REVIEW

Epigenetic regulation in B-cell maturation and its dysregulation in autoimmunity

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B cells have a critical role in the initiation and acceleration of autoimmune diseases, especially those mediated by autoantibodies. In the peripheral lymphoid system, mature B cells are activated by self or/and foreign antigens and signals from helper T cells for differentiating into either memory B cells or antibody-producing plasma cells. Accumulating evidence has shown that epigenetic regulations modulate somatic hypermutation and class switch DNA recombination during B-cell activation and differentiation. Any abnormalities in these complex regulatory processes may contribute to aberrant antibody production, resulting in autoimmune pathogenesis such as systemic lupus erythematosus. Newly generated knowledge from advanced modern technologies such as next-generation sequencing, single-cell sequencing and DNA methylation sequencing has enabled us to better understand B-cell biology and its role in autoimmune development. Thus this review aims to summarize current research progress in epigenetic modifications contributing to B-cell activation and differentiation, especially under autoimmune conditions such as lupus, rheumatoid arthritis and type 1 diabetes.

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INTRODUCTION

Although increasing evidence has indicated a pivotal role of B cell in the initialization and acceleration of autoimmune disorders, the molecular mechanisms underlying dysregulated B-cell activation and differentiation are still poorly defined. Genome-wide association studies have identified hundreds of gene polymorphisms associated with B-cell functions and differentiation,\textsuperscript{1–3} which may increase the susceptibility to autoimmune development. As the concordance rate of autoimmune diseases is <50% in monozygotic (MZ) twins,\textsuperscript{4} the epigenetic differences in genomic distribution of 5-methylcytosine (5-mC) DNA and histone modifications among MZ twins can alter the gene expression profile and contribute to their disease susceptibilities.\textsuperscript{5–7} Moreover, these epigenetic differences appear to result from environmental factors, such as infection, diet, and drugs.\textsuperscript{8} Therefore, the synergistic effects of both genetically and environmentally induced epigenetic modifications may contribute to the etiopathogenesis of autoimmune diseases.

Epigenetic modifications mainly comprise DNA methylation/demethylation, histone modification and non-coding RNAs, which can ultimately determine gene expression and thereby have important roles in various biological processes, such as cell growth, apoptosis, development, differentiation, immune response and aging.\textsuperscript{8} It has been shown that DNA methylation/demethylation regulates T-cell differentiation and cytokine production.\textsuperscript{9–11} In addition, histone modifications and non-coding RNAs also contribute to this regulation. Here we focus on reviewing the epigenetic modifications in the activation and differentiation of B cells and their implications in the understanding of autoimmune pathogenesis.

The main epigenetic modifications

\textbf{DNA methylation.} DNA methylation is defined as a potentially heritable and stable epigenetic alteration, which is the first recognized and intensively investigated epigenetic modification of DNA. DNA methylation is a biochemical process in which a methyl group is added to a cytosine or adenine residue at the...
fifth position on the pyrimidine ring, locking the gene transcription in the ‘off’ status. Therefore, DNA methylation acts as a flag indicating the repression of gene transcription, which is a process involved in many important biological processes. DNA methylation is mediated by methyltransferases, including DNMT1, DNMT3a and DNMT3b. Notably, every methyltransferase shows distinguished capacities. During DNA replication, DNMT1 usually sustains the methylation status while other two methyltransferases participate in de novo methylation.

DNA demethylation occurs during the programmed failure in transmission of a methylation pattern, which results in reactivation of transcription of silenced genes. DNA demethylation occurs though the sequential iterative oxidation of 5-mC while the final modified group is removed by thymine DNA glycosylase (TDG) to yield cytosine instead of 5-mC. During this process, oxidation of 5-mC to 5-hydroxymethylcytosine (5-hmC) is mainly mediated by Ten-eleven translocation (TET) family dioxygenase enzymes, including TET1, TET2 and TET3, which can subsequently oxidize 5-hmC to 5-formylcytosine (5-fC) and 5-carboxycytosine (5-CaC), thereby displaying the order of 5-mC, 5-hmC, 5-fC and 5-CaC. In addition, both 5-fC and 5-CaC could be removed by TDG, which can further trigger base excision repair. (Figure 1)

**Histone modification.** Histone modification is a covalent posttranslational modification that regulates gene expression via changing chromatin structure or recruiting other modifications, thereby involving numerous biological processes. It has been well established that nucleosome is formed by 146 base pairs corresponding to two turns of DNA wrapped around a histone core, which displays two repeated sets of H2A, H2B, H3 and H4. These histones possess small protein ‘tails’ from the nucleosomes that are available for modifications, including acetylation, methylation, ubiquitination, phosphorylation and sumoylation. Acetylation and deacetylation can add or remove an acetyl group, which are mediated by histone acetyltransferases and histone deacetylases (HDACs), respectively. Histone methylation, defined as transferring 1, 2 or 3 methyl groups to arginine or lysine residues, is mainly mediated by histone methyltransferases and other enzymes, such as EZH2, G9a, SUV39-h1, ESET, SETDB1 and so on. The consequences of histone methylation depend on both modified residue and the number of methyl groups. Generally, acetylation promotes gene expression by opening the chromatin, while methylation switches the chromatin to the tight status, showing the opposite effects (Figure 2). For example, H3K4me3 activates gene transcription, whereas H3K27me3 and H3K9me3 result in gene silencing. Similar to methylation, ubiquitination on histones is implicated in both activation and repression of gene transcription. Many enzymes have been identified to control the addition and removal of ubiquitin. The ubiquitination on H2A and H2B has been found to have an essential role in numerous biological processes, such as transcription initiation, elongation and repression and DNA repair. Phosphorylation can occur at all four histone tails that contain acceptor sites, which is mediated by protein kinases. These four modifications can directly regulate histone–DNA interactions and also recruit non-histone proteins to chromatin. And the combinations of these modifications presenting on the same or the other histone tails have been reported as ‘histone codes’, which is deciphered by proteins that present specific binding motifs for each modification.

**MicroRNAs (miRNAs).** With a length of 21–25 base pairs, miRNAs belong to non-coding RNAs that regulate posttranscriptional and posttranslational gene expression. miRNAs bind to the 3’-untranslated region of specific target mRNA, resulting in mRNA cleavage, degradation or block translation (Figure 3). miRNAs, similar to other epigenetic regulations, involve numerous biological processes, including cell cycle, differentiation, apoptosis and innate and adaptive immune responses. Increasing evidence has shown that aberrant levels of miRNAs in different cell subtypes and tissues are associated with the pathogenesis of various diseases, facilitating them as potential non-invasive biomarkers for prediction and diagnosis, as well as potential treatment targets. To date, most work on non-coding RNAs in B-cell differentiation and antibody response has mainly focused on miRNAs. Moreover, miRNAs cross-talk with histone modification and DNA methylation, synergically regulating biological processes.

**Epigenetic modifications in B-cell activation and differentiation**

**Epigenetic modification in B-cell activation.** In the peripheral immune system, naive B cells display an inactive epigenetic status, showing genome-wide DNA hypermethylation and

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**Figure 1** DNA methylation and demethylation process.
Histone deacetylation, among which very few genes are expressed except for B-cell lineage genes such as Cd19, Pax5, Ebf1 and Spib, exhibiting active epigenetic status. Upon encountering antigens, naïve matured B cells divide and then differentiate into germinal center (GC) B cells, and further differentiate into either plasma or memory B cells. During B-cell activation, the active epigenetic status of Igh, Cd19, Pax5, Ebf1 and Spib persists, while genome-wide DNA is hypomethylated, leading to increased levels of histone acetylation and miRNA expression.

It has been well characterized that B-cell activation needs two major signals. Primary stimuli comprise dual B-cell receptor and Toll-like receptor binding to antigenic epitopes and pathogen-associated molecular patterns, respectively. Co-stimulatory signals are derived from CD40 and CD40L ligation, as well as signals from transmembrane activator and calcium-modulator and cyclophilin ligand interactor I (TACI) ligated with a proliferation-inducing ligand and B-cell-activating factor of the TNF family. The process induces several histone-modifying enzymes that activate H3K4me3, H3K9ac and H3K14ac in the promoter regions of activation-induced cytidine deaminase (AID) and miRNA host genes, as well as other somatic hypermutation (SHM)/class switch DNA recombination (SHM/CSR) factor genes. Moreover, removal of repressive H3K27me3 and H3K9me3 leads to chromatin decondensation. Recent evidence suggests that miRNAs, such as mir-16 and mir-155, decrease AID and Blimp expression in B cells. In contrast, AID regulates DNA methylation dynamics in GC B cells. For B-cell activation, secondary stimuli include cytokines such as interferon-γ, interleukin-4 and transforming growth factor-β, which activate transcription factors that interact with selected Ih promoters and initiate germline Ih-S-Ch transcription, which then facilitate primary stimuli-induced histone modification-related enzymes to bind with RNA polymerase II to form a complex and then interact with the Sgl1 region, catalyzing histone modifications in the S region for CSR targeting.

Both DNA methylation and histone modification have an essential role in the SHM machinery, which targets V(D)J DNA through transcription. Remarkably, in comparable transcription of both alleles, only the demethylated allele can be hypermutated, indicating an essential role of DNA methylation in SHM. In an array-based genome-wide chromosomal...
imbalance and DNA methylation analysis, CREBBP and AID have been found to be possible modulators of both genetic and epigenetic co-evolution.\textsuperscript{49} DNA demethylation promotes H3K4me3, H3K9ac, H3K14ac and H4K8ac, which present enrichments in the V(D)J region, thereby leading to an ‘open’ chromatin status.\textsuperscript{50} In addition, histone modifications are capable of recruiting of DNA polymerases on the stage of DNA repair during SHM. For example, H2BK120 ubiquitination (ub) and H2AK119 (ub) are co-localized with error-prone translesion DNA polymerase η in AID-containing foci.\textsuperscript{44} H2BS14 phosphorylation has been found to mark the V(D)J region and this process is associated with AID regulation and perhaps recruit DNA repair-related factors.\textsuperscript{33}

Epigenetic modification in B-cell differentiation. After the GC response, B cells ultimately differentiate into plasma cells. Although memory B cells are not capable of secreting antibodies, they can further experience SHM and/or CSR and then differentiate to plasma cells upon subsequent antigen exposure.\textsuperscript{51} Epigenetic modifications are involved in these processes, though how these stimuli and signals contribute to B-cell differentiation remains partially understood.

Epigenetic modifications in plasma cell formation. B lymphocyte-induced maturation protein 1 (Blimp-1, encoded by Prdm1) has a central role in the differentiation of plasma cells. Overexpression of Blimp-1 in peripheral mature B cells promotes J-chain upregulation and antibody production. Moreover, the knockdown of Blimp-1 expression in plasma cells retains plasma cell-related transcriptional markers but loses the capacity to produce antibodies.\textsuperscript{52} Prior to differentiation, Prdm1 is suppressed by Bcl-6. The increased expression of Prdm1 may result from the release of Bcl-6-bound HDACs, thereby increasing the histone acetylation levels on the promoter region of Prdm1.\textsuperscript{53,54} Furthermore, the HDAC inhibitor trichostatin A is capable of enhancing the expression of Blimp-1\textsuperscript{55} and CD138, suggesting a critical role of histone acetylation in B-cell differentiation.\textsuperscript{55} Moreover, the expression of Blimp is regulated by several miRNAs, such as mir-125b,\textsuperscript{56} mir-127,\textsuperscript{57} mir-9,\textsuperscript{58} mir-30,\textsuperscript{57} mir-146a\textsuperscript{59} and let7b.\textsuperscript{60} In contrast, Blimp-1 can also regulate miRNAs such as mir-21.\textsuperscript{61} Additionally, mir-155, highly expressed by GC B cells, has been found to be associated with B-cell differentiation. In mir-155 knockout mice, reduced GC B cells and memory B cells are found with decreased high-affinity IgG1 antibodies.\textsuperscript{62-64}

Blimp-1 is the transcription repressor of Bcl6, Pax5 and Spib, which, in return, suppress Blimp-1 expression and B-cell differentiation.\textsuperscript{65} Blimp-1 induces histone deacetylation in the promoter region of these genes, which display low histone acetylation levels in plasma cells.\textsuperscript{66} Blimp-1 decreases c-Myc expression to maintain the stable status of plasma cells via similar epigenetic mechanisms.\textsuperscript{66} Furthermore, Blimp-1 has been found to bind to H3K9 methyltransferase G9a, therefore recruiting this enzyme to the promoter regions of Spib and Pax5 and leading to gene silencing.\textsuperscript{67}

Epigenetic modifications in memory B-cell formation. Epigenetic modifications also contribute to the differentiation of memory B cells. The hallmark genes of memory B cells, such as CD38 in mouse and CD27 in human, seem to be controlled by histone modifications.\textsuperscript{68,69} In quiescent memory B cells, histone lysine methylation levels are reduced compared with active memory B cells.\textsuperscript{70} Enhancer of zeste homolog 2 (Ezh2), with the ability of catalyzing H3K27me3, displays high levels in human GC B cells. The inhibition of Ezh2 activation in GC B cells can result in a reduction of memory B-cell percentage, GC reactions and antibody response,\textsuperscript{71} indicating an important role for histone methylation in GC reactions and memory B-cell differentiation, which might be associated with suppression of Prdm-1 and Irf4 transcription by Ezh2. In addition, histone acetyltransferase monocytic leukemia zinc finger protein has been revealed as a modulator in memory B-cell formation, by affecting the primary and secondary antibody responses.\textsuperscript{72}

DNA methylation contributes to memory B-cell differentiation, a notion supported by the evidence that DNMTs are highly expressed by memory B cells while immune-related genes display distinctive DNA methylation patterns.\textsuperscript{73}

Figure 4 The involvement of epigenetic modifications in B-cell differentiation.
Furthermore, mir-125b and let-7 negatively regulate Blimp-1 expression. Both mir-16 and mir-15a have been observed to regulate memory B cell via targeting Bcl-2. mir-223 contributes to B-cell differentiation though targeting LMO2, an important transcription factor in this process; mir-155 regulates AID expression and has an vital role in the differentiation of memory B cells.

Therefore, epigenetic modifications coordinate with transcription factors in the activation of SHM and CSR during B-cell differentiation, determining cell fate and homeostasis (Figure 4).

**Dysregulated epigenetic mechanisms in B cells contributing to autoimmune diseases**

As described above, epigenetic modifications are closely involved in the activation and differentiation of B cells. Thus dysregulated epigenetic modifications in B cells may result in autoimmune pathogenesis.

**Systemic lupus erythematosus.** Systemic lupus erythematosus (SLE) is a multi-organ autoimmune disease characterized by abundant autoantibodies in the circulation, which predominately affects females during their reproductive years. Numerous lines of evidence have shown a key role of abnormal epigenetic regulations in its pathogenesis. As the main source of pathogenic autoantibodies, B cells have been well documented as a major player in the pathogenesis of SLE. Recent clinical trials of B-cell-targeting therapies prove to be effective. DNA hypomethylation has been investigated in B cells from lupus patients, which contribute to B-cell auto-reactivity. Altered expression of HRES1/p28 in lupus B cells is found to be mediated by DNA methylation. A decreased methylation level of LINE-1 has been reported in B cells from SLE patients. A role of DNA demethylation in B cells is supported by the findings that adoptive transfer of DNMT1 inhibitor-treated B cells into syngeneic mice resulted in increased production of antinuclear antibodies. Although it is clear that DNA demethylation in V(D)J region and Igh 3′-LCR contributes to antibody production, little is known of this process during SLE. In addition, a lower level of DNA methylation has been observed in auto-reactive B cells, which might be a consequence of reduced DNMT1 and DNMT3b expression, or AID-mediated active DNA demethylation.

In SLE patients, increased levels of miR-30a have been reported in B cells. The level of miR-30 negatively correlates with Lyn, a key negative regulator of B-cell activation. Both miR-155 and miR-181b have been found to negatively regulate the expression of AID, thereby affecting antibody diversity. In regulatory B cells, the expression level of miR-15a has been found to show positive correlation with the serum level of anti-dsDNA antibodies in lupus mice. Our recent studies have demonstrated that increased expression of miR-1246 in B cells from lupus patients affects EBF1 expression and therefore promotes costimulatory molecule expression and antibody production by B cells. In addition, increased levels of mir-21 and mir-17-92 have been observed in lupus B cells, which may contribute to autoimmune development. Recently, the microRNA profiling of B-cell subset has been proposed as biomarkers in lupus. Conversely, miR-150 is decreased in MRL-lpr mouse B cells, which may result from reduced acetylation status and repression of the mir-150 host gene.

**Rheumatoid arthritis.** Rheumatoid arthritis (RA) has been defined as a chronic inflammatory autoimmune disorder that immune system primarily attacks the joints, in which synovial fibroblasts are believed to initiate RA. Epigenetic regulation has become an intensive research field in the studies of the pathogenesis of RA. Several epigenetic abnormalities have been reported in RA, such as increased DNA methylation, aberrant histone acetylation and differentially expressed miRNAs.

B cells are recognized to be involved in RA via two major mechanisms: antigen presentation and autoantibody production. Autoantibodies against type II collagen, rheumatoid factor and citrullinated proteins have been found in the blood and synovial fluid of 70% of patients with early RA. As described before, epigenetic modifications tightly regulate antibody production, indicating that epigenetically regulated B-cell activation and differentiation have an important role in RA. However, few studies have revealed the association of epigenetic regulations in B cells in RA. Increased levels of mir-155 are found in B cells from the synovium and affect B-cell function by targeting PU.1. Moreover, mir-29a has been demonstrated to regulate B-cell proliferation and antibody secretion in mice with collagen-induced arthritis and contribute to the disease pathology, indicating that mir-29a is a potential therapeutic target in RA. In recent studies, histone deacetylases and their inhibitors have shown therapeutic effects in RA mouse models via immune suppression and inflammatory regulation.

**Type 1 diabetes.** Type 1 diabetes (T1D) is an organ-specific autoimmune disorder in which aberrantly activated immune cells target pancreatic beta cells. T1D was believed to be a T-cell-mediated disorder. However, recent studies have suggested a pathogenic role of B cells in T1D. Two main mechanisms are involved in the pathogenesis of T1D by B cells: one is antigen presentation by B cells, whereas the other one is autoantibody production by islet antigen-specific B cells. T1D usually occurs in genetically susceptible individuals and is triggered by environmental factors. Epigenetic mechanisms might partially exert the influences of environmental factors, especially diet, on T1D.

In a recent epigenome-wide association study, 406 365 CpGs in 52 MZ twin pairs discordant for T1D in CD4+ T cells, CD19+ B cells and monocytes were analyzed. A substantial enrichment of differentially variable CpG positions was observed in these three different cell types from T1D twins, suggesting the contribution of DNA methylation of
Table 1: A summary of dysregulated epigenetic modifications in B cells in diseases

| Diseases | Modifications | Targeting genes | Consequences | Reference |
|----------|---------------|-----------------|--------------|-----------|
| **DNA methylation** | | | | |
| SLE | DNA demethylation | Global DNA | Auto-reactive B cells | 82 |
| SLE | DNA demethylation | HRES1/p28 | HERV dysregulation | 83 |
| SLE | DNA hypomethylation | LINE-1 | — | 84 |
| SLE | Lower levels of DMNT1 and DNMT3b, DNA demethylation | Global DNA | Auto-reactive B cells | 85 |
| T1D | An enrichment of differentially variable CpG positions | — | — | 126 |
| **MicroRNAs** | | | | |
| SLE | mir-30a, increased | Lyn | Overactive B cells | 88 |
| SLE | mir-155 and mir-181b, increased | AID | Regulating B-cell antibody diversification | 89,90 |
| SLE | mir-15a in regulatory B cells, increased | — | — | 91 |
| SLE | mir-1246, increased | EBF1 | Overactive B cells | 92 |
| SLE | mir-21, mir-17-92, increased | — | — | 93,94 |
| RA | mir-155 | PU.1 | Affecting B-cell function | 111,112 |
| RA | mir-29a | — | Regulating B-cell proliferation and antibody production | 113 |

Abbreviations: RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

B cells to T1D development. Although there is little evidence showing the association of epigenetic modifications in B cells with the pathogenesis of T1D, epigenetic drugs such as 5-Aza,127 HDACs128,129 and HDAC inhibitors130,131 may exert their therapeutic effects on T1D via modifying B-cell activation and differentiation. Thus further studies on the potential link between abnormal epigenetic regulation of B cells and T1D may broaden our understanding of T1D pathogenesis (Table 1).

CONCLUDING REMARKS
Recent findings of epigenetic regulations enable us to better understand the complex processes of B-cell activation and differentiation. However, further epigenetic studies are needed to define the role of B cells in the pathogenesis of autoimmune diseases such as lupus, systemic sclerosis, RA and T1D, in which epigenetic treatments, such as HDAC inhibitors, have shown therapeutic effects. Remarkably, B cells from circulation and local B cells from inflammatory sites can now be analyzed by single-cell sequencing and other advanced techniques. With the advent of the epigenomic era, new technologies will facilitate the investigation of epigenetic dysregulation in B cells and its implication in disease pathogenesis, which may lead to the identification of potential biomarkers and novel therapeutic targets.

CONFLICT OF INTEREST
The authors declare no conflict of interests.

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AUTHOR CONTRIBUTIONS
HW wrote the manuscript. YD, YF, DL, KM, XW and MZ conducted editing and LL and QL revised the manuscript.

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