the transcriptional silencing region is highly packaged, while the chromatin structure is loosed in the active transcriptional region, which facilitates the binding of transcription regulators (11,12). Increasing evidence indicates that epigenetic modifications, including chromatin remodeling, DNA methylation, histone modifications, lncRNAs and miRNA activity, are key drivers of chromatin structural dynamics and gene regulation (13,14). The processes of chromatin remodeling (with nucleosome sliding as an illustrative example), DNA methylation, major histone modifications, and miRNA-mediated regulation are illustrated in Fig. 1.

Chromatin remodeling. Chromatin remodeling is an ATP-dependent process that modulates nucleosome architecture to regulate both transcription initiation and elongation. Of note, four principal families of remodelers have been defined based on their Swi2/Snf2-like ATPase domains: SWI/SNF (such as BAF, PBAF and WINAC complexes), ISWI (such as ACF and NURF complexes), CHD (such as NURD complexes) and INO80/SWR1 (such as SRCAP and Tip60/EP400 complexes) (15,16). These complexes target specific genomic loci through interactions with sequence-specific transcription factors or histone marks, where they function as coactivators or corepressors. Mechanistically, chromatin remodelers promote gene activation or repression by sliding or evicting nucleosomes, exchanging core histones for histone variants, or altering nucleosome spacing to fine-tune DNA accessibility for the transcriptional machinery (15,17). Beyond transcriptional control, remodelers also coordinate with histone-modifying enzymes and the RNA polymerase II complex to ensure proper promoter clearance, pause release and elongation processivity, and they play critical roles in development, cell differentiation and disease pathogenesis (18).

DNA methylation. As a prototypical epigenetic mark, DNA methylation persists throughout the lifespan of the cell. During the methylation process, a methyl group is covalently added to a specific base in the DNA sequence, catalyzed by DNA methyltransferases (DNMTs). DNMT3A, DNMT3B, and the catalytically inactive DNMT3L establish *de novo* methylation patterns in mammals, while DNMT1 maintains these patterns during DNA replication (19). DNA methylation is reversible; it can be actively removed by ten-eleven translocation (TET) enzymes or passively lost through replication-dependent dilution (20). In eukaryotes, methylation occurs predominantly at cytosine residues in CpG dinucleotides (5'-CpG-3'), although adenine methylation has also been observed. DNA methylation exerts a profound impact on gene expression by interfering with transcription factor binding, influencing chromatin compaction, and recruiting methyl-CpG binding domain proteins (21).

Histone modifications. Four core histones and their variant isoforms assemble into the fundamental repeating unit of chromatin, the nucleosome. These nucleosomal histones undergo a variety of covalent post-translational modifications, such as methylation, acetylation, phosphorylation, ADP-ribosylation, ubiquitination, and SUMOylation, which collectively constitute a complex 'histone code' (22). A cohort of specialized enzymes catalyzes the 'writing', 'erasing' and 'reading' of these marks. For instance, histone acetylation is catalyzed by histone acetyltransferases (HATs) such as PCAF, GCN5 and the CREBBP/p300 complex, whereas histone deacetylases (HDACs), including HDAC1-3 and the sirtuin family (SIRT1-7), remove acetyl groups to facilitate chromatin compaction and transcriptional repression (23,24). Histone methylation is installed by histone methyltransferases (HMTs), including the KMT2 family, PRC2 complex, SUV39H1/2, and PRMT1, which deposit mono-, di- and tri-methyl marks on lysine (K) or arginine (R) residues (25). Conversely, histone demethylases (KDMs), such as LSD1/KDM1A and members of the jumonji domain family, 'erase' methyl modifications in

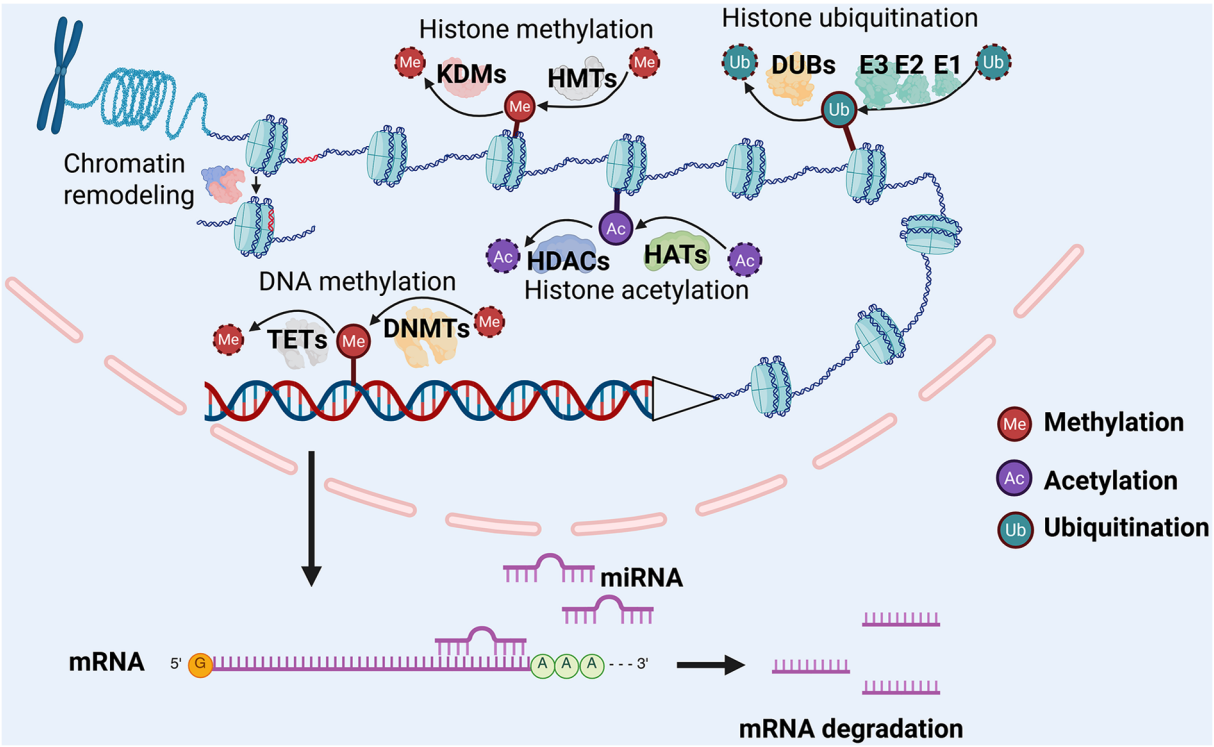

Figure 1. Major epigenetic mechanisms. Chromatin remodeling is an ATP-dependent process that modulates nucleosome architecture. DNA methylation is catalyzed by DNMTs and removed by TETs. Histone acetylation is installed by HATs and removed by HDACs. Histone methylation is catalyzed by HMTs and reversed by KDMs. Histone ubiquitination is mediated through a sequential cascade of E1 activating enzymes, E2 conjugating enzymes, and E3 ligases, and is reversed by DUBs. miRNAs bind to complementary sequences in target mRNAs, leading to transcript degradation. DNMTs, DNA methyltransferases; TETs, ten-eleven translocation enzymes; HATs, histone acetyltransferases; HDACs, histone deacetylases; HMTs, histone methyltransferases; KDMs, histone demethylases; DUBs, histone deubiquitinases; miRNA, microRNA.

a residue- and methylation-state-specific manner (25). Histone ubiquitination involves a cascade of reactions that covalently attach ubiquitin to lysine side chains, mediated by the E1 activating enzyme, E2 conjugating enzyme, and E3 ligases (such as RNF20/40 and RING1A/B). This modification is reversed by deubiquitinases, such as USP16, USP22 and BAP1 (26,27). Functionally, these histone modifications modulate chromatin biophysics, govern the recruitment or exclusion of transcriptional regulators, and delineate distinct chromatin domains, such as euchromatin and heterochromatin, thereby providing a pivotal epigenetic layer of gene expression control (28).

miRNAs. miRNAs are a class of non-coding RNAs, ~21 to 25 nucleotides in length, that primarily regulate gene expression at the post-transcriptional level (29). Intergenic miRNAs possess independent promoters and are transcribed as discrete transcriptional units, whereas intragenic miRNAs share promoters with their host genes; additionally, a number of miRNAs are arranged in polycistronic clusters and co-transcribed as a single primary transcript (primary microRNAs, pri-miRNAs) (30). Within the nucleus, the microprocessor complex (Drosha-DGCR8) cleaves pri-miRNAs to release ~70-nucleotide stem-loop precursor miRNAs (pre-miRNAs) (31). Pre-miRNAs are exported from the nucleus by Exportin-5 in a Ran-GTP-dependent manner. In the cytoplasm, the RNase III enzyme Dicer and TRBP cleave pre-miRNA to produce a miRNA duplex (32,33). This duplex is then loaded into an Argonaute protein in an ATP-dependent manner, leading to passenger strand ejection and mature single-stranded miRNA formation (34). In addition to this canonical pathway, certain miRNAs arise via non-canonical (Drosha-independent and/or Dicer-independent) pathways (35). Accumulating evidence indicates that miRNAs orchestrate diverse biological processes, such as cell differentiation, apoptosis and immune responses, and that aberrant miRNA expression contributes to various pathologies, highlighting their potential as therapeutic targets (30,36).

lncRNAs. lncRNAs are transcripts typically >200 nucleotides with minimal protein-coding potential (37,38). The majority of lncRNAs are transcribed by RNA polymerase II and undergo 5' capping, splicing and 3' polyadenylation. Despite low sequence conservation and generally weaker expression than protein-coding genes, lncRNAs exhibit highly tissue-, cell type- and developmental stage-specific expression. Advances in RNA sequencing, single-cell transcriptomics, multi-omics and RNA-protein interaction studies have established that lncRNAs play critical regulatory roles in embryonic development, immune modulation, and tumorigenesis, rather than representing mere transcriptional noise (38,39).

lncRNAs regulate gene expression through diverse mechanisms, including epigenetic, transcriptional, post-transcriptional and macromolecular complex-mediated processes (40,41). Some recruit chromatin modifiers, such as PRC2, to induce H3K27me3 and other repressive histone marks, thereby modulating chromatin accessibility and gene

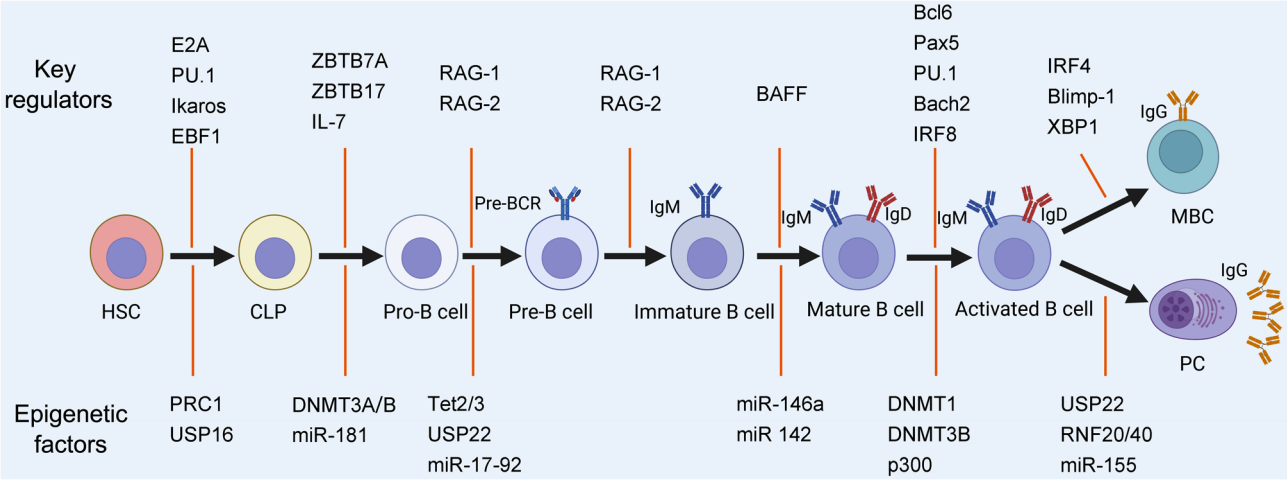

Figure 2. Roles of epigenetic regulators in B-cell lymphopoiesis. HSC, hematopoietic stem cell; CLP, common lymphoid progenitor; Pro-B cell, progenitor B cell; Pre-B cell, precursor B cell; MBC, memory B cell; PC, plasma cell.

silencing (42). Enhancer-associated lncRNAs regulate nearby gene transcription by altering enhancer-promoter interactions and local chromatin architecture (43). Certain lncRNAs function as competing endogenous RNAs, sequestering miRNAs and relieving repression of target mRNAs (41,44). lncRNAs can also interact with mRNAs, miRNAs, or RNA-binding proteins to influence splicing, stability, localization and translation (41).

3. Epigenetic regulation of B-cell development and differentiation

B-cell development and differentiation. Early B-cell development in the BM is orchestrated by chemokines (such as C-X-C motif chemokine ligand 12 and C-X-C motif chemokine ligand 13) and cytokines (such as IL-7 and stem cell factor) produced by stromal cells (45-47). The transcription factors, ZBTB7A and ZBTB17, are indispensable for the transition of CLPs to pre-pro-B-cells through modulation of Notch signaling, JAK-STAT5 pathway and IL-7R signaling (48,49). Rearrangement of the immunoglobulin heavy-chain gene segments is the hallmark of pro-B-cells and requires expression of RAG-1 and RAG-2 (50). In addition, pro-B-cells express terminal deoxynucleotidyl transferase, which increases antigen-receptor diversity by adding non-templated nucleotides at V(D)J junctions. Pro-B-cells also express the surrogate light chain (VpreB/λ5), which pairs with μ heavy chains to form the pre-B-cell receptor (pre-BCR). Pre-BCR signaling then drives progression to the large and subsequently small pre-B-cell stages. Subsequently, light-chain gene rearrangement occurs under strict allelic and isotypic exclusion, ensuring each B-cell expresses either κ or λ light chains exclusively. B-cells enter IgM-expressing immature B-cells after completing both heavy and light chains rearrangement.

In peripheral lymphoid tissues, B-cell activator of the TNF-α family (BAFF) signals provided by the follicle are important for B-cell survival (51). The mature B-cells differentiate into MBCs and PCs when activated by antigens in the peripheral lymphoid tissues. In addition to antigenic signals, TD or TI co-stimulation signals are also required for the B-cell activation. TI antigens typically drive differentiation into short-lived PCs, whereas TD responses initiate germinal center (GC) response (52). Within GCs, immunoglobulin genes undergo class-switch recombination (CSR) and somatic hypermutation (SHM) (53). GC responses are governed by a transcriptional network in which Bcl6, Pax5, PU.1, Bach2 and IRF8 enforce the GC B-cell program, whereas Blimp-1 (encoded by *Prdm1*), IRF4 and XBP1 drive differentiation into MBCs and PCs (54). Bcl6 is essential for GC B-cell identity by upregulating *Bach2* and repressing *Prdm1*, thereby preventing premature Blimp-1-mediated differentiation (55). Blimp-1 represses *Bcl6* and other B-cell fate factors, while inducing *Irf4* and *Xbp1*. Deletion of *Prdm1* in mice abolishes PC formation (56). IRF4 further reinforces PC differentiation by activating *Prdm1* and repressing *Bcl6* (54).

In addition to the intricate networks of transcription factors, an increasing body of evidence suggests that epigenetic regulation plays a pivotal role in B-cell development and differentiation. The involvement of epigenetic regulators in B-cell lymphopoiesis is illustrated in Fig. 2.

DNA methylation in B-cell development and differentiation. In the immune system, B-cells exhibit a highly dynamic DNA methylation landscape, particularly during differentiation. Approximately one-third of CpG sites undergo methylation changes throughout B-cell development (57). The transition from naïve B-cells to GC B-cells is characterized by extensive methylome remodeling, whereas subsequent shifts from GC B-cells to MBCs and PCs involve comparatively modest alterations (58). Notably, CTCF-binding sites exhibit dynamic methylation changes during B-cell maturation, indicating subset-specific epigenetic regulation within the immune system (59). Furthermore, DNA methylation also influences SHM by targeting V(D)J gene segments and promoting an open chromatin state in coordination with histone modifications (60,61).

B-cells respond to a wide array of immunological stimuli, such as pathogens, commensal microbes, tumors and other environmental cues (1,62). During immune responses, activation-induced cytidine deaminase (AID) drives SHM and CSR

by deaminating deoxycytidine to deoxyuracil, thereby generating U:G mismatches that are processed to effect antibody diversification (63). The precise control of AID expression is essential to maintain genomic integrity. In naïve B-cells, *Aicda* (the gene encoding AID) is transcriptionally silenced by promoter hypermethylation (64), whereas upon activation, it undergoes demethylation-dependent induction. Moreover, the differentiation of MBC is dependent on DNA methylation, where high levels of DNMTs are observed (58).

De novo DNA methylation, mediated by DNMT3A and DNMT3B, plays a critical role in constraining B-cell activation (65). The conditional deletion of *Dnmt3a/b* in murine pro-B-cells leads to hyperresponsive B-cells upon antigen challenge, manifested by increased GC formation, elevated numbers of PCs and higher serum antibody titers (65). Of note, this deletion does not impair early B-cell development or maturation, indicating that *de novo* DNA methylation primarily restricts activation rather than differentiation in naive B-cells (65). Further analysis has revealed that DNMT3A/B-mediated methylation represses genes involved in activation and chromatin accessibility (66). By contrast, the deletion of *Dnmt3a/b* during early B-cell development (using Mb1-Cre system) results in premature immunoglobulin κ light chain rearrangement, associated with the downregulation of IL-7 signaling and an increased expression of E2A, an essential regulator of V(D)J recombination (66). This underscores the importance of DNA methylation in immunoglobulin gene rearrangement. During the naïve-to-GC transition, GC B-cells display widespread hypomethylation, particularly at AID target loci, while upregulating DNMT1 to maintain methylation homeostasis amid rapid proliferation (67). The loss of DNMT1 in GC B-cells diminishes their numbers, highlighting the indispensability of DNMT1 for GC maintenance (67). However, during somatic differentiation, DNA demethylation is equally crucial for the activation of tissue-specific genes. The conditional ablation of Tet2 and Tet3, the enzymes responsible for DNA demethylation, in B-cells results in impaired differentiation and functional competence (68). Tet2- and Tet3-mediated demethylation is required for the activation of genes governing B-cell lineage commitment, highlighting the coordinated roles of methylation and demethylation in B-cell biology (68).

Histone modifications regulate B-cell development and differentiation. Histone post-translational modifications are a core epigenetic mechanism that regulate gene expression by remodeling chromatin and recruiting effector proteins (22,69). In general, histone acetylation is associated with transcriptional activation, whereas specific methylation marks are frequently associated with gene repression (70). Histone phosphorylation, mediated by protein kinases, modulates DNA-histone interactions and facilitates the assembly of DNA repair and transcriptional complexes. In addition, the ubiquitination of histones H2A and H2B contribute to both gene regulation and DNA damage repair (71).

B-cell development occurs in two sequential phases: An antigen-independent stage in the BM and an antigen-dependent stage in peripheral lymphoid tissues (1). During the latter, naive B-cells undergo CSR and SHM upon activation, eventually differentiating into MBCs and PCs (4). These differentiation steps coincide with marked changes in histone modification patterns. In resting naïve B-cells, chromatin at the immunoglobulin heavy-chain (*IgH*) locus is enriched in repressive marks and depleted of activating modifications, resulting in a compact configuration and low transcriptional activity (72). Upon activation, extensive histone remodeling leads to the induction of genes essential for B-cell effector function. For example, stimulation with lipopolysaccharide and IL-4 has been shown to result in a marked increase in histone H3 acetylation at regulatory elements of the *Aicda* locus (73). These elements also become enriched in H3K9ac, H3K14ac, and H3K4me3 and undergo DNA demethylation, thereby enabling robust AID expression (73). Moreover, activated B-cells exhibit increased expression of the histone acetyltransferase p300, resulting in global histone hyperacetylation. p300-mediated histone lysine acetylation at the Bruton's tyrosine kinase (Btk) promoter enhances *Btk* transcription, thereby potentiating BCR signaling and B-cell activation (74).

Histone ubiquitination also critically influences B-cell development. The major H2A ubiquitin ligase, polycomb repressive complex 1 (PRC1), along with the deubiquitinase USP16, controls H2A ubiquitination. PRC1 is essential for HSC self-renewal (75), and *Usp16* deletion significantly reduces CLPs (76), highlighting a role for H2A ubiquitination in early lymphopoiesis. Similarly, the ubiquitination of H2BK120ub, catalyzed by the RNF20/RNF40 complex and removed by the SAGA-associated deubiquitinase USP22, is essential for CSR by facilitating DNA double-strand break repair during activation (77,78). *Rnf20* or *Rnf40* knockdown diminishes H2Bub levels and impairs CSR in CH12 cells (78), and the conditional deletion of *Usp22* in pre-B-cells disrupts classical non-homologous end joining and antigen-specific IgG1 production without affecting early B-cell development in the BM and periphery (77). In summary, these findings demonstrate that histone ubiquitination is particularly critical for DNA repair processes during antigen-driven B-cell differentiation.

miRNAs and lncRNAs play critical roles in B-cell development and differentiation. Previous studies have delineated stage-specific miRNA networks governing B-cell biology. For example, miR-181 and the miR-17-92 cluster promote early B-cell development (79,80). By contrast, the constitutive expression of miR-150 and miR-34a blocks pro-B-cell to pre-B-cell transition. Mechanistically, miR-150 and miR-34a interfere with early B-cell development by targeting the transcription factors, C-Myb and Foxp1, respectively (81,82). Moreover, studies have demonstrated that the miR-212/132 cluster regulates immunoglobulin gene rearrangement by directly targeting *Sox4* mRNA (83).

During peripheral maturation, transitional B-cells differentiate into splenic follicular or marginal zone (MZ) B-cell subsets. miR-146a deficiency in murine models causes selective depletion of MZ B-cells via Numb-mediated inhibition of Notch2 signaling (84). A complex network of cytokines (such as IL-6, IL-21 and BAFF) and transcription factors (such as Bcl6, Blimp-1 and IRF4) regulates GC responses and antibody affinity maturation (54,55). miR-155 regulates GC reactions and $IgG1^+$ B-cell differentiation by modulating cytokine production and targeting multiple genes, including

the transcription factor PU.1 (85,86). Another critical regulator is miR-142, which plays a pivotal role in B-cell homeostasis. miR-142-deficient mice develop immunoproliferative disorders characterized by an expansion of MZ B-cells and a reduction in B1 B-cells, partly due to the derepression of BAFF (87). Collectively, these findings underscore the intricate miRNA-mediated networks that ensure proper B-cell lineage specification, function and immune competence.

In B-cell development and differentiation, lncRNAs have emerged as key regulatory nodes (88). Numerous lncRNAs display stage-specific expression from hematopoietic stem cells to mature B-cells, plasma cells and memory B-cells (88,89). Expression profiling across developmental stages reveals thousands of lncRNAs associated with proliferation, V(D)J recombination, maturation and immune memory formation (90,91). Early B-cells exhibit IgH locus-associated lncRNAs enriched at topologically associating domain anchors and enhancers, suggesting roles in 3D genome organization and antibody repertoire diversification (92,93). Moreover, lncRNA-CSR^{IgA} promotes the recruitment of regulatory proteins to a proximal CTCF-binding site, thereby reshaping chromosomal interactions within the topologically associated domain (TAD^{lncCSRIgA}) and long-range contacts with the 3' RR super-enhancer, ultimately facilitating CSR to IgA (93). LncHSC-1 and LncHSC-2 are required for HSC self-renewal and differentiation; their knockdown in stem and progenitor cells (Sca-1^{+}) impairs commitment to the B-cell lineage (94). Furthermore, XIST is necessary for the sustained silencing of a set of X-linked immune-related genes (such as TLR7) in B-cells; XIST depletion reactivates these loci and drives differentiation of CD11c^{+} atypical memory B-cells implicated in the pathogenesis of SLE (95).

4. Epigenetic dysregulation in B-cell-mediated autoimmune diseases

The emergence of autoreactive B-cells and their secreted autoantibodies during B-cell development and differentiation drives the onset of autoimmune diseases, primarily including SLE, RA, primary Sjögren's syndrome (pSS), multiple sclerosis (MS) and type 1 diabetes mellitus (T1DM). Emerging evidence suggests that epigenetic dysregulation in B-cells contributes to aberrant B-cell development and differentiation, thereby promoting autoimmune pathogenesis (summarized in Table SI).

SLE. SLE is a chronic, relapsing-remitting systemic autoimmune disease characterized by immune dysregulation (96). B-cells, as the main source of pathogenic autoantibodies, play a pivotal role in the pathogenesis of SLE (97). The low concordance rate of SLE among monozygotic twins indicates that epigenetic regulation is critically involved in the development of SLE (98). In recurrent SLE twin pairs, interferon-stimulated genes (ISGs) in B-cells exhibit hypomethylation, whereas key upstream regulators such as *TNF* and *EP300* are hypermethylated (98). Similarly, the persistent hypomethylation of CpG sites within ISGs has been observed in SLE patient B-cells (99). Fali *et al* (100) reported that DNA hypomethylation in SLE B-cells leads to the overexpression of HRES1/p28, being associated with disease activity. Furthermore, compared with healthy children and adult patients with SLE, B-cells from pediatric patients with SLE display a distinctive chromatin accessibility landscape, with increased accessibility at non-coding genomic regions that regulate inflammatory activation, indicating that epigenetic dysregulation-induced aberrant expression of regulatory elements controlling B-cell activation plays a critical role in the pathogenesis of pediatric SLE (101). In a murine model, the adoptive transfer of B-cells treated with a DNMT1 inhibitor into syngeneic mice resulted in increased antinuclear antibody production (102). Conversely, the deficiency of the demethylases Tet2 and Tet3 leads to hyperactivation of lymphocytes and spontaneous SLE-like autoimmunity (103). Mechanistically, Tet2 and Tet3 remove methylation marks and cooperate with HDAC1/2-mediated deacetylation to suppress *Cd86* expression upon self-antigen engagement, thereby preventing excessive autoreactive B-cell activation (103). Collectively, these studies demonstrate that alterations in B-cell DNA methylation are closely linked to the pathogenesis of SLE.

In addition to DNA methylation, the dysregulation of histone methylation and acetylation critically contributes to the pathogenesis of SLE. During B-cell activation, T-helper cell-derived co-stimulatory signals upregulate the histone demethylases KDM4A and KDM4C, coincident with global reductions in H3K9me2 and H3K9me3 levels (104). These demethylases cooperate with NF-κB p65 to target and activate WDR5, which mediates H3K4 methylation at cyclin-dependent kinase inhibitor (*CDKN*) gene loci, thereby restraining excessive B-cell proliferation (104). In B-cells from patients with SLE, the downregulation of *KDM4A/C* and *WDR5*, accompanied by reduced *CDKN* expression, is associated with heightened B-cell activation and proliferation (104). Moreover, in a previous study, the overexpression of the HMT EZH2 was observed in peripheral blood B-cells and leukocytes from patients with SLE (105). The inhibition of EZH2 with 3-deazaneplanocin A in MRL/lpr mice reduced splenocyte H3K27me3 levels, attenuated anti-dsDNA antibody production and ameliorated lupus-like pathology (105). Compared with healthy donors, B-cells from patients with SLE exhibit the hypoacetylation of histones H3 and H4 (106). The expression and enzymatic activity of the histone deacetylases HDAC6 and HDAC9 are markedly upregulated in B-cells from MRL/lpr mice relative to control mice (107). Moreover, the loss of histone acetyltransferase activity from a single *Ep300* allele in mouse B-cells leads to the development of an autoimmune disease that closely resembles the pathological features of SLE (108). In the area of chromatin remodeling, the literature search performed for the present review identified no available studies to date that have reported alterations in chromatin-remodeling complexes in B-cells and their associations with SLE and other autoimmune diseases. Further investigations in this area are thus warranted (7).

The dysregulated expression of miRNAs in B-cells also contributes to autoimmune pathogenesis. In patients with SLE, B-cells exhibit a decreased expression of Lyn, a critical negative regulator of B-cell activation (109). miR-30a specifically targets Lyn mRNA through the binding to the 3' untranslated region (3'-UTR), and the observed upregulation of miR-30a in SLE B-cells is strongly associated with a decreased expression of Lyn and subsequent B-cell hyperactivation (109). EBF1

promotes B-cell activation and proliferation via the activation of the AKT signaling pathway. However, miR-1246 counteracts this process by interacting with the 3'-UTR of EBF1 mRNA to mediate its degradation (110). In SLE B-cells, the abnormal activation of AKT-p53 signaling downregulates miR-1246, thereby enhancing EBF1 expression and exacerbating B-cell activation (110). In MRL/lpr mice, miR-7 is upregulated and targets PTEN to down-modulate the PTEN/AKT pathway, thereby driving spontaneous GC formation and the generation of autoreactive antibody-secreting PCs (111). B6.Sle123 mice, a spontaneous genetic model of SLE, exhibit an increased expression of miR-21 in both B- and T-cells, which regulates cellular proliferation and apoptosis (112). Notably, the *in vivo* silencing of miR-21 using tiny seed-targeting LNA significantly ameliorates splenomegaly, a hallmark autoimmune manifestation in these mice (112). Research on B/W lupus mice has revealed elevated miR-15a levels in B-10 cells, being associated with autoantibody titers (113). Moreover, mice with the lymphocyte-specific overexpression of the miR-17-92 cluster develop spontaneous autoimmune manifestations. Mechanistically, the miR-17-92 cluster drives lymphocyte proliferation and breaks self-tolerance by directly repressing the pro-apoptotic protein Bim and the tumor suppressor, PTEN (114).

RA. RA is a chronic, systemic autoimmune disorder characterized by progressive synovial inflammation, cartilage degradation and bone erosion, primarily affecting diarthrodial joints (115,116). As one of the most prevalent inflammatory arthropathies, RA affects ~0.5-1% of the global population (116). Synovial tissue samples from patients with RA demonstrate prominent infiltration of B-cells and PCs. Notably, approximately 80% of patients with well-established RA exhibit characteristic autoantibodies, such as anti-citrullinated protein antibodies and rheumatoid factor, highlighting the pivotal role of B-cell-mediated immunity in the pathogenesis of RA (117).

In an epigenome-wide association study (EWAS) on patients with RA, 64 differentially methylated CpG sites and six dysregulated biological pathways were consistently identified in B-cells across three different replication cohorts (118). Among these, the key B-cell activation gene *CD1C* exhibited significant hypermethylation in B-cells from RA patients (118). B-cells from patients with early-stage RA also exhibit a decreased expression of DNMT1 and DNMT3A, concomitant with a global decrease in DNA methylation (119). Methotrexate (MTX) treatment partially reversed these epigenetic alterations by restoring DNMT1 and DNMT3A expression in B-cells (119). In the proteoglycan-induced arthritis (PGIA) murine model, the promoter hypomethylation-driven *Zbtb38* overexpression in B-cells promotes the progression of arthritis by suppressing IL-1 receptor 2 expression and inhibiting key anti-inflammatory pathways (120). Conversely, the administration of the DNA methyltransferase inhibitor 5-azacytidine (AzaC) has been shown to ameliorate autoimmune arthritis in PGIA mice by downregulating AID in B-cells, impairing CSR and GC responses, and reducing IgG1 production (121). As demonstrated in a previous study, compared with healthy controls, the expression of class I HDACs was significantly decreased in peripheral blood mononuclear cells from patients with RA, whereas nuclear HAT activity was markedly increased (122). This imbalance resulted in increased acetylation of histone H3 and upregulation of genes encoding pro-inflammatory cytokines, thereby contributing to the pathogenesis of RA (122).

The dysregulated expression of miRNAs in B-cells further contributes to the development of RA. In a previous study, small RNA sequencing revealed the differential expression of 27 miRNAs in B-cells from patients with RA in remission following treatment with MTX, compared to the healthy controls. The predicted targets of these miRNAs were enriched in pathways governing B-cell activation, differentiation, and BCR signaling (123). Compared with healthy controls, miR-155 (an essential regulator of GC and PC differentiation) is markedly upregulated in peripheral blood B-cells from patients with RA (124). In synovial tissue, miR-155 expression inversely correlates with the transcription factor PU.1. The inhibition of endogenous miR-155 in RA B-cells restores PU.1 levels and reduces autoantibody production (124). A high expression of miR-155 has also been observed in $CD14^+$ synovial cells, where it downregulates the anti-inflammatory phosphatase SHIP-1 and promotes the release of pro-inflammatory cytokines (125). Conversely, miR-155 inhibition in RA $CD14^+$ synovial cells has been shown to decrease TNF-α secretion (125). Moreover, the genetic deletion of miR-155 prevents collagen-induced arthritis in mice, identifying miR-155 as a potential therapeutic target in RA (125).

pSS. pSS is a chronic systemic autoimmune disease characterized by the lymphocytic infiltration of exocrine glands, resulting in inflammation and tissue destruction of the salivary and lacrimal glands, and clinically manifesting as xerostomia (dry mouth) and keratoconjunctivitis sicca (dry eyes) (126). Beyond classic exocrine involvement, pSS often presents with systemic complications, including interstitial lung disease, renal tubular acidosis, peripheral neuropathy, as well as hematological abnormalities, such as cytopenias and B-cell lymphoproliferative disorders, reflecting its complex immunopathogenesis (127,128). Emerging evidence implicates epigenetic dysregulation and B-cell hyperactivity with autoantibody production as key drivers of pSS. For example, anti-SSA/Ro antibodies are detected in ~33-74% of cases, and anti-SSB/La antibodies are detected in 23-52% of cases (128).

Epigenome-wide analyses have demonstrated that DNA methylation changes in peripheral B-cells of patients with pSS far exceed those observed in T-cells, with genes involved in B-cell signaling, inflammation and autoimmunity exhibiting significant methylation alterations (129). Specifically, ISGs, including *PARP9*, *IFI44L* and *MX1* are markedly hypomethylated in B-cells of patients with pSS, being associated with their transcriptional upregulation and B-cell expansion (129,130). In a genome-wide DNA methylation study of labial salivary gland biopsies, 7,820 differentially methylated sites associated with disease status were identified, 5,699 hypomethylated and 2,121 hypermethylated, and enrichment analysis revealed that genes crucial for B-cell differentiation and function (such as *SPI1*, *CD19*, *CD79B*, *PTPRCAP* and *TNFRSF13B*) were predominantly hypomethylated, highlighting the pivotal role of B-cell DNA methylation alterations in pSS (131). Furthermore, in another study, active histone marks, including H3K4me2, H3K4me3, H3K36me3, H3K9ac and H3K27ac, were shown to

be significantly enriched at promoters and enhancers harboring Sjögren's syndrome risk variants in B-cells from patients with pSS, suggesting that epigenetic mechanisms contribute to the regulation of these promoters and enhancers (132).

The transcriptome sequencing of B-cell subsets from patients with pSS has revealed the significant upregulation of the lncRNA *LINC00487* in $CD38^{+}IgD^{+}$ (immature B-cells), $CD38^{-}IgD^{+}$ (Bm1 cells), $CD38^{high}IgD^{+}$ (pre-GC B-cells) and $CD38^{+}IgD^{-}$ (MBCs) subsets, with *LINC00487* expression levels being positively associated with the clinical disease activity score (133). Furthermore, in a previous study, comparative miRNA expression profiling revealed significant disparities between B- and T-cells in patients with pSS. Peripheral B-cells from patients with pSS exhibited the significant dysregulation of 24 miRNAs, with 11 upregulated and 13 downregulated miRNAs, compared to the healthy controls (134). In both discovery and independent replication cohorts, miR-30b-5p, miR-222-3p, miR-19b-3p, miR-26a-5p, and miR-378a-3p were consistently dysregulated (134). Notably, miR-30b-5p targets the 3'-UTR of BAFF, and its downregulation in pSS B-cells is associated with BAFF overexpression (134). Elevated BAFF levels have also been observed in salivary gland-infiltrating B-cells (135). Collectively, these studies highlight the critical contribution of non-coding RNA dysregulation in the B-cell-mediated pathogenesis of pSS.

MS. MS is a chronic immune-mediated demyelinating disorder of the central nervous system (CNS), characterized by inflammatory lesions, axonal damage and progressive neurological disability (136,137). Accumulating evidence over the past decade has demonstrated that B-cells play a pivotal role in the pathogenesis of MS by producing autoantibodies, presenting antigens, and secreting pro-inflammatory cytokines, thereby exacerbating damage to the CNS (138,139). An abnormal cytokine profile has been observed in B-cells from patients with MS, with activated B-cells exhibiting the excessive production of pro-inflammatory cytokines, including TNF-α, lymphotoxin and granulocyte-macrophage colony-stimulating factor (140,141). Moreover, clinical trials of B-cell-depleting therapies in relapsing-remitting MS (RRMS) have yielded strikingly positive outcomes, further underscoring the contribution of B-cells to disease activity (142).

The genome-wide DNA methylation profiling of T-cells, monocytes and B-cells from patients with RRMS, secondary progressive MS and healthy controls has revealed a preponderance of differentially methylated positions (DMPs) in B-cells (143). These DMPs are predominantly located within genes associated with lymphocyte signaling pathways (143). In a previous study on patients with RRMS in remission under various treatments, the analysis of $CD19^{+}$ B-cell methylomes identified a large hypermethylated region encompassing the transcriptional start site of the lymphotoxin-α (*LTA*) locus (144). Additionally, four MS-associated loci, including *SLC44A2*, *LTBR*, *CA*RD11 and *CXCR5*, exhibited significant methylation changes (144), suggesting that B-cell-specific DNA methylation, particularly at the *LTA* locus, may contribute to the pathogenesis of MS. Moreover, in another study, an integrative analysis of MS immune-cell GWAS data and histone-modification profiles revealed that MS genetic risk loci in B-cells are enriched at active enhancers and promoters marked by H3K4me1, H3K4me3 and H3K27ac, indicating that MS genetic risk associations preferentially localize to active enhancer and promoter regions (145).

The dysregulated expression of miRNAs in B-cells also influences the progression of MS. In a previous study, the transcriptomic analyses of peripheral B-cells from untreated patients with MS revealed the marked downregulation of *IRF1* and *CXCL10*; the suppression of the IRF1/CXCL10 axis may foster a pro-survival phenotype in these cells (146). Mechanistically, the upregulation of miR-424 in B-cells of patients mediates the downregulation of IRF1 and CXCL10 (146). In RRMS lymphocyte subsets, purified $CD19^{+}$ B-cells exhibit an increased expression of miR-497 alongside decreased levels of miR-92, miR-153, miR-135b, miR-422a and miR-189 relative to healthy volunteers (147). A comprehensive expression analysis of 1,059 miRNAs in B-cells from healthy volunteers, treatment-naïve patients with RRMS and natalizumab-treated patients with RRMS identified 49 differentially expressed miRNAs in untreated patients compared to healthy volunteers, including miR-25, miR-19b, miR-106b, miR-93 and miR-181a (148). Target prediction and pathway analyses indicated that these miRNAs predominantly regulate B-cell receptor signaling pathway, PI3K pathway, and PTEN pathway (148). Notably, natalizumab treatment upregulated 10 miRNAs, including miR-106b, miR-19b and miR-191 (148). Furthermore, hyperactivated B-cells in MS secrete pro-inflammatory cytokines, including TNF-α and lymphotoxin. The elevated expression of miR-132 in these cells enhances TNF-α and lymphotoxin production by inhibiting SIRT1 activity (149).

T1DM. T1DM is a chronic autoimmune disorder characterized by the immune-mediated destruction of insulin-producing pancreatic β-cells, culminating in absolute insulin deficiency (150). Although T-cells have traditionally been considered the primary mediators of pancreatic tissue injury, accumulating evidence indicates that B-cells also contribute significantly to the pathogenesis of T1DM (151). To investigate the influence of B-cell epigenetic factors on the progression of T1DM, a genome-wide DNA methylation study was performed on purified B-cells from three pairs of monozygotic twins discordant for T1DM and six pairs of unaffected monozygotic twins. This analysis identified 88 CpG sites with altered methylation in B-cells from the T1DM-affected twins (152). Functional enrichment analysis revealed that genes harboring these differentially methylated sites are predominantly involved in immune-response pathways (152). In a separate investigation involving 52 pairs of monozygotic twins discordant for T1DM, methylation profiling at 406,365 CpG sites in B-cells, monocytes, and $CD4^{+}$ T-cells uncovered multiple cell-type-specific differentially variable positions (DVPs) related to cell-cycle control and metabolic processes in the T1DM-affected twins compared with their healthy co-twins and unrelated healthy controls (153). Notably, significant DVPs were observed at loci encoding the B-cell transcriptional regulators NRF1 and FOXP1, highlighting a postnatal role for DNA methylation in the pathogenesis of T1DM (153). Compared with healthy controls, peripheral blood lymphocytes from individuals with T1D have been shown to exhibit a significant increase in H3K9me2 at genes

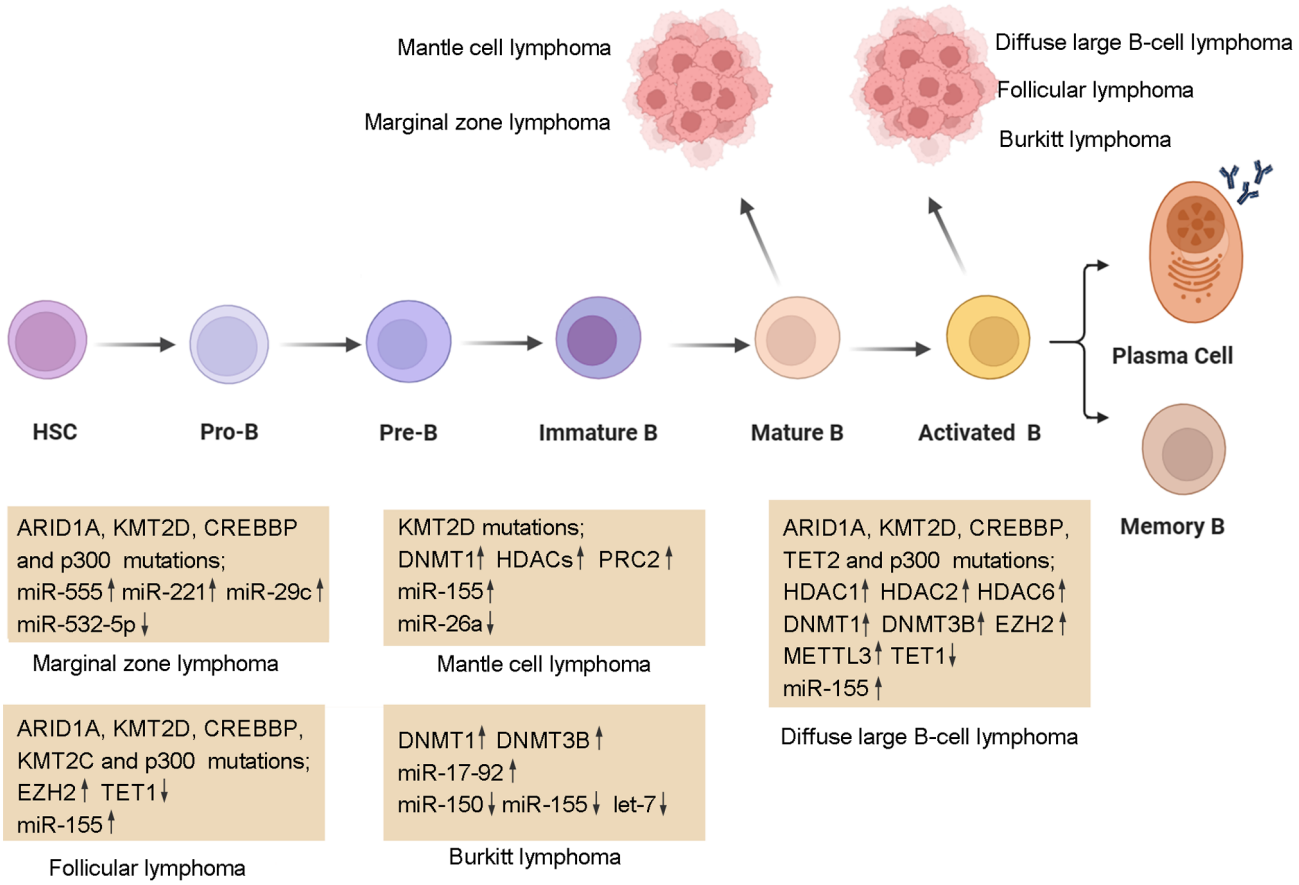

Figure 3. Schematic representation of epigenetic dysregulation in B-cell lymphomas. Diffuse large B-cell lymphoma primarily arises from activated or GC B cells; representative epigenetic alterations include mutations in ARID1A, KMT2D, CREBBP, TET2 and p300, and overexpression of HDAC1, HDAC2, HDAC6, DNMT1, DNMT3B, EZH2, METTL3 and miR-155. Follicular lymphoma originates from GC B cells; representative epigenetic alterations include mutations in ARID1A, KMT2D, CREBBP, KMT2C, and p300, overexpression of EZH2 and miR-155, and downregulation of TET1. Mantle cell lymphoma mainly arises from mature B cells; representative epigenetic changes include KMT2D mutations, overexpression of DNMT1, HDACs, PRC2 components, and miR-155, and downregulation of miR-26a. Burkitt lymphoma arises from GC B cells; representative epigenetic alterations include overexpression of DNMT1, DNMT3B and the miR-17-92 cluster, and downregulation of miR-150, miR-155, and members of the let-7 family. Marginal zone lymphoma originates from mature B cells; representative epigenetic dysregulation includes recurrent mutations in ARID1A, KMT2D, CREBBP, and p300, overexpression of miR-555, miR-221 and miR-29c, and downregulation of miR-532-5p. In the image, the upward arrows (↑) indicate an increased expression and the downward arrows (↓) indicate a decreased expression.

involved in autoimmune and inflammatory pathways (154). These findings indicate that altered histone methylation at key genomic loci in lymphocytes is associated with T1DM (154). Complementary studies in murine models have demonstrated that the diabetes-protective *Idd9.3* locus encodes miRNA-34a, which impairs B-cell development and maturation by targeting the core regulatory factor Foxp1, thereby conferring resistance to the onset of T1DM (155).

5. Epigenetic dysregulation in B-cell lymphomas

B-cell non-Hodgkin lymphoma (B-NHL) is a highly heterogeneous malignancy originating from B-cells and accounts for ~85-90% of all lymphoma cases (6). Based on the cell of origin, molecular characteristics and clinical behavior, B-NHL can be classified into several distinct subtypes, including DLBCL, FL, MCL, Burkitt lymphoma (BL) and marginal zone lymphoma (MZL). The present review focuses on the role of dysregulated epigenetic mechanisms in the pathogenesis and progression of B-NHL (illustrated in Fig. 3). The roles of dysregulated epigenetic enzymes in B-NHL are summarized in Table SII.

DLBCL. DLBCL is the most common and aggressive subtype of B-NHL, representing ~30-40% of all B-NHL cases (156,157). Gene expression profiling further stratifies DLBCL into GC B-cell-like (GCB) DLBCL, activated B-cell-like (ABC) DLBCL and unclassified groups (158). Loss-of-function mutations in the SET domain of histone lysine N-methyltransferase 2D (KMT2D) represent the most frequent epigenetic abnormality in DLBCL, occurring in ~30-40% of cases (159,160). Mechanistically, KMT2D deficiency impairs H3K4 methylation and dysregulates the expression of specific gene sets, including those involved in JAK-STAT, Toll-like receptor, CD40 and BCR signaling pathways, as well as tumor suppressors, such as *SOCS3*, *TNFRSF14* and *TNFAIP3* (161). Consequently, KMT2D mutations promote malignant B-cell proliferation by disrupting the coordinated activation of B-cell signaling cascades and the expression of anti-oncogenic regulators (161). Furthermore, loss-of-function mutations in the histone acetyltransferases CREBBP and p300 are found in ~40% of DLBCL cases (159,162). These mutations reduce the acetylation of BCL6 and p53, thereby perturbing BCL6 inactivation and p53-mediated tumor suppression and

enhancing tumor cell resistance to DNA damage (163). The overexpression of the HDACs, HDAC1, HDAC2 and HDAC6, together with global H4 hypoacetylation, also contributes to transcriptional repression (164). In particular, HDAC6 plays a critical role in coping with proteotoxic stress by regulating the acetylation-dependent stability of the HSP90 and mediating the binding of misfolded proteins to the dynein motor for transport to aggresomes (165-167).

Dysregulated DNA methylation further contributes to the pathogenesis of DLBCL. DNMT1 and DNMT3B are overexpressed in DLBCL, and are associated with an advanced clinical stage, therapeutic resistance, and, specifically for DNMT3B, significantly shorter overall survival and progression-free survival (168). Research has demonstrated that DNMT1 modulates cell-cycle progression and DNA replication, as DNMT1 knockdown in GCB-DLBCL cell lines markedly suppresses the expression of *CDK1*, *CCNA2*, *E2F2*, *PCNA*, *RFC5* and *POLD3* (169). By contrast, the DNA demethylase TET2 functions as a tumor suppressor and harbors loss-of-function mutations in DLBCL (170). Murine models demonstrate that the knockout of *Tet1* and *Tet2* promotes the development of DLBCL (171,172). Moreover, transcriptional downregulation of *TET1* has been observed in patients with DLBCL and FL (173). EZH2, the catalytic subunit of PRC2, is overexpressed in >70% of aggressive B-cell lymphomas and is associated with high proliferation rates (174). Furthermore, gain-of-function mutations of EZH2 (most frequently at Y641 and A677) are predominate in GC-type DLBCL and FL (175). Moreover, a mutation of EZH2 promotes the growth of GC-type DLBCL by recruiting PRC2 to silence *PRDM1* (176).

Recent evidence has also highlighted dysregulated RNA methylation and miRNAs in DLBCL. The N^6-Methyladenosine (m^6A) 'writer' METTL3 and global m^6A levels are upregulated in DLBCL tissues and cell lines, and METTL3 knockdown inhibits proliferation by reducing m^6A modification of pigment epithelium-derived factor mRNA, thereby impairing DLBCL progression (177). The miR-17-92 cluster is overexpressed in DLBCL and FL. Mechanistically, overexpressed miR-17-92 cooperates with c-MYC to promote B-cell lymphoma growth by enhancing lymphoma cell proliferation and suppressing apoptosis (178,179). In a previous study, the analysis of miRNA profiles from 58 DLBCL cases revealed that, compared to normal tissues, miR-155, miR-210, miR-106a, and miR-17-5p were significantly upregulated, whereas miR-95, miR-150, miR-139, miR-145, miR-149, miR-328, miR-10a, miR-99a, miR-320, miR-151 and let-7e were downregulated (180). Notably, miR-155 plays a crucial role in the pathogenesis of DLBCL by inhibiting apoptosis and promoting cell proliferation through the activation of the PI3K/AKT signaling pathway (181).

FL. FL, the second most common subtype of B-NHL, accounts for ~25% of all B-NHL cases. FL originates from GC B-cells and is characterized by the t(14;18)(q32;q21) translocation, which leads to the overexpression of the anti-apoptotic gene *BCL2* (182). Among the KMT2 family members, KMT2D and KMT2C have been implicated in the pathogenesis of FL (183,184). Of note, ~72% of patients with FL harbor KMT2D mutations, the majority of which are nonsense or frameshift alterations resulting in reduced KMT2D protein expression (183). In addition, gain-of-function mutations in EZH2 are observed in ~7.2% of FL cases (185). Mechanistically, mutant EZH2 drives FL initiation by epigenetically reprogramming B-cells and remodeling the immune microenvironment: It promotes the follicular dendritic cell (FDC)-mediated replacement of T-cell help, thereby facilitating the gradual expansion of GC B-cells (186). CREBBP is also recurrently mutated in over 50% of FL cases (163). In a *Bcl2*-overexpressing mouse model, GC-specific *Crebbp* deletion accelerates FL development (187). Mutations in the SWI/SNF complex subunit ARID1A reduce *RUNX3* expression, resulting in decreased RUNX3/ETS1-driven *FAS* transcription (188). The consequent downregulation of FAS renders FL cells resistant to FAS ligand-induced apoptosis (188). The comparative profiling of miRNA expression in FL and DLBCL vs. normal lymph nodes has revealed the overexpression of miR-155, miR-106a, miR-149, miR-210 and miR-139 in both malignancies. Notably, miR-20a/b and miR-194 are selectively upregulated in FL; these miRNAs enhance tumor cell proliferation and survival by targeting *CDKN1A* and *SOCS2*, respectively (189).

MCL. MCL is a rare B-NHL, accounting for ~5-7% of all lymphomas (190). The defining genetic hallmark of MCL is the t(11;14)(q13;q32) chromosomal translocation; this translocation places the cyclin D1 gene (*CCND1*) under the control of the *IgH* enhancer, leading to cyclin D1 overexpression and consequent disruption of normal cell-cycle control (191). Beyond cyclin D1 dysregulation, MCL cells frequently acquire secondary genetic alterations that impact multiple signaling pathways, including recurrent mutations in MYC, ATM, TP53 and NOTCH1 (192-194).

Epigenetic dysregulation also plays a pivotal role in the pathogenesis of MCL. Genome-wide DNA methylation profiling has revealed highly heterogeneous methylation patterns in MCL tumor tissues compared with normal lymphoid counterparts. Specifically, WNT pathway inhibitors and several tumor suppressor genes show significant hypermethylation (195). Moreover, DNMT1 is upregulated in MCL, and treatment with arsenic trioxide inhibits WNT/β-catenin signaling and reduces DNMT1 levels, thereby inducing apoptosis and attenuating proliferation in MCL cell lines (196). Hypomethylation within the downstream region of the *SOX11* oncogene has been identified in MCL tumors, suggesting that epigenetic mechanisms may regulate *SOX11* expression (197).

Histone modifications further contribute to MCL biology. HDACs are overexpressed in MCL, and pharmacologic HDAC inhibition induces cell-cycle arrest and apoptosis in these cells (198,199). *KMT2D* is among the most frequently mutated genes in both DLBCL and MCL (200). Loss-of-function KMT2D mutations reduce H3K4 methylation and drive neoplastic proliferation in MCL (201). Furthermore, the PRC2 complex is overexpressed in MCL cell lines, promoting tumor-cell proliferation and survival by epigenetically silencing the cyclin-dependent kinase inhibitor gene *CDKN2B* (202).

miRNAs provide an additional layer of epigenetic regulation in MCL. A study of the miRNA expression profiles in 30 patients with MCL revealed that, compared to normal B-cells, 18 miRNAs were significantly downregulated and 21 miRNAs were significantly upregulated in MCL tissues (203). Notably,

miR-142-3p/5p, miR-29a/b/c and miR-150 were significantly downregulated, whereas miR-155 and miR-124a were markedly upregulated (203). A separate study reported that miR-26a, miR-31, miR-27b and miR-148a were significantly downregulated, whereas miR-370, miR-617 and miR-654 were upregulated in MCL tissues compared to reactive lymphoid tissues. Notably, MAP3K2 (a predicted target of miR-26a) was upregulated in MCL tissues and plays a crucial role in the activation of the alternative NF-κB pathway (204).

BL. BL is a GC-derived B-NHL, accounting for ~1-5% of all NHL cases. BL is characterized by MYC dysregulation secondary to chromosomal translocations such as t(8;14)(q24;q32). Overexpression of DNA methyltransferases DNMT1 and DNMT3B has been observed in primary BL specimens, and treatment of BL cell lines with the DNMT inhibitor 5-aza-2'-deoxycytidine significantly inhibits cellular proliferation by reducing the protein levels of DNMT1 and DNMT3B (205). miR-155 expression is significantly downregulated in BL, where it binds to the 3'-UTR of AID mRNA, promoting its degradation and thereby suppressing AID-mediated MYC-IGH translocations (206). miR-150 is also downregulated in BL and directly targets c-Myb and Survivin (207). The re-expression of miR-150 in the Raji cell line has been shown to diminish cell proliferation, suggesting that miR-150 may serve as a potential therapeutic target of BL (207). Compared with other types of NHL, BL exhibits the upregulation of the miR-17-92 cluster and the downregulation of let-7 family miRNAs, miR-146a, miR-155 and the miR-29 family (208). In addition, reduced levels of let-7 family, miR-132, miR-125b-1 and miR-154 contribute to increased expression of MYC and other oncogenes in BL (209).

MZL. MZL accounts for ~5-15% of all B-NHL. It can be subdivided into three distinct subtypes: Extranodal marginal zone lymphoma (EMZL), splenic marginal zone lymphoma (SMZL) and nodal marginal zone lymphoma (NMZL) (210). EMZL represents >60% of MZL cases and is associated with chronic inflammation triggered by autoimmune disorders or infectious agents. This subtype is characterized by recurrent genetic translocations, including t(11;18)(p21;q21) in API2-MALT1, t(14;18)(p32;q21) in IGH-MALT1 and t(1;14)(p22;q32) in BCL10-IGH, which collectively drive transcriptional dysregulation of *BCL10*, *MALT1* and *FOXP1* (211-213). By contrast, these translocations are not detected in NMZL and SMZL (210). However, NMZL and SMZL share recurrent somatic mutations in *KMT2D, NOTCH2, PTPRD, TNFAPI3* and *KLF2* (214).

Epigenetic alterations play a critical role in the pathogenesis of MZL. In SMZL, frequent mutations occur in chromatin regulators, such as KMT2D, ARID1A, p300 and CREBBP (215). The genome-wide methylation profiling of SMZL has revealed hypermethylation and the transcriptional silencing of multiple tumor suppressors (*KLF4*, *DAPK1*, *CDKN1C*, *CDKN2D* and *CDH1/2*) alongside hypomethylation and overexpression of oncogenes in the NF-κB, AKT/PI3K, BCR and IL-2 signaling pathways (216). Compared with reactive lymphoid hyperplasia, NMZL exhibits the upregulation of miR-555, miR-221 and miR-29c, and the downregulation of miR-532-5p. Predicted targets of miR-555 and miR-221 include CD10 and LMO2, respectively, whereas miR-532-5p targets BCR-related kinases, such as SYK and LYN, the overexpression of which is associated with enhanced tumor cell proliferation (217).

6. Biomarkers and therapeutic targets

Biomarkers. Epigenetic modifications are dynamic and reversible, and serve as valuable biomarkers in B-cell-mediated autoimmune diseases and lymphomas (summarized in Table SIII). Alterations in DNA methylation, histone modification and non-coding RNAs contribute to disease classification, prognosis and to the prediction of the therapeutic response (218). In SLE, B-cells exhibit global hypomethylation, particularly at interferon-related genes such as IFI44L, PARP9 and MX1, which are strongly associated with disease activity (219). Additional regulators involved in inflammatory and chromatin networks also display aberrant epigenetic states (220). In patients with SLE, defective DNA methylation in B-cells leads to the overexpression of the endogenous retrovirus HRES1/p28, with the dysregulation of the Erk/DNMT1 signaling pathway and autocrine IL-6 signaling playing key roles (100). Notably, intervention with anti-IL-6 receptor antibodies can restore DNA methylation and effectively suppress HRES1/p28 expression, providing a novel therapeutic strategy for the disease. At the miRNA level, miR-30a upregulation promotes B-cell activation by suppressing Lyn (109), whereas reduced miR-1246 increases EBF1 expression and enhances AKT signaling, promoting B-cell activation and proliferation (110). In pSS, B-cells display widespread methylome and transcriptome dysregulation affecting inflammatory and B-cell signaling pathways, including ISGs; the hypomethylation of PARP9, IFI44L and MX1 is associated with B-cell expansion (221,222). The downregulation of miR-30b-5p contributes to the excess expression of BAFF.

In RA, EWAS analyses have identified multiple differentially methylated loci with biomarker potential (223). Early-stage RA is characterized by decreased DNMT1/3A expression and global hypomethylation, while MTX may partially restore methylation patterns and predict treatment response (119). The upregulation of miR-155 enhances autoantibody production by suppressing PU.1, contributing to pathogenic B-cell responses (124). In MS, B-cell methylation alterations are prominent. Patients with RRMS exhibit differential methylation, including the hypermethylation of the IL2RA promoter and changes at SLC44A2, LTBR, CARD11, and CXCR5, implicating epigenetic regulation in disease susceptibility and progression (224). Upregulated miR-424 suppresses the IRF1-CXCL10 pathway and promotes a survival phenotype, whereas miR-132 enhances TNF-α and lymphotoxin expression by targeting SIRT1, strengthening inflammatory B-cell responses (146,149).

Recent studies have identified two prognostic molecular signatures in DLBCL: A six-gene m^6A regulator signature (ALKBH5, FMR1, HNRNPC, RBM15B, YTHDC2 and YTHDF1) and an eight-gene mitochondria-related signature (PCK2, PUSL1, ACP6, PDK4, ALDH4A1, C15orf61, THNSL1 and COX7A1) (225,226). Both signatures demonstrated potent prognostic performance, stratifying patients into high- and low-risk groups with distinct survival patterns,

immune infiltration characteristics, and predicted responses to immunotherapy. These findings underscore the prognostic relevance of m^6A regulation and mitochondrial metabolism in DLBCL, and provide promising biomarkers for precision risk assessment and therapeutic guidance. The overexpression of DNMT3B predicts a poor survival, whereas the loss of TET2 disrupts AID-mediated DNA demethylation in GC B-cells, resulting in aberrant DNA hypermethylation that alters gene regulation and promotes lymphomagenesis (168,227).

In FL, gain-of-function EZH2 mutations (such as Y641) reprogram GC B-cells by reducing their dependence on T-follicular helper cells, promoting centrocyte survival and slow expansion within FDC networks, thereby establishing an aberrant immunological niche that underlies indolent tumor growth (186). Concurrently, the epigenetic dysregulation of GC B-cells through mutations in KMT2D and CREBBP perturbs transcriptional programs controlling proliferation, differentiation and microenvironment interactions, contributing to malignant transformation and immune niche remodeling (228). Collectively, these epigenetic alterations highlight critical mechanisms by which GC B-cells evolve into FL and provide potential targets for microenvironment-focused therapeutic strategies. In MCL, integrative DNA methylome analyses reveal widespread epigenetic heterogeneity with hypermethylation of B-cell-unrelated regions and recurrent hypomethylated differentially methylated regions associated with *SOX11*, suggesting that epigenetic reprogramming of distal regulatory elements contributes to tumorigenesis and clinical behavior (197).

Therapeutic targets. Epigenetic regulatory pathways provide multiple druggable targets for B-cell-associated autoimmune diseases and B-cell lymphomas, and several inhibitors have already entered clinical use or advanced stages of clinical development (summarized in Table SIII). Mutations in EZH2 are observed in ~22% of GC-derived lymphomas, including FL and DLBCL (175). The FDA-approved EZH2 inhibitor, tazemetostat, has demonstrated clinical activity in patients with *EZH2* mutant relapsed or refractory FL (229,230). An open-label, single-arm, phase II clinical trial reported that oral tazemetostat administered at 800 mg twice daily achieved an objective response rate of 69% in the *EZH2* mutant cohort vs. 35% in the *EZH2* wild-type cohort (230). Moreover, in GC-DLBCL cases that are insensitive to EZH2 inhibition, combination therapeutic approaches targeting compensatory pathways, for example, the cholesterol biosynthesis pathway, have shown promise in preclinical models (231). KMT2D loss-of-function mutations represent another major alteration in GC-derived lymphomas (159). Haploinsufficiency of *KMT2D* disrupts H3K4 methylation at enhancers, resulting in global impairment of enhancer activity and consequent dysregulation of genes involved in differentiation and immune regulation (161). Preclinical studies have shown that pharmacological inhibition of members of the KDM5 family of H3K4 demethylases, which functionally antagonize KMT2D, can restore H3K4 methylation levels and suppress tumor growth in KMT2D-mutant models (232). However, as KDM5 family members exhibit significant functional redundancy, therapeutic efficacy may require the simultaneous inhibition of multiple paralogs (232). CREBBP alterations impair histone acetylation at enhancers and promoters that regulate genes involved in immune responses and cellular differentiation (233). Mechanistic analyses have indicated that CREBBP loss creates a dependency on class I histone deacetylase activity, notably HDAC3 (233). The selective inhibition of HDAC3 reverses the epigenetic reprogramming induced by CREBBP mutations, restores the expression of tumor-suppressor and antigen-presentation genes, and demonstrates anti-B-cell lymphoma activity in preclinical models (233,234). In addition, combination regimens pairing the pan-HDAC inhibitor vorinostat with rituximab (a monoclonal antibody targeting CD20) have improved outcomes in patients with B-cell lymphoma (235). Moreover, *in vitro* research has demonstrated that the PRC2 inhibitor, pyrroloquinoline quinone, exerts potent inhibitory effects on the proliferation of B-cell lymphoma cells (236).

The aberrant expression of HDACs plays a crucial role in the development of autoimmune diseases, and inhibitors targeting HDACs have shown immense promise in the treatment of these disorders (237,238). Compared with age-matched control mice, MRL/lpr lupus model mice exhibit an elevated expression and activity of HDAC6 and HDAC9 during both the early and late stages of disease (107). Preclinical studies have demonstrated that the HDAC6-selective inhibitor, ACY-738, suppress multiple B-cell activation pathways, reduces PC formation and attenuates GC responses in lupus-prone mice (238,239). Treatment with the DNMT inhibitor, 5'-azacytidine, an FDA-approved anticancer agent, induces hypomethylation of the *Ahr* gene, downregulates *Aicda* expression, attenuates GC responses and diminishes IgG1 production, ultimately leading to marked amelioration of RA-like disease in mice (121). Taken together, these findings establish a strong rationale for developing novel epigenetic therapies in autoimmune diseases and lymphomas.

7. Conclusions and future perspectives

B-cells allow response against a large number of antigens from various pathogens and confer the important feature of immune memory. Extensive research has shown that DNA methylation, post-translational histone modifications, and miRNAs together constitute the epigenetic landscape governing B-cell differentiation and function. Technological advances, particularly in single-cell transcriptomics, whole-genome bisulfite sequencing and next-generation sequencing, have greatly deepened our understanding of these regulatory mechanisms during B-cell development and differentiation. Specifically, distinct B-cell subsets exhibit dynamic epigenetic profiles, while immature B-cells display genome-wide DNA hypermethylation and histone deacetylation, whereas activated B-cells exhibit elevated histone lysine methylation. Dysregulation of epigenetic modifications frequently contributes to the pathogenesis of autoimmune diseases and lymphomas.

Over the past decades, high-throughput sequencing approaches have provided extensive insights into the mechanisms through which epigenomic dysregulation contributes to B-cell-mediated autoimmunity and lymphomagenesis. Aberrant DNA methylation patterns, altered histone-modifying enzyme activities, and imbalances in miRNA and

lncRNA expression act in concert to promote autoreactive B-cell expansion, pathogenic autoantibody production and pro-inflammatory cytokine release, thereby facilitating malignant transformation. Unlike irreversible genetic mutations, epigenetic modifications are reversible and thus represent attractive therapeutic targets. Preclinical and clinical evidence demonstrates that selective inhibitors targeting these epigenetic enzymes, such as EZH2 inhibitors, KDM5 inhibitors, HDAC3/HDAC6 inhibitors and DNMT inhibitors, can restore normal epigenetic landscapes, suppress malignant B-cell proliferation, attenuate autoimmune responses, and improve disease outcomes (121,229,232,234). Moreover, combination strategies that integrate epigenetic modulators with chemotherapeutic agents or therapies targeting compensatory pathways further enhance therapeutic efficacy and overcome resistance mechanisms (231,240). These findings collectively provide a strong rationale for the continued development and clinical translation of epigenetic therapies, highlighting their promise as precision interventions for both B-cell malignancies and autoimmune disorders.

The pathogenesis of B-cell-derived autoimmune diseases and lymphomas involves complex interactions among genetic, epigenetic and microenvironmental factors. Although significant progress has been made in elucidating epigenetic contributions, further studies are required to define the precise molecular events that drive disease initiation and progression. Future efforts integrating multi-omics analyses, single-cell sequencing and spatial epigenomics will be critical for elucidating these mechanisms. Moreover, the identification of reliable biomarkers is essential for early diagnosis and the development of targeted therapies. The comprehensive characterization of B-cell epigenetic landscapes using high-throughput technologies will accelerate biomarker discovery and facilitate personalized treatment strategies in B-cell autoimmune diseases and lymphomas.

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Authors' contributions

YL, YG and JZ wrote the manuscript. RR provided the overall concept and framework of the manuscript and revised it. All authors have read and agreed to the published version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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