Epigenetic alterations underlying autoimmune diseases

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Abstract
Recent breakthroughs in genetic explorations have extended our understanding through discovery of genetic patterns subjected to autoimmune diseases (AID). Genetics, on the contrary, has not answered all the conundrums to describe a comprehensive explanation of causal mechanisms of disease etiopathology with regard to the function of environment, sex, or aging. The other side of the coin, epigenetics which is defined by gene manifestation modification without DNA sequence alteration, reportedly has come in to provide new insights towards disease apprehension through bridging the genetics and environmental factors. New investigations in genetic and environmental contributing factors for autoimmunity provide new explanation whereby the interactions between genetic elements and epigenetic modifications signed by environmental agents may be responsible for autoimmune disease initiation and perpetuation. It is aimed through this article to review recent progress attempting to reveal how epigenetics associates with the pathogenesis of autoimmune diseases.

Introduction
Epigenetics is commonly defined as stable and heritable changes in gene expression without alterations in DNA sequence. As a result, it appears that the epigenetic phenomenon is of outstanding importance for controlling the patterns of gene expression during the cell cycle, development, and in response to environmental or biological changes. Indeed, the concept of epigenetics explains how cells with a limited number of genes can differentiate into various cell types and how a phenotype can be inherited through daughter cells [1]. Accordingly, epigenome and/or epigenotype can be regarded as a cell-specific and stable pattern of gene expression dictated by different epigenetic mechanisms.

Epigenetic settings are different in various conditions. To enumerate a few, epigenetic circumstances can be modified with ageing process and can become impressed by environmental influences, providing an explanation for the experimental link observed among environmental factors, aging, and the development of autoimmune diseases [2]. Furthermore, the predisposition of women to autoimmunity may be explained somewhat through the role of X chromosome inactivation, a remarkable epigenetic event [3].

In an autoimmune condition, there is a pathogenic state in which the immune system fails to discriminate self-compartmental organs, leading to the promotion of an immune response against its own cells and tissues. There is a general consensus that autoimmune diseases (AIDs) are the consequence of genetic predisposition together with environmental triggers [4–6]. On the other hand, the largely incomplete concordance rates of autoimmune diseases in monozygotic twins strongly support other alternative mechanisms involved in gene expression regulation ultimately causing disease circumstances and autoimmunity.

Epigenetic factors have been linked with numerous diseases, such as cancer, autoimmune diseases, heart, and skin disorders. Particularly in respect of AIDs, disease onset, progression, and outcome seem to be under the impression of environmental factors that can change epigenetic marks [7]. Considering the drugs that can reverse aberrant gene expression profiles are readily available, the identification and subsequent manipulation of epigenetic markers involved in disease development may provide an important novel therapeutic tool for autoimmune disorders. In this review, we attempt to outline how epigenetics might contribute to explain some of the remaining uncertainties in AID pathogenesis.

Epigenetic mechanisms
DNA methylation
Methylation of DNA is an integral epigenetic component of cellular development and differentiation as well as a basis for a number of human diseases. DNA methylation is

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accomplished by transferring of a methyl group from S-adenosylmethionine (SAM) to the S'-carbon position of the pyrimidine ring of cytosine, and accordingly contributes to the epigenome by covalently modifying the structure of DNA. At first, CpG sites methylation was believed to result in transcriptional repression by directly blocking the binding of transcription factors to DNA; however, it appears nowadays that this is not the main mechanism whereby methylated DNA suppresses gene expression. Instead, the methylated DNA requires proteins which contain a methylated DNA-binding domain (MBD). MBD-containing proteins contribute links between methylated DNA and histone modifications that reorganize chromatin and suppress the expression of gene. DNA methylation may permanently change the expression of genes in cells because of cell division and differentiation from embryonic stem cells into particular tissues. These alterations are normally eternal and one directional, preventing a cell from reverting to a stem cell or converting into a different cell type. Methylation of DNA is normally removed during zygote formation and re-built through consecutive cell divisions during development. Nevertheless, the latest researches show that hydroxylation of methyl groups happens rather than complete removal of methyl groups in the zygote [8–11]. DNA methylation forms the basis of chromatin structure, which authorizes a cell to develop into various organs or perform multiple functions. DNA methylation also plays an important role in the expansion of almost all types of cancer [12]. DNA methylation has a specific impact of decreasing gene expression and has been found in every vertebrate examined [13]. CpG islands are typically common near transcription start sites and promoter regions. Normally, a C (cytosine) base followed immediately by a G (guanine) base (a CpG) is rare in vertebrate DNA because the Cs in such an arrangement tends to be methylated. This methylation contributes to discern the newly synthesized DNA strand from the parent strand, which aids in the final steps of DNA proofreading after being duplicated. Nonetheless, over the course of evolutionary time, methylated Cs tends to turn into Ts because of spontaneous deamination. Consequently, CpGs are relatively rare unless there is a selective pressure to keep them or a region is not methylated for some other reason. CpG islands are known as regions where CpGs are present at significantly higher levels than is typical for the genome as a whole. Special characters for identifying CpG islands are the following: GC content has to be 50% or greater, length has to be greater than 200 bp, and the ratio of observed number to the expected number of CG dinucleotides has to be greater than 0.6. The ratio of observed to expected CpG is calculated according to the following formula: Obs/Exp CpG = number of CpG * N/(number of C * number of G); in which N represents the length of sequence [14].

CpG islands are the key for regulatory functions, and almost half of all genes are present in promoter regions. Alteration in CpG island methylation may, indeed, change chromatin form, typically being able to modify the interactions between promoter and transcription factors. As a result, in most situations, both acquisition and somatic maintenance of such methylation state make the decrease of gene expression. Furthermore, CpG-methylated sites can also collaborate with special proteins containing specific domain called the methyl-CpG-binding domain. Methyl-CpG-binding domain proteins have been suggested to decrease gene expression by attaching to methylated DNA, a process that would lead to chromatin remodeling and finally heterochromatin formation [10].

Histone methylation

Histone methylation can modify the nucleosomal structure and these changes could influence its cooperation with other proteins, especially when considering gene transcription processes. Methylation of histones can either increase or decrease the gene expression, depending on which amino acids are methylated, and the number of methyl groups that are added to these residues. As we mentioned before, histone methylation can be associated with either transcriptional repression or activation. For instance, tri-methylation of histone H3 at lysine 4 (H3K4me3) is an active point for gene transcription. Nevertheless, di-methylation of histone H3 at lysine 9 (H3K9me2) is a signal for silencing of gene transcription. Methylation events which decrease the interaction between histone tails and DNA could increase the gene transcription process, because they enable the DNA to the transcription factor proteins [11,15]. Lysine and arginine residues both have amino groups and could be methylated. Lysine is able to be mono-, di-, or tri-methylated with a methyl group replacing each hydrogen of its NH3+ group. Also, arginine is able to be mono-, or di-methylated because of free NH2 and NH2+ groups. Different amounts of methylation can suggest different functions, for instance, in the methylation of the H4K20 residue. Mono-methylated H4K20 (H4K20me1) and H4K20me3 are associated with the heterochromatin formation and, therefore, repress the transcription. However, H4K20me2 plays an important function in the DNA repair procedure [16]. Histone methylation is performed by histone methyltransferases (HMT). HMTs are histone-modifying enzymes that catalyze the transfer of one, two, or three methyl groups to lysine and arginine residues of histone proteins. The addition of methyl groups occurs at particular lysine or arginine residues on histones H3 and H4 [17]. Two major types of histone methyltransferases exist, lysine specific (which can be SET domain containing or non-SET domain containing) and arginine specific [18–20]. In both types of histone methyltransferase, S-adenosyl methionine (SAM) serves as a cofactor and methyl donor group [17,21–23]. In eukaryotic cells, the genome is tightly condensed into chromatin, so enzymes, such as histone methyltransferase, must overcome this inaccessibility [24]. Methylation of histones is biologically important because it is the principal epigenetic modification of chromat in that determines gene expression, genomic stability, stem cell maturation, cell lineage development, genetic imprinting, DNA methylation, and cell mitosis [18].

Histone acetylation

Acetylation and deacetylation of histone are important parts of gene regulation. These modifications are typically catalyzed by “histone acetyltransferase” (HAT) and “histone deacetylase” (HDAC) activities. Histone acetylation is the procedure where an acetyl group is transferred from one
molecule to histone. Histone deacetylation is an opposite reaction where an acetyl group is removed from a histone [25]. Acetylated histones organize chromatin into nucleosomes and finally heterochromatin structure. Acetylation eliminates the positive charge on the histones, decreasing the interaction of the histones with the DNA which is negatively charged with phosphate groups. As a consequence, the heterochromatin is transformed into the euchromatin structure which is associated with the greater level of gene transcription. This euchromatin structure can be reversed by HDAC activity [26]. The acetylation and deacetylation mechanisms take place on the NH3+ groups of lysine. These residues are located on the tails of histones that make up the nucleosome of packaged dsDNA. Acetylation mechanism is supported by enzyme known as histone acetyltransferase (HAT). HAT molecules provide the transfer of an acetyl group from the acetyl coenzyme-A (acetetyl-CoA) to the NH3+ group on lysine. The deacetylation process is supported by enzyme known as histone deacetylase (HDAC) which catalyzes the removal of the acetyl group [27,28]. Acetylation has the effect of changing the overall charge of the histone tail from positive to neutral, so leading to a decrease in the attachment of DNA with histones. By doing this, the DNA is more relaxed and accessible for transcription factors so that they are able to reach the DNA. Thus, acetylation of histones, which is performed by HAT, is known to increase the gene expression through transcription activation. Deacetylation performed by HDAC molecules has an opposite effect. By deacetylation of the histone tails, the DNA becomes more packed, because of opposite charge of histone and DNA, making it more inaccessible for transcription factors to bind to the DNA. This leads to decreased levels of gene expression and is known as a gene silencing process [29–31]. Histone modifications can not only provide changes in secondary structural but can also cause many structural changes in faraway locations which certainly effects function. It has been shown that, even past one replication, after many cell generations, genes expression may still be influenced. In the absence of the inhibitor, after many cell generations, the gene expression was still overexpressed, showing that modifications can be preserved through many replication processes such as mitosis and meiosis [32] (Figure 1).

**Micro-RNA**

Micro-RNAs are a group of post-transcriptional regulators which are involved in many biological procedures such as development, differentiation, proliferation, and apoptosis. Micro-RNAs approximately have 22 nucleotides which decrease translation by binding to mRNA and eventually degradation of target mRNA. They are encoded by genome and transcribed by RNA polymerase II, which is the same way accurate to ordinary protein-coding RNAs, and were recently studied in autoimmune diseases and chronic inflammatory conditions [10]. The majority of miRNA genes are intergenic and so supposed to be transcribed as separate units. Almost 40% of miRNA genes may be located in the non-protein coding genes and in introns or even in exons of long non-protein-coding transcripts [33]. The polymerase usually attaches to a promoter, near the DNA sequence encoding regions, and forms the hairpin loop of the pri-miRNA. The transcript is capped at the 5'-end, with a specially modified nucleotide polyadenylated with multiple adenosines [34,35]. The hairpins in a pri-miRNA, which have a double-stranded RNA structure, are identified by a nuclear protein known as DGC8R or Pasha. DGC8R is linked with the Drosha protein, an enzyme that cuts RNA to develop the Microprocessor complex [36]. In this complex, the catalytic RNase III domain of Drosha which is oriented by DGC8R releases the hairpins from pri-miRNAs by cleaving approximately 11 nucleotides from the hairpin base. The product of this procedure at its 3'-end has a two-nucleotide overhang, usually known as a pre-miRNA [37]. Exportin-5, which is a nucleocytoplasmic shuttler, exports the Pre-miRNA hairpins out of the nucleus. This protein identifies a two-nucleotide overhang left at the 3'-end of the pre-miRNA hairpin by the RNase III enzyme Drosha. Exportin-5-mediated transport to the cytoplasm is energy dependent, using GTP bound to the Ran protein [38]. In the cytoplasm, the RNase III enzyme Dicer cleaves the pre-miRNA hairpin. This endoribonuclease interacts with the 3'-end of the hairpin and cuts away the loop joining the 3' and 5' arms, generating an incomplete miRNA [39,40]. The complete and mature miRNA is part of an active RNA-induced silencing complex (RISC) containing Dicer and many associated proteins [41]. Argonautes which contain two conserved RNA binding domains are needed for miRNA-induced silencing. They attach to the mature miRNA and orient it for interaction with the target mRNA [42]. Gene silencing may happen either by mRNA degradation or by preventing mRNA from translation [43]. Complete matching with the target mRNA promotes degradation of the RNA [44]. Micro-RNAs that are partially matched with the target mRNA can also speed up deadenylation, causing mRNAs to be degraded faster [45]. Degradation of miRNA-targeted mRNA is well known, but translational suppression is carried out through mRNA degradation, translational inhibition, or in a combination way of these two processes, which are highly debated [46,47] (Figure 2).

**Epigenetic modifications in autoimmune diseases**

Numerous and continues endeavors in the field of epigenetics have resulted in the identification of relations between epigenetic modifications and autoimmune diseases (Table 1). Specific epigenetic alterations associated with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), ankylosing spondylitis (AS), Sjögren’s syndrome (SjS), inflammatory bowel disease (IBD), psoriasis, type 1 diabetes (T1D), and primary biliary cirrhosis (PBC) are summarized below.

**Rheumatoid arthritis**

Rheumatoid arthritis (RA) is a disabling autoimmune disease characterized by systemic inflammation and presence of autoantibodies. It causes pain, stiffness, and loss of function in many joints including those in the hands and feet. It is a multifactorial disorder which seems to be the manifestation of genetics, environmental factors, and autoimmune responses, which collectively trigger the onset and persistence of inflammatory circumstance [48].
The most involved cells in the epigenetic modifications of RA are RA synovial fibroblasts (RASF) which have been believed just as innocent cells for many years. But recent studies indicate that RASFs play an important role in the pathogenesis of RA via epigenetic modification which can activate them intrinsically and drive them to production of...
<table>
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<td>RA</td>
<td>Global DNA hypomethylation; Cpg island hypermethylation of DR3 [52] IL-6 promoter hypermethylation in PBMCs [53] LINE-1 aberrant methylation [51]</td>
<td>H3K27 methylation; HAT dominance activity [55, 56]</td>
<td>Up-regulation: miR-155 [57], miR-146 [58], miR-203 [60], miR-223 [59]</td>
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<td>Psoriasis</td>
<td>Different methylation of LAT in CD4+ T cells [180] Hypermethylation of BP230 [109] Hypermethylation of TNFSF7 [110]</td>
<td>–</td>
<td>Up-regulation: miR-16, miR-221, let-7i [103], miR-29 [105], miR-21 [107]</td>
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<td>AS</td>
<td>Detectable methylation level of SOCS-1 in serum of HLA-B27-positive patients [102]</td>
<td>–</td>
<td>Up-regulation: miR-574-3p, 768-3p [112], miR-146 [113]</td>
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<td>IBD (CD)</td>
<td>Increased methylation of TEPP in CD patients [181] Different Cpg methylation of Bcl3, PPARG, STAT3, OSM, STAT5, IL12RB, SOXI, COL18A1, LMTK2, CASP2, TJP2, SMAD2, HCK, IL12B, and LMO1 in IBD patients [182]</td>
<td>H4 hyperacetylation in patients with CD [186]</td>
<td>Up-regulation: miR-16, miR-21, miR-23a, miR-24, miR-29a, miR-126, miR-195, let-7f [128] miR-28-5p, miR-151-5p, miR-199a-5p, miR-340, miRplus-E1271, miR-103-2, miR-362-3p, miR-380-3p, miRplus-E1035, miRplus-F1159 [187] Down-regulation: miR-192, miR-375, miR-422b [128] miR-505 [187]</td>
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<td>IBD (UC)</td>
<td>Hypermethylation of IL-27, IL-19, TNF, MST1, and NOD2 in CD patients [183] Lower methylation level of STAT4 promoter in IBD patients [184] Altered methylation of THRAP2, FANCC, TNFSF4, TNFSF12, FUT7, CARD9, ICAM3, ILSRB in IBD patients [119] Different methylation of CF1, SPINK4, THY1/C9D9 in UC patients [185]</td>
<td>–</td>
<td>Up-regulation: miR-20, miR-21, miR-23a, miR-24, miR-29a, miR-126, miR-195, let-7f [128]</td>
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<td>Psoriasis</td>
<td>DNA hypermethylation in PBMCs [132] Hypomethylation in p15 [133], and p21 [133], hypermethylation in p16INK4a [134], hypermethylation in SHP-1 [135]</td>
<td>Global histone H4 hypoacetylation [136]</td>
<td>Up-regulation: miR-203 [139], miR-146a [142], miR-210 [145] Down-regulation: miR-125b [143], miR-221/2 [144]</td>
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<td>T1D</td>
<td>Hypermethylation of insulin DNA [153]</td>
<td>Abnormal histone H3K9me2 [155]</td>
<td>Up-regulation: miR-326 [156], miR-146a [157] Down-regulation: miR-21a, miR-93 [158], miR-20b, miR-31, miR-99a, miR-100, miR-125b, miR-151, miR-335, and miR-365 [157]</td>
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RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; MS, multiple sclerosis; AS, ankylosing spondylitis; SJShogren’s syndrome; IBD, inflammatory bowel disease; CD, Crohn’s disease; UC, ulcerative colitis; T1D, type 1 diabetes; PBC, primary biliary cirrhosis.
inflammatory cytokines [49]. Global hypomethylation in RASFs has been documented in RA by a reduced DNMT1 and LINE1 gene expression, resulting in increased activity of these cells and perpetuation and exacerbation of the disease [50,51]. Furthermore, methylation of single gene promoters including promoters for DR3 (death receptor 3) [52] in RASF, eventuating in malfunction of apoptosis processes, and IL6 [53] in PBMCs of RA patients is altered. CD40L gene which is positioned on the inactivated X chromosome has an overexpression in CD4+ T cells from females, but not male RA patients, suggesting a reasonable explanation for relatively high prevalence of RA in woman compared with men [54].

Histone modifications including acetylation and deacetylation are more shifted to HAT activity in RA patients, leading to an increased transcriptional level. Treatment by HDAC inhibitors such as FK228 has been observed to have potential in reducing the joint swelling, synovial inflammation, and bone erosion in the animal models and in vivo studies [55,56].

Involvement of micro-RNAs in RA pathogenesis was confirmed when miR-155 [57] and miR-146 were further upregulated in RASF and RA synovial tissue, respectively, by exerting proinflammatory cytokines including TNF-α and IL-1β [58]. T lymphocytes of RA patients show dysregulated expression of miR-223 [59]. Upregulation of miR-203 through a decreased DNA methylation in RASFs has been revealed to be correlated with a high expression level of IL-6 and matrix–metalloprotease-1 (MMP-1) [60].

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic and systemic autoimmune disease that appears in a wide range of clinical symptoms. The predominant characteristic of SLE is the production of autoantibodies against nuclear and/or cytoplasmic antigens [10,61]. In addition to genetic factors, epigenetic modifications are believed to play a key role in the pathogenesis of lupus which might be explained through different concordance rates of SLE between monozygotic twins [14]. Furthermore, global DNA hypomethylation and abnormal expression of methylation-related genes, down-regulation of DNMT1 and MBD4, and overexpression of MBD2 and MeCP2 in CD4+ T cells have been documented in SLE [62].

The main reason of high prevalence of SLE in women than men still remains unknown. Investigations have established that SLE is an epigenetic disease with impaired T cell DNA methylation. Demethylation of CD40LG and perhaps other genes on the inactive X chromosome from SLE CD4+ T cells of the women may describe why women are primarily affected by SLE [63]. On the other side, DNA demethylation, which in turn reacts with the inactive X chromosome in female, eventuates in a demethylated CD4+ T cells, which express high level of CD40LG and consequently overstimulate B cells to produce IgG [64].

Elevated mRNA expression of gadd45A (growth arrest and DNA damage-induced 45α), a gene which reduces epigenetic silencing of genes by removing methylation marks [65], is inversely proportional with global DNA hypomethylation in CD4+ T cells from SLE patients. Increased expression of gadd45A results in overexpression of CD11a and CD70 mRNA, which is accompanied by increased autoreactivity and excessive B cell stimulation in gadd45A-transfected CD4+ T cells. Overexpression of gadd45A causes CD11a promoter hypomethylation. Transfection of gadd45A small-interfering RNA represses the autoreactivity of SLE CD4+ T cells and leads to significant increases in the methylation levels of the CD11a and CD70 promoter regions. By promoting DNA demethylation in SLE CD4+ T cells, overexpression of gadd45A may be a contributing factor to lupus-like autoimmunity [66]. High-mobility group box protein 1 (HMG1) can bind to Gadd45a and, perhaps through involving DNA demethylation in CD4+ T cells during lupus flare, can culminate in overexpression of CD11a and CD70 mRNA [67]. Moreover, demethylation of the CD70 promoter region and overexpression of CD70 mRNA are established in CD4+ T cells from patients with subcutaneous lupus erythematosus (SCLE) [68]. Other epigenetic alterations which cause impairments in the CD11a and CD70 regulatory regions, which in turn results in the development of autoreactivity and autoantibody overproduction in SLE patients, are combined effect of aberrant DNA methylation and histone acetylation in CD4+ T cells. Reduced expression and activity of the transcription factor RFX1 in SLE CD4+ T cells eventuate in DNA hypomethylation and histone hyperacetylation in CD4+ T cells through impaired and declined by recruiting the DNMT1 and HDAC1 to the CD11a and CD70 promoters. The consequence of downregulation of CD11a and CD70 mRNAs by reducing RFX1 in CD4+ T cells is sufficient to cause lupus-like T and B cell hyperactivity. It appears that downregulation of RFX1 is somewhat and somehow responsible for CD4+ T cells hyperactivity and autoimmune responses in SLE [69]. It seems that DNA methylation abnormalities may develop SLE through the key players of immune cell activation, namely CD11a and CD70.

IL-10 and IL-13 play important roles in Th2 cell differentiation and production of autoantibodies in SLE patients [70]. It has been shown that activity-related disease increases IL10 and IL13 expression in CD4+ T cells from SLE patients which stem from demethylation of specific CpG islands within IL10 enhancer and IL13 promoter regions [71].

DNA methylation changes in the novel key target genes such as NLRP2, CD300LB, and SIRP3, as well as changes in the critical pathways, like the adherens junction, and leukocyte transendothelial migration has been observed in SLE patients which are correlated with different clinical phenotypes. Additionally, specific sets of micro-RNAs are controlled by DNA methylation in SLE patients [72].

Histone acetylation effects on genes are not completely understood in SLE. However, early studies unraveled a global histone H3 and H4 hypoacetylation in active lupus CD4+ T cells. Moreover, global histone H3K9 hypomethylation, but not H3K4, in both active and inactive lupus CD4+ T cells has been established. Chromatin modifier genes have also been observed to be aberrantly expressed in SLE. Albeit an overexpression of SIRT1 mRNA, downregulation of CREBBP, P300, HDAC2, HDAC7, SUV39H2, and EZH2 have been documented in SLE CD4+ T cells [73]. Moreover, animal study has implied on the role of SIRT1 as an important
histone acetylation regulator, in which administration of SIRT1-siRNA into the MRL/lpr mice eventuated in SIRT1 expression suppression, which in turn resulted in the elevation of global histone H3 and H4 acetylation levels in CD4+ T cells [74]. Furthermore, alteration of transcript level of histone methyltransferases (HMTs) and histone demethylases (HDMs) has been documented in CD4+ T cells of MRL/lpr mice [75].

To shed further light on the role of RFX1 in the epigenetic alterations in SLE, it has been shown that RFX1 recruits SUV39H1 to the promoter regions of the CD11a and CD70 genes in CD4+ T cells, thereby regulating local H3K9 tri-methylation levels [76]. This is in accord with the study which resulted in role of RFX1 in SLE CD4+ T cells in DNA hypomethylation and histone hyperacetylation through reduced recruiting of the DNMT1 and HDAC1 to the CD11a and CD70 promoters [69]. In another study, Zhou et al. found that histone H3 acetylation and dimethylated H3 lysine 4 (H3K4me2) levels were significantly elevated in TNFSF7 promoter in CD4+ T cells from patients with lupus. Moreover, the MeCP2 protein levels within the TNFSF7 promoter declined in patients with active lupus [77]. It seems that aberrant histone modifications within the TNFSF7 promoter alongside with other regulations may contribute to the development of lupus via increasing CD70 expression in CD4+ T cells.

Increased histone H3 lysine 27 trimethylation (H3K27me3) enrichment at the hematopoietic progenitor CD4+ T cells. In vitro stimulation of TLR2 in CD4+ T cells from SLE patients caused upregulation of H3K4 tri-methylation (H3K4me3) and H4 acetylation levels, while downregulating H3K9 tri-methylation level in the IL-17A promoter region. In addition, it also increased H4 acetylation levels and decreased H3K9 tri-methylation (H3K9me3) levels in the IL-17F promoter region. It seems that overexpression of TLR2 contributes to immune reactivity and promotes IL-17A and IL-17F expression through histone modifications in SLE T cells. In vitro stimulation of TLR2 in CD4+ T cells from SLE patients caused upregulation of H3K4 tri-methylation (H3K4me3) and H4 acetylation levels, while downregulating H3K9 tri-methylation level in the IL-17A promoter region. In addition, it also increased H4 acetylation levels and decreased H3K9 tri-methylation (H3K9me3) levels in the IL-17F promoter region. It seems that overexpression of TLR2 contributes to immune reactivity and promotes IL-17A and IL-17F expression through histone modifications in SLE [78].

Moreover, receptors of the innate immune system may impress histone modifications in SLE T cells. In vitro stimulation of TLR2 in CD4+ T cells from SLE patients caused upregulation of H3K4 tri-methylation (H3K4me3) and H4 acetylation levels, while downregulating H3K9 tri-methylation level in the IL-17A promoter region. In addition, it also increased H4 acetylation levels and decreased H3K9 tri-methylation (H3K9me3) levels in the IL-17F promoter region. It seems that overexpression of TLR2 contributes to immune reactivity and promotes IL-17A and IL-17F expression through histone modifications in SLE [79].

Mounting evidence has described the micro-RNAs as an important regulator of gene expression altered in lupus patients. On one hand, there is downregulation of miR-125a which results in an increment of RANTES in T cells, and lower expression of miR-146a as a regulator of TLR signaling pathway that leads to an aberrant function of type 1 INF. On the other hand, upregulation of miR-21 and miR-148a affects DNA methylation by reducing DNMT1 expression and more activating CD11a and CD70. These events collectively may suggest a validation to explain the autoreactivity of B and T cells in SLE [80,81]. Furthermore, Zhao et al. demonstrated that the expression of 11 micro-RNAs was significantly altered in CD4+ T cells from patients with SLE in comparison with that in CD4+ T cells from control subjects. It was found that miR-142-5p, miR-142-3p, miR-31, miR-186, and miR-197 were downregulated and miR-1246, miR-574-5p, miR-1308, miR-638, miR-7, and miR-126 were increased. Overexpression of miR-126 was inversely correlated with DNA methyltransferase 1 (Dnmt1) protein levels. The miR-126 was observed to directly inhibit the Dnmt1 translation and, therefore, eventuate in reduced Dnmt1 protein levels. The overexpression of miR-126 in CD4+ T cells from healthy donors culminated in demethylation and upregulation of genes encoding CD11a and CD70, thereby T-cell and B-cell hyperactivities [82].

A downregulation of miR-142-3p and miR-142-5p has been observed in SLE CD4 T cells compared with healthy controls. Expression levels of miR-142-3p/5p correlated with the putative SLE-related targets signaling lymphocytic activation molecule-associated protein (SAP), CD84, and IL-10. Moreover, a decrease in miR-142 expression correlated with changes to histone modifications and DNA methylation levels upstream of the miR-142 precursor sequence in SLE CD4+ T cells [83].

Decreased expression level of miR-1246, which specifically targeted the EBF1mRNA, has been established in B cells from SLE patients. Activated B cells in SLE can decrease the expression of miR-1246 through the AKT-P53 signaling pathway, resulting in increased expression of EBF1, therefore, promoting further activation of B cells [84].

Systemic sclerosis

Systemic sclerosis (SSc) is an autoimmune fibrotic disorder with the main features of accumulation of the collagen, making a thickened skin, inflammation, and broad vasculopathy [85]. The exact etiology of the disease still remains unclear. However, beyond the complicated genetic mechanisms, epigenetic modifications are crucial factors that hopefully can provide more explanations for etiopathogenesis of SSc.

Early studies had shown that there was a global DNA hypomethylation in the CD4+ T cells as well methylation-related genes such as downregulation of DNMT1, MBD3, and MBD4 [62]. Recent surveys, also, identified a global CpG DNA hypomethylation state in SSc compared with healthy controls. The CD40L, overexpression due to global DNA hypomethylation in CD4+ T lymphocytes of female SSc patients has been demonstrated as a predominant feature of the disease [86]. CD70 has also been observed to be highly expressed in SSc due to the demethylated TNFSF7 promoter region in SSc CD4+ T cells [87]. Elevated CD11a expression levels have been observed in CD4+ T cells from SSc patients and inversely correlated with the methylation levels of the CD11a regulatory sequences, which is lower in SSc patients than in controls. Treatment of CD4+ T cells with 5-azacytidine (5-azaC) culminated in decreased CD11a promoter methylation and caused CD11a overexpression. SSc CD4+ T cells and 5-azaC-treated CD4+ T cells showed increased proliferation of CD4+ T cells, increased production of IgG by co-cultured B cells, and induced expression of COL1A2 mRNA by co-cultured fibroblasts. On treatment with anti-CD11a, the stimulatory effects disappeared. Therefore, it can be concluded that demethylation of CD11a and, thus, CD11a overexpression in CD4+ T cells may mediate immunological abnormalities and fibrotic processes in SSc patients [88]. Moreover, hypermethylation in promoter of Friend leukemia integration 1 transcription factor (FLI-1), a collagen transcription suppressor, has been confirmed by
treatment with DNMT inhibitor 2-deoxy-5-azaC which leads to the restoration of FLI-1 expression in SSc fibroblasts [89,90].

Besides methylation alterations, there is also evidence of histone modifications of relevant genes in SSc but the reliable proofs should be provided. More investigation showed that implementation of HDAC inhibitor (Trichostatin A) can reduce the expression of COL1A1 and FN1 genes encoding collagen type 1 [80,91]. Interestingly, histone H3 Lys27 trimethylation is generally increased in fibroblasts and it has an inhibitory impact on fibroblast formation. Furthermore, other studies have identified histone modifications in B cells, such as global histone H4 hyperacetylation and H3 hypomethylation, leading to skin thickness and disease activity [92]. Evaluation of H3 and H4 acetylation in the promotor region of the FLI1 gene in SSc and normal fibroblasts has established a significant reduction in the acetylated forms of H3 and H4 in SSc fibroblasts [90]. H3K27me3 is increased in SSc FBs in comparison with controls and inhibition of H3K27me3 stimulates the release of collagen in SSc fibroblasts as well in a bleomycin-induced experimental fibrosis model [93].

Global levels of H3K27me3 are lower in the CD4+ T cells of SSc patients than in those of healthy controls. This implies that certain genes such as CD40L, CD70, and CD11a, which are overactivated in response to the demethylation of their promoter region, may be under this alteration impression. Furthermore, JMJD3, one of the H3K27 demethylases, is overexpressed in SSc CD4+ T cells. Therefore, there is a negative correlation between the mRNA levels of JMJD3 and global H3K27me3. JMJD3 overexpression in CD4+ T cells of SSc patients is related to lower levels of H3K27me3, which further results in the removal of DNA methylation of the promoter region [94].

It seems that miRNAs dysregulation such as miR-21 upregulation and decreased level of miR-29, which are demonstrated to be associated with the fibrotic condition, play a pivotal role in the pathogenesis of SSc [95]. Upregulation of miR-142-3p [96] and miR-29-5p and down-regulation of miR-29 miR-196a, miR-145, miR-152, miR-150, and miR-129-5p have also been documented in SSc patients [95].

Ankylosing Spondylitis

Ankylosing spondylitis (AS) is a chronic inflammation and causes axial bony ankylosis, enthesopathy, and peripheral arthritis [97,98]. It is nowadays a consensus that human leucocyte antigen (HLA)-B27 is the most important risk factor for AS [99]. The misfolded HLA-B27 heavy-chain homodimer in an animal model has shown that HLA-B27 is of great importance in the pathogenesis of AS [100]. It appears that misregulation of T cells through dysfunction of HLA-B27 can contribute to the inflammatory responses in AS patients [101].

In the DNA methylation modification perspective occurred in AS patients, through a study by Lai et al., it has been demonstrated that methylation of SOCS-1 can be detected in serum of HLA-B27-positive AS patients but not in B27-positive healthy controls. Methylation level of SOCS-1 was shown to correlate with the degree of inflammation with respect to sacroiliitis, acute phase reactant, erythrocyte sedimentation rate, and C-reactive protein, as well as cytokine level of IL-6 and TNF-α [102].

Micro-RNAs have been focused more on AS than others. Three miRNAs with upregulated expression: miR-16, miR-221, and let-7i, have been observed in T cells from AS patients. Among these micro-RNAs, let-7i and miR-221 were found to be correlated positively with the Bath AS Radiology Index (BASRI) for lumbar spine. The study suggests that the increased expression of let-7i in AS T cells contributes to the immunopathogenesis of AS via enhancing the Th1 (IFN-γ) inflammatory response [103]. In another study by Huang et al., the miR-29 was investigated in AS patients. Negative regulation of Dickkopf homolog 1 (Dkk-1) in Wnt signaling pathway might contribute to new bone formation in AS [104]. It was found that miR-29, which directly targets the Dkk-1 mRNA, had upregulated expression in the PBMCs of AS patients in comparison with RA patients and healthy individuals. The study revealed no correlation between miR-29a expression in the PBMCs of AS patients and level of ESR and CRP, as well as the Bath AS Disease Activity Index (BASDAl) and the Bath AS Functional Index (BASFI) scores of patients. The authors concluded that miR-29a was a useful diagnostic marker for new bone formation in AS and might be a promising therapeutic tool in the future [105].

The binding of miR-21 to programmed cell death 4 (PDCD4) could inhibit the expression of PDCD4 and further induce the activation of osteoclasts [106]. Huang et al. observed a significantly higher level of miR-21, PDCD4 mRNA, and collagen cross-linked C-telopeptide (CTX) in AS patients. MiR-21 expression was seen to be negatively correlated with PDCD4 mRNA expression in patients with AS who were taking neither NSAID nor DMARD. Furthermore, significantly positive correlations between miR-21 expression with PDCD4 mRNA expression and CTX level were observed in patients with AS who were taking sulphasalazine. Positive correlations of miR-21 and CTX level were also observed in AS patients with disease duration less than 7 years and active disease. It appears that the expression of miR-21 might have a role in the development of AS [107].

Sjögren’s syndrome

In the Sjögren’s syndrome (SjS), there is a chronic autoimmune circumstance of the exocrine glands with associated lymphocytic infiltration to the affected glands. Dryness of the mouth and eyes in the SjS results from the involvement of salivary and lacrimal glands [108].

Given that bioinformatics analysis of the bullous pemphigoid antigen 1 (BP230) gene sequence has demonstrated the presence of CpG islands in the upstream of the gene, it might impress the gene expression. Gonzalez et al. observed that BP230 mRNA levels were decreased, while protein levels were increased, and the gene promoter region was hypermethylated. Downregulation of BP230 mRNA levels may be explained by gene hypermethylation. The authors postulated that epigenetic alterations of BP230 are produced in response
to factors present in the damaged salivary glands of SjS patients [109].

In another investigation, CD70, an autoimmunity-associated gene encoded by TNFSF7 (*tumor necrosis factor superfamily member 7*) gene expression, was found to be significantly increased and correlated with a decrease in TNFSF7 promoter methylation in CD4+ T cells from primary SjS patients compared with controls. It was concluded that demethylation of the CD70 promoter may contribute to CD70 overexpression in primary SS CD4+ T cells, and may contribute to autoreactivity in this patients [110].

Most of the studies attempting to disclose the etiopathology of SjS have focused on genetic, environmental, and immune-mediated factors. However, the triggering and initiating factors remain unclear to date [111]. Nevertheless, a series of studies in the viewpoint of epigenetic modifications, particularly concentrating on miRNAs, have been embarked in recently. Although the salivary glands of SjS patients have been reported to overexpress miR-574-3p and 768-3p [112], the NOD mice with associated SjS demonstrated the overexpression of miR-150 and 146 in both target tissues and in peripheral lymphocytes [113]. The salivary glands and peripheral lymphocytes of SjS patients also demonstrated upregulation of miR-146 [113].

**Inflammatory bowel disease**

Inflammatory bowel disease (IBD) is a category of inflammatory situations of the colon and small intestine. Chronic autoimmune situations are typically affected by the gastrointestinal tract and colon and result in Crohn’s disease (CD) and ulcerative colitis (UC), respectively. Major specifications of both types of IBD are mucosal inflammation, diarrhea, weight loss, and abdominal pain. Aberrant and dysregulated immune response toward commensal bacteria of gut may elicit chronic inflammation of the intestinal mucosa [114].

Gloria et al. [115] early reported that DNA methylation contributes to the pathogenesis of UC. After that, on one hand, several studies were carried out to elucidate DNA methylation context in IBD patients. Among many, surveys showed a high level of promoter methylation of E-cadherin, p16 (P16INK4a), CDH1, GDNF, and MDRI in UC patients [116,117]. Mounting studies, on the other hand, have shown that there is significant difference in DNA methylation circumstance between inflamed and normal tissues from UC and CD patients [118–120]. Also, with regard to diagnosis perspective, DNA promoter hypermethylation in CD patients’ serum has been possible and valuable using the cancer-specific and highly methylated gene, TCERGIL [121].

Moreover, it has been demonstrated that the expression regulation of the Toll-like receptor 2 (TLR2), TLR4, and its co-receptor MD2 in intestinal epithelial cells (IECs) is determined through DNA methylation and histone deacetylation [122–124]. Additionally, it has been shown that TLR4 methylation levels are much lower in the large intestine of germ-free mice in comparison with the fully colonized wild-type components [125]. Furthermore, histone modifications regulate the intestinal epithelial expression of the antimicrobial peptide human b-defensin 2 (hBD2) [126]. It can be concluded that epigenetic marks may respond directly to the presence of the local microflora. Olszak et al. demonstrate that expression of CXCL16 (chemokine receptor ligand) was regulated by DNA hydroxymethylation. According to their survey, it appears that epigenetic marks at this locus depend on early life exposure to bacteria [127]. These data suggest that commensal bacteria play a role in intestinal tolerance through epigenetic modulations as well exposure occurs during specific time periods.

Sigmoid colon biopsy miRNA microarray profiles for healthy subjects and patients with active UC, inactive UC, chronic active CD, irritable bowel syndrome, and microscopic colitis were compared. The comparison demonstrated that three miRNAs (miR-192, miR-375, and miR-422b) were significantly decreased in the UC tissues, while eight miRNAs (miR-16, miR-21, miR-23a, miR-24, miR-29a, miR-126, miR-195, and let-7f) were significantly increased in active UC tissues [128].

Considering different clinical manifestations, genetic associations, gene expression profiles, and immune function between CD and UC, the micro-RNA pattern seems logical to be distinguished between these two circumstances. Thereupon, miRNA microarray analysis performed on sigmoid colon pinch biopsies of CD and UC patients disclosed that expression of miR-23b, miR-106, and miR-191 was elevated in tissues of patients with active CD, whereas miR-19b and miR-629 were decreased in Crohn’s colitis patients. However, it was observed that miR-16, miR-21, miR-223, and miR-594 were upregulated in chronically active terminal ileal CD tissues [129]. On the contrary, none of the Crohn’s colitis related miRNAs were observed to be differently expressed in UC tissues. Nonetheless, two (miR-21 and miR-16) out of the four altered miRNAs in Crohn’s ileitis were also dysregulated in UC [128,129].

**Psoriasis**

Psoriasis is a common, chronic, relapsing/remitting, immune-mediated, and organ-specific autoimmune disease characterized by skin lesions due to excessive proliferation and abnormal differentiation of keratinocytes. Aberrant immune responses by various immune cells including T cells, dendritic cells, and inflammatory cytokines appear to be involved in the pathogenesis of psoriasis [130,131].

Several altered DNA methylation patterns have been observed in patients with psoriasis. A DNA hypermethylation in skin lesions and PBMCs of Psoriasis patients has been shown [132]. Moreover, CpG methylation pattern has been documented to be hypomethylated in p15 [133], hypomethylated in p21 [133], hypermethylated in p16INK4a [134], and hypomethylated in SHP-1 [135].

Global histone H4 hypoacetylation has been found in PBMCs from patients with psoriasis, and was inversely correlated with disease activity. However, global levels of H3 acetylation and H3K4/H3K27 methylation were almost equal between psoriatic patients and controls [136]. Furthermore, the expression and the function of histone acetyltransferases (HATs) and histone deacetylase (HDACs), which maintain the balance between histone acetylation and deacetylation, are also altered in psoriasis [136–138].
The most outstanding micro-RNA in psoriasis seems to be miR-203, the first skin-specific miRNA ever identified, which is upregulated in psoriatic skin lesions [139]. miR-203 is believed to target the suppressor of cytokine signaling-3 (SOCS-3), which is the negative regulator of the STAT3 pathway [140]. Through regulating the production of inflammatory cytokine and chemokine by direct targeting of serine/threonine 40, miR-31 has been observed to contribute to inflammation in psoriatic skin lesions [141]. miR-146a (upregulated) [142], miR-125b (downregulated) [143], and miR-221/2 (downregulated) [144] are among the micro-RNAs which have been indicated to be aberrantly regulated in psoriatic patients. Overexpression of miR-210 has been observed in CD4+ T cells from patients with psoriasis vulgaris (PV). FoxP3 mRNA is a target of miR-210 in CD4+ T cells and its expression is suppressed in healthy controls, resulting in impaired immunosuppressive functions of Treg cells in CD4+ T cells. Moreover, inhibition of miR-210 leads to increased FoxP3 expression, which in turn reverses the immune dysfunction in CD4+ T cells from patients with PV [145].

Type 1 diabetes

Type 1 diabetes (T1D) is a chronic and T-cell-mediated autoimmune disease [146]. It appears that T1D develops in individuals with genetically susceptible background and the predisposing genetic polymorphisms have been recognized in MHC class II (DR, DQ) loci, CTLA4, insulin, PTPN22, and IL-rRA [147,148]. T1D has shown a growing incidence over the past decades and several recent studies have focused on infectious agents and environmental exposures to dietary antigens, in addition to genetic susceptibility [149,150].

A pancreatic damage can trigger the autoimmune response against the tissue and lead to the activation of mechanisms for tissue repair like cellular proliferation, which in turn can ultimately express the epigenome status [151,152]. On one hand, in comparison with healthy controls, it was shown that methylation level of insulin gene was increased in patients with new-onset of T1D [153]. On the other hand, modulation of lymphocyte maturation procedures and cytokine gene expression mediated by epigenetic modifications can play a role in T1D [154]. This issue was revealed when altered H3K9 dimethylation was associated with overexpression of CLTA4 [155].

Micro-RNA assessment in peripheral blood lymphocytes from T1D patients has led to the identification of miR-326 overexpression which correlated with disease severity. This can be explained somehow through predicted targets for miR-326 that are involved in immune response regulation, erythroblastosis virus E26 oncogene homolog 1, and vitamin D receptor [156]. Furthermore, miRNA expression profiling in T1D regulatory T cells depicted upregulation of miR-146a and downregulation of miR-20b, miR-31, miR-99a, miR-151, miR-125b, miR-335, miR-365, and miR-100 [157]. On the contrary, expression of miR-21a and miR-93 is downregulated in PBMCs of T1D patients [158].

Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) is an autoimmune disorder of liver with the hallmark of high titers of antimitochondrial antibodies reactive with PDC-E2. In PBC, increased levels of polyclonal IgM as well inflammatory cytokines such as IL-1, IL-6, TNF-α, and IFN-γ are usual. In the pathological perspective, there is a lymphocytic infiltration in the portal area and selective destruction of intrahepatic bile ducts in PBC, which may develop to cirrhosis of the liver and liver failure ultimately [159,160].

Recently, a genome-wide study demonstrated that methylation profiles of 60 genes differed in discordant twins for PBC and their siblings. The affected twins showed hypermethylation of these 60 genes in comparison with healthy twins. Of the 60 differentially methylated genes, 51 genes carried by X chromosome and the rest nine genes were identified on autosomal chromosomes [161]. On the other hand, previously, it was established that CLIC2 and PIN4 genes showed aberrant methylation of CpG sites within transcription start sites (TSS) in the PBMCs of affected twins from discordant PBC twins [162,163]. Another study for exploring the methylation modification in PBC reported significantly declined levels of DNA methylation of the CD40L promoter in PBC CD4+ T cells; the lower methylation level was observed to be inversely correlated with the levels of serum IgM in PBC patients [164]. Furthermore, previously, overexpression of hepatic CD40L mRNA in PBC patients was established in comparison with healthy individuals and other liver disorders [165].

Beta-arrestin 1 is a regulator of G protein-coupled receptor and plays an essential role in T cell activation, survival, and homeostasis [166]. The regulatory role of Beta-arrestin 1 through establishing the acetylation of histone H4 at the promoter region of Bcl2 gene in CD4+ T cells in an animal model of MS has been observed [167]. Overexpression of β-arrestin 1 in T lymphocytes from PBC has been documented. Plus, the hepatic mRNA level of β-arrestin 1 in PBC patients correlated positively with the Mayo risk score. Overexpression of β-arrestin 1, through promoting the acetylation of histone H4 in the promoter regions of CD40L, LIGHT, IL17, and IFN-γ and decreased acetylation of histone H4 in the promoter regions of TRAIL, APO2, and HDAC7A, eventuated in intensified T cell proliferation and elevated interferon production [168].

Within the space of devising more sophisticated techniques like microarray, over almost 200 miRNAs with different expressions have been identified in PBC patients. However, some of them have been validated by real-time PCR, which are listed in Table 1.

Where do we stand and what is beyond epigenetic modifications for autoimmune disease?

Numerous studies recently have deepened our insight into causal mechanisms of autoimmune disease and emphasized on the importance of epigenetics in the initiation and development of autoimmunity in specific conditions. Nowadays, there is no doubt that epigenetic mechanisms are responsible for orchestrating immune cells development, plasticity, aging, homeostasis, and stress responses as documented with mounting researches. A striking movement has been initiated to understand the roles played by DNA methylation, histone modifications, and higher order
chromatin remodeling and non-coding RNAs. Within the space of past few years, a bulk progress have taken place with respect to genome-wide DNA methylation mapping [169] and histone modifications with new perspective arising [170,171] in terms of environmental epigenetics specially [172]. Several cell processes from differentiation to development and function are believed to be signed by epigenetic regulation, including tumor cells [173] and immune cells in autoimmune diseases [174]. Further investigations may hopefully gain a bigger window to new classes of therapeutic approach and epigenetic therapies, through improving the understanding of epigenetic mechanisms and the identification of target molecules in this pathway [175,176]. However, being armed with meticulous comprehension in respect of the role that epigenetic modifications play in the development of autoimmunity is likely to expand the visions for controlling or preventing autoimmune disease through the use of drugs that target proteins controlling chromatin modifications (e.g., HDAC inhibitors), DNA methylation (e.g., inhibitors of DNA methyltransferases), specific micro-RNAs, or other potential epigenetic mechanisms.

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Declaration of interest
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