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Epigenetics of inflammatory arthritis

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Abstract

Purpose of review—Aberrant epigenetic changes in DNA methylation, histone marks, and noncoding RNA expression regulate the pathogenesis of many rheumatic diseases. The present article will review the recent advances in the epigenetic profile of inflammatory arthritis and discuss diagnostic biomarkers and potential therapeutic targets.

Recent findings—Methylation signatures of fibroblast-like synoviocytes not only distinguish rheumatoid arthritis (RA) and osteoarthritis (OA), but also early RA from late RA or juvenile idiopathic arthritis. Methylation patterns are also specific to individual joint locations, which might explain the distribution of joint involvement in some rheumatic diseases. Hypomethylation in systemic lupus erythematosus (SLE) T cells is, in part, because of active demethylation and 5-hydroxymethylation. The methylation status of some genes in SLE is associated with disease severity and has potential as a diagnostic marker. An integrative analysis of OA methylome, transcriptome, and proteome in chondrocytes has identified multiple-evidence genes that might be evaluated for therapeutic potential. Class-specific histone deacetylase inhibitors are being evaluated for therapy in inflammatory arthritis.

Summary—Disease pathogenesis is regulated by the interplay of genetics, environment, and epigenetics. Understanding how these mechanisms regulate cell function in health and disease has implications for individualized therapy.

Keywords

ankylosing spondylitis; epigenetics; histone; inflammatory arthritis; methylation; microRNA; osteoarthritis; rheumatoid arthritis; systemic lupus erythematosus

INTRODUCTION

Recent data using genome-wide methods indicate that epigenetics contributes to the pathogenesis of inflammatory synovitis. The studies most relevant to synovial pathology have involved rheumatoid arthritis (RA), primarily because clinical samples are available from arthroplasty and biopsy. Although this is the most relevant tissue, some data using peripheral blood cells also implicate epigenetically marked pathways that could have an

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Conflicts of interest

There are no conflicts of interest.

impact on the joint. Thus, this review will focus primarily on synovial epigenetics in RA, but will discuss the evolving status of blood mononuclear cell DNA methylation and additional epigenetic signatures in other diseases.

The contribution of genetics to disease susceptibility in RA and systemic lupus erythematosus (SLE) has been clearly defined. Class II major histocompatibility (MHC) risk alleles in RA and SLE are the dominant risk alleles, but over 100 non-MHC risk alleles have also been identified [1]. However, genetic predisposition explains disease onset in a relatively small percentage of patients [2]. Studies on identical twins who are discordant for RA or SLE indicate that environmental or behavioral factors such as smoking, diet, ultraviolet light, and exposure to toxins can synergize with genetic predisposition to accelerate the onset and severity of disease [3]. The link between environment and the genome is largely mediated by epigenetic marks that decorate the DNA, including DNA methylation and histone modification (Fig. 1) [4]. Noncoding RNA can also influence gene regulation and contribute to nongenetic risk [5,6]. Understanding how these mechanisms control gene expression and cell function in physiological and pathogenic conditions has implications for disease prevention and individualized therapy.

RHEUMATOID ARTHRITIS AND DNA METHYLATION

DNA methylation involves adding a methyl group from S-adenosyl methionine (SAM) to a cytosine residue in the context of a CpG dinucleotide. CpG methylation is regulated by several families of proteins that function as ‘writers’, namely DNA methyltransferases (DNMTs), ‘readers’, which include the methyl-CpG-binding domain proteins (MBD) and ‘erasers’ that demethylate CpG, such as ten-eleven translocation (TET) enzymes [7]. In general, a low level or lack of DNA methylation in the promoter CpGs favors the formation of transcription complexes and gene transcription. Conversely, methylation of promoter CpGs favors a closed chromatin conformation and blocks transcription, resulting in gene silencing [8]. CpG islands located within the gene body, enhancers or introns are also regulated by methylation but the effects on gene expression are more complex and not well understood [9].

Fibroblast-like synoviocytes

Compared with osteoarthritis (OA) and/or normal FLS, some studies suggest that RA synoviocytes are globally hypomethylated, which has been linked to increased activity of spermidine/spermine N1-acetyl transferase, causing excessive consumption of SAM [10,11]. However, genome-wide studies using chip technology did not show differences in global methylation between RA and OA FLS; nevertheless, there is agreement that the FLS are differentially methylated compared with controls [12]. The differentially methylated loci (DML) in RA are associated with genes involved in cell migration, focal adhesion, and extracellular matrix interactions, which is consistent with the invasive nature of RA [13]. This methylation signature in the cells remains constant for many months in culture and suggests that they are ‘imprinted’ by their sojourn through the rheumatoid synovium [14].

Methylation patterns of FLS from patients with early RA differed from late stage RA, although they formed a distinct RA subgroup that was easily distinguished from OA by

hierarchical clustering (Fig. 2) [15]. The differences were localized to genes related to Wnt, integrin, and PDGF signaling and suggest that cell imprinting related to differentiation, adhesion and proliferation changes during the evolution of the disease. Other forms of arthritis, notably juvenile idiopathic arthritis, are also imprinted and form a subset in the RA super-group (Fig. 2) [15]. Thus, the presence of inflammation could contribute to abnormal methylation with more subtle variations that are dependent on the type of arthritis or stage of disease (Fig. 2). The observation is supported by data indicating that DNMTs are regulated by cytokines like IL-1 and TNF in control FLS and can mimic some of the DMLs in RA FLS [16].

Perhaps more interesting, the methylomes in RA and other diseases also vary depending on their joint of origin (Fig. 3) [17▪▪,18▪▪]. The methylation patterns of either RA or OA FLS derived from the hip differed compared with the knee, particularly in genes associated with cell differentiation like homeobox (HOX) and Wnt families. Similar joint-specific patterns are also apparent in mouse FLS and support the notion that epigenetics help determine synovial function that is tailored to the biomechanics of specific joints [18▪▪]. However, when the disease independent genes and pathways are subtracted from RA, a new group of RA-specific pathways emerge that could relate to distinct joint-specific disease mechanisms. Several key pathways were identified, including JAK-STAT and IL-6 signaling, which was also confirmed by documenting joint-specific transcriptomes [17▪▪].

Candidate gene approaches have shed light on potential RA pathogenic genes. For example, hypomethylation of pro-inflammatory proteins such as CXCL12 and IL-6 and the transcription factor TBX5 have been documented and correlate with increased gene expression in RA FLS [19,20]. Increased TBX5 expression increases the production of pro-inflammatory cytokines, IL-8, CCL20, and CXCL2 [21]. To identify novel pathogenic genes using unbiased methodology, integrative analysis using three data-sets – RA GWAS risk alleles, DMLs, and differentially expressed genes (*DEGs*) was performed in RA and OA FLS [22]. Of several triple-evidence genes, *ELMO1* was highly expressed in RA FLS and knock-down of *ELMO1* decreased cell migration.

A follow-up integrative analysis expanded the promoter DMLs to include enhancers identified two more unexpected multievidence genes, *LBH* and *PTPN11* [23,24]. *LBH* gene variants are associated with SLE, coeliac disease, and RA [25–28]. *LBH* deficiency blocks S-phase in the cell cycle in RA FLS and increases DNA damage because of impaired DNA repair mechanisms [29]. Furthermore, *LBH* deficiency *in vivo* also leads to cell-cycle abnormalities and increased arthritis severity in the serum transfer mouse model [29]. The methylation status of an enhancer DML in combination with a risk variant regulates the enhancer function and *LBH* expression, demonstrating how genetic risk and epigenetic marks can interact to alter cell function [23]. *PTPN11*, which encodes the protein tyrosine phosphatase SHP2, is highly expressed in RA FLS, where it regulates cell migration [24]. SHP2 inhibition attenuates arthritis in the serum transfer model, indicating that it is a potential therapeutic target. Increased expression of *PTPN11* in RA FLS is controlled, in part, by methylation of a novel intronic enhancer with a glucocorticoid-receptor binding site [24].

Peripheral blood mononuclear cells

Monitoring methylation changes might be a useful tool to predict and assess the course of disease and response to therapeutics. Recent studies have evaluated the methylation status in easily accessible tissues such as blood or synovial fluid to determine if they mirror synovial pathology. One study showed that fibroblasts isolated from RA synovial fluid showed similar methylation changes as tissue-derived synoviocytes and suggests that these cells might be used as a surrogate for tissue-derived FLS [30]. Another study showed that naïve blood T cells in RA are hypermethylated at loci similar to RA FLS [31]. Recently, a link between DNA methylation in T cells and response to DMARD treatment in early RA was explored [32]. A combination of a hypermethylated CpG in *ADAMTSL2* promoter and a hypomethylated CpG in *BTN3A2* distinguished responders from nonresponders. Another study reported that patients with RA who responded to etanercept had four hypomethylated CpGs located within an exon of the *LRPAP1* gene [33]. These interesting but small studies need to be replicated in larger cohorts.

RHEUMATOID ARTHRITIS AND HISTONE MARKS

The nucleosome consists of a short segment of DNA wrapped around an octamer of four histone proteins (H2A, H2B, H3, and H4) (Fig. 1) [34]. The histones can be posttranslationally modified in many ways, including acetylation, methylation, ubiquitination, phosphorylation, and sumoylation [35]. Histone methylation can be permissive or repressive. For example, tri-methylation of H3 at lysine 4 (H3K4me3) signals gene transcription whereas tri-methylation of lysine 27 (H3K27me3) indicates repressed histone conformation. Histone acetyl-transferases (HATs) are ‘writers’ of acetylation on lysines, whereas bromodomain proteins (BRD) function as ‘readers’ that recognize acetylated lysines. Histone deacetylases (HDACs) are acetylation ‘erasers’ that favor a closed chromatin and inhibition of transcription. HDACs can be divided into four groups: class I (HDAC1–3, 8), class II (HDAC4–7, 9,10), class III sirtuins (Sirt1–7), and class IV (HDAC11) [36]. Although class I HDACs are ubiquitous, class II HDACs are tissue specific.

Initial studies evaluating the activity of HATs and HDACs in RA synovial tissue gave contradictory results, possibly due to different selection criteria of patients [37,38]. Later studies showed that TNF levels in RA synovial tissuess correlated with HDAC1, HDAC2, and HDAC3 expression [39]. In contrast, HDAC5 expression in RA synovial tissue negatively correlated with disease activity and IL-6 expression, suggesting an anti-inflammatory role in RA [40]. No correlations were observed for HDAC8 or the other class II HDACs. FLS from patients with RA and OA express HDACs 1 to 11 but only HDAC1 expression was consistently elevated in RA [39]. Sirtuins 1 to 7 are also expressed in RA FLS but their role in RA is controversial. Some studies showed that SIRT1 expression was increased in RA synovium compared with OA [41]. In RA FLS, TNF-induced SIRT1 expression increased IL-6 and IL-8 expression and reduced apoptosis. Other studies showed that RA FLS expressed lower levels SIRT1 mRNA and protein compared with normal FLS [42]. High expression of SIRT1 inhibited MMP1 and MMP13 expression. However, in some preclinical studies, SIRT1 levels were decreased in the joint tissue of mice with collagen-

induced arthritis (CIA) and *SIRT1* deletion in myeloid cells increased disease severity in a serum transfer arthritis model [43,44].

HDAC inhibitors (HDACi) have been extensively studied in cancer and are being explored in RA. Givinostat, a pan-class I/II HDACi, reduced inflammatory cytokines in RA FLS and decreased inflammation in arthritis models and is currently being explored in juvenile idiopathic arthritis [45–48]. A selective HDAC3/6 inhibitor significantly reduced IL-1β-induced interferon response genes, IL-6, IL-8, MMP1, and MMP3 and blocked STAT1 phosphorylation [49]. HDAC3 knockdown recapitulated the inhibitory effect of pan-HDACi, suggesting that it is the most relevant HDAC therapeutic target for RA. A novel HDAC6i, CKD-L, reduced pro-inflammatory cytokines and increased IL-10 expression in RA PBMCs and effectively reduced synovial inflammation in CIA [50]. Finally, I-BET151, a selective inhibitor of the bromodomain and extra-terminal (BET) proteins, reduced joint swelling and inflammation in a serum transfer arthritis model and inhibited osteoclastogenesis and bone loss [51▪]. In RA FLS, I-BET151 blocked MMP1, MMP3, IL-6, and IL-8 production in response to TNF, IL-1β, or TLR ligands. I-BET151 also reduced proliferation and chemoattractant properties of RA FLS [52]. Similar results were seen with another BET inhibitor, JQ1, suggesting that this family of proteins may be promising therapeutic targets [53].

RHEUMATOID ARTHRITIS AND MICRORNA

Noncoding RNA are RNA molecules that are transcribed from DNA but are not translated into protein. They are grouped by size; microRNA (miRNA) are usually 22–23 nucleotides whereas long noncoding RNA (lncRNA) are over 200 nucleotides [54]. miRNA can be encoded within intergenic regions, introns, or exons of protein coding regions. miRNA associates with RISC to regulate transcription by binding and cleaving mRNA and by blocking access to the translation machinery [54]. A summary of miRNA expression in RA FLS has been previously described [4]. A brief description of key miRNAs implicated in disease is provided below.

A recent study identified over 380 differentially expressed miRNAs in RA and OA FLS [55]. Of these, miR-10a was highly expressed in OA but was markedly reduced in RA FLS and synovial tissue. Pro-inflammatory cytokines such as TNF and IL-1β downregulated miR-10a expression through the NF-κB pathway. miRNA-10a targeted several genes in the TNF/IL1 signaling pathway such as *TAK1*, *IRAK5* and *BTRC* [55]. Mimics of miR-10a inhibited expression of IL-6, IL-8, MCP1, MMP1, and MMP13 and reduced FLS proliferation, migration, and invasion. Another study showed that miR-10a also targeted *TBX5*, a transcription factor in RA FLS [56]. As noted above, the *TBX5* promoter is hypomethylated in RA FLS, which correlates with its overexpression, and contributes to induction of pro-inflammatory cytokines such as IL-8, CXCL2, and CCL20 [21].

miR-27a expression was also markedly reduced in RA synovial tissue, FLS and serum compared with normal controls [57]. An miR-27a mimic significantly inhibited migration and invasion of RA FLS by decreasing expression of MMP2, MMP9 and MMP13 and invasion-related proteins, Rac1, Cdc42, and RhoA. Also, miR-27a inhibited TLR4 and NF-

κB p65 protein levels. miR-27a targets follistatin-like protein 1, a pro-inflammatory mediator that is overexpressed in RA synovium and serum, particularly in ACPA+ patients [58]. Interestingly, another study demonstrated that miR-27a expression is suppressed by the lncRNA ZFAS1, which was overexpressed in RA synovial tissue and FLS compared with normal [59].

In contrast to miR-10a and miR-27a, miR-34a is overexpressed in RA FLS [60]. Two studies showed that miR-34a deficiency decreased incidence and clinical symptoms of CIA in mice [61,62]. Treatment with miR-34a antagomir reduced of TNF, IL-17A, IL-6, IL-21, IL-35, IFNγ, and IL-10 expression in the joint and serum of the arthritic mice [61].

SYSTEMIC LUPUS ERYTHEMATOSUS

Aberrant DNA methylation in peripheral blood $CD4^+$ T cells is potentially associated with dysregulated adaptive immunity and the loss of self-tolerance in SLE. Candidate gene analysis showed that immune-associated genes such as ITGAL (CD11a), TNFSF7 (CD70), perforin, and killer Ig-like receptor molecules (KIR) in $CD4^+$ T cells are overexpressed [63]. Studies have shown that gene expression can be enhanced by the loss of repressive histone marks such as H3K27me3. For instance, ITGAL expression is enhanced by JMJD3, a histone demethylase that is overexpressed in lupus CD4+ T cells (Fig. 4) [64▪]. The loss of histone methylation on H3K27 is inversely related to JMJD3 expression and positively correlated with higher disease activity.

Many X-linked genes such as *CD40LG* and *CXCR3* are also hypomethylated and might contribute to female predominance of the disease [65]. Genome-wide DNA methylation studies show profound promoter hypomethylation in other genes, most notably in the TLR and type I interferon response pathways [66,67]. Abnormal interferon epigenetic marks could play a role in the well described interferon signature in SLE. Differential methylation correlates with increased expression *IFIT1*, *STAT1*, *MX1*, *IFIT3*, and *IFI44L* and is associated with autoantibody production and higher disease activity [68–70]. Naive peripheral blood $CD4^+$ T cells in SLE also have transcriptomes with higher expression of interferon-regulated genes and are poised for hyper-responsiveness prior to activation [71]. Hypermethylated genes have also been observed in SLE, including CD3ζ in peripheral blood $CD4^+$ T cells [72], and correlate with lupus-related thrombocytopenia and hemolytic anemia. These methylation data have potential clinical implications, and IFI44L and CD3ζ are being evaluated as diagnostic markers for lupus [73▪].

DNA hypomethylation and DNMT expression in lupus peripheral blood $CD4^+$ T cells can be regulated by MAPKs, GADD45α, PP2A, and RFX1 [63,66,74]. Recent data indicate that ultraviolet B exposure reduced DNA methylation by inhibiting DNMT1 activity, suggesting that UV light might decrease methylation and increase expression of genes associated with SLE [75,76]. Others have shown that lupus T cells expressed lower levels of DNMT1 and DNMT3a, also resulting in a loss of methylation [77]. Recent data show that lupus T cells have increased 5-hydroxymethylation, which is an intermediate epigenetic mark between DNA methylation and demethylation [78]. This study showed that over 2700 genes were differentially hydroxymethylated in lupus $CD4^+$ T cells, many of which are involved in

immune regulation. In addition, lupus T cells expressed higher levels of TET2 and TET3, which are demethylases that actively catalyze the conversion of 5-methylcytosine to 5-hydroxymethylcytosine [78]. Active demethylation further inhibits DNMT1 activity in lupus T cells. Finally, noncoding RNAs, which regulate many facets of disease pathogenesis, also contribute to DNA hypomethylation. MicroRNAs such as miR-126, miR-21, and miR-148a are markedly overexpressed in lupus $CD4^+$ T cells. These miRNAs can reduce DNMT1 expression and activity directly by binding DNMT1 mRNA or indirectly through the Ras–MAPK pathway [79,80].

ANKYLOSING SPONDYLITIS

DNA methylation studies in ankylosing spondylitis have identified over 1600 hypermethylated loci in the peripheral blood of patients with ankylosing spondylitis, most of which are located in HLA genes [81]. Genes such as *DNMT1* and *BCL11B* were hypermethylated but their expression did not correlate with clinical manifestations of ankylosing spondylitis [82,83]. miRNA expression profiles in ankylosing spondylitis blood showed 19 DEGs. Of these, miR-146a and miR-155 levels were increased compared with control and only miR-155 expression correlated with disease index [84].

OSTEOARTHRITIS

OA is traditionally thought of as a degenerative disease, but it often has a prominent inflammatory component. Several studies have determined differentially methylated genes in OA chondrocytes but there is little or no overlap between them [85,86]. A recent study took an integrative approach to analyze methylation, gene expression, and proteomic data from paired, intact, and degraded OA tissue chondrocytes [87▪▪]. This proof of concept study identified three differentially regulated genes namely, *AQP1*, *Col1A1*, and *CLEC3*, in intact and degraded chondrocytes in all three datasets. miRNA and lncRNA expression in OA chondrocytes have been shown to regulate genes involved in matrix degradation, chondrocyte homeostasis, and inflammation pathways [86]. Increased expression of HDACs 1, 2, and 7 has been observed in OA chondrocytes, which suggests that class-specific HDACi might be useful in OA therapy [88].

CONCLUSION

Epigenetics is still a relatively young field in rheumatic disease, but the data already implicate DNA methylation, noncoding RNA, and histone marks as key participants in disease mechanisms. Persistent epigenetic marks in cells suggests that they are imprinted, and the information can be mined to understand disease pathogenesis and the key pathways that contribute to inflammation and matrix destruction. These pathways could be leveraged to identify novel therapeutic targets that would not be readily apparent by simply reading the literature. Alternatively, epigenetic modulators that regulate DNMTs or HDACs could potentially remodel the chromatin and revert the imprinted cells to a more normal state. This intriguing possibility takes advantage of the plasticity in the distribution of marks and could help return a pathogenic cell to homeostasis.

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KEY POINTS

- Epigenetic imprinting through DNA methylation, histone marks and noncoding RNA occurs in inflammatory arthritis and could contribute to disease pathogenesis.
- Pathogenic epigenetic modifications can vary depending on location, cell type, and the course of disease.
- Epigenetic modulators are promising therapeutic approaches to inflammatory diseases.

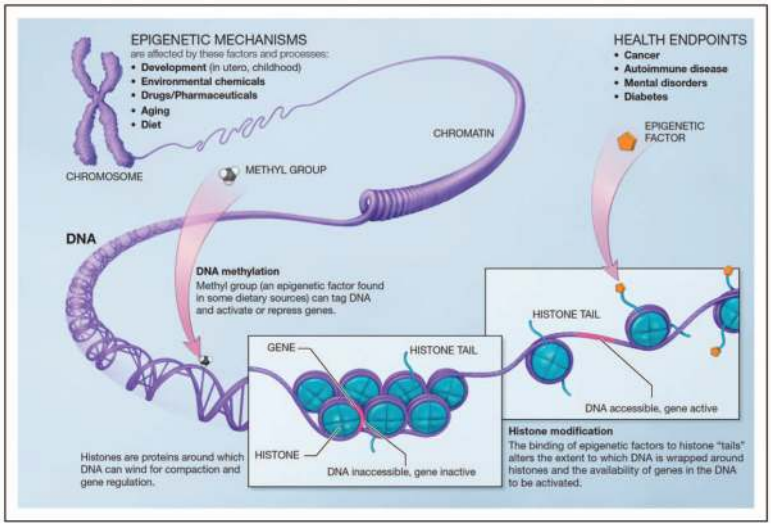

FIGURE 1.

Epigenetic mechanisms in inflammatory arthritis. Epigenetics is defined as the study of heritable changes that do not involve changes in the DNA sequence. Epigenetic modifications such as DNA methylation, histone modification, and noncoding RNA translate extracellular or environmental stimuli to switch on and off gene expression and therefore regulate cell function. Aberrant gene expression can compromise cellular function, contributing to disease pathogenesis. Source: Creative Commons (National Institutes of Health) https://commonfund.nih.gov/epigenomics.

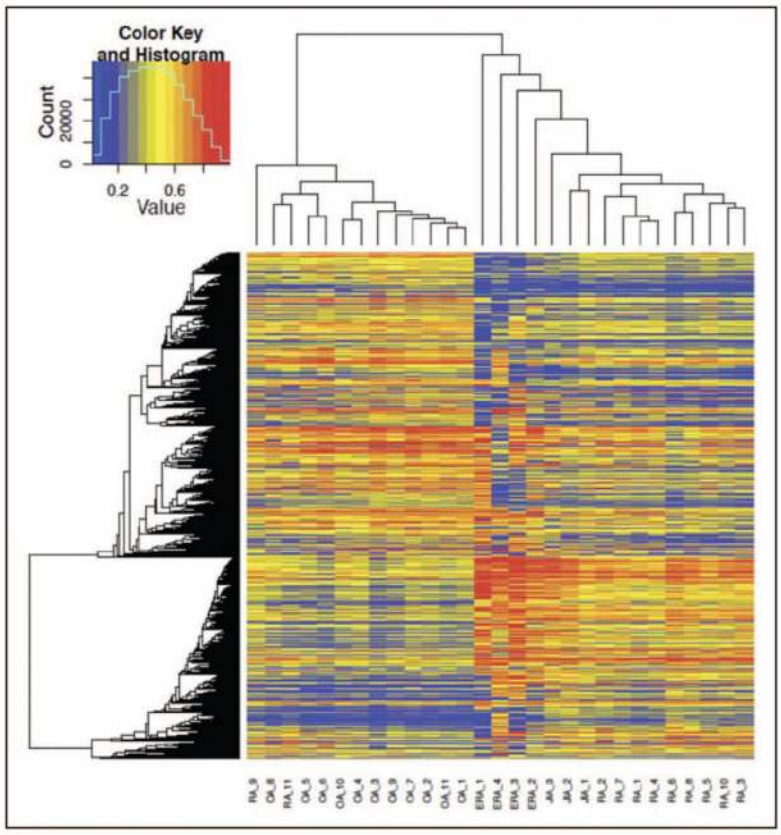

FIGURE 2.

Unique methylation signatures in disease. Hierarchical clustering of differentially methylated loci shows segregation of RA and OA signatures. Early rheumatoid arthritis (ERA) clusters with late RA but forms a distinct subgroup, and other forms of inflammatory arthritis such as juvenile idiopathic arthritis (JIA) also cluster with RA, but form a distinct subgroup. Source: [15]. OA, osteoarthritis; RA, rheumatoid arthritis.

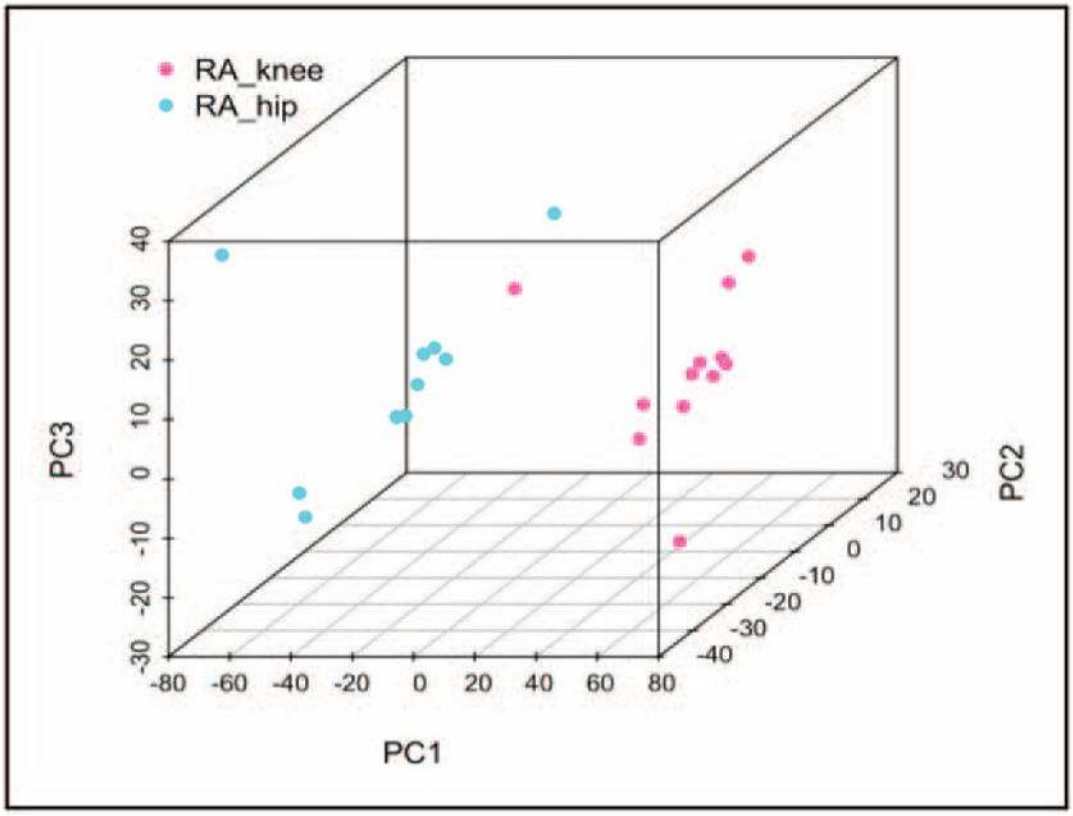

FIGURE 3.

Joint location-specific DNA methylation patterns in RA. Principle component analysis shows that hip and knee fibroblast-like synoviocytes have distinct DNA methylation patterns. Source: [17▪▪]. RA, rheumatoid arthritis.

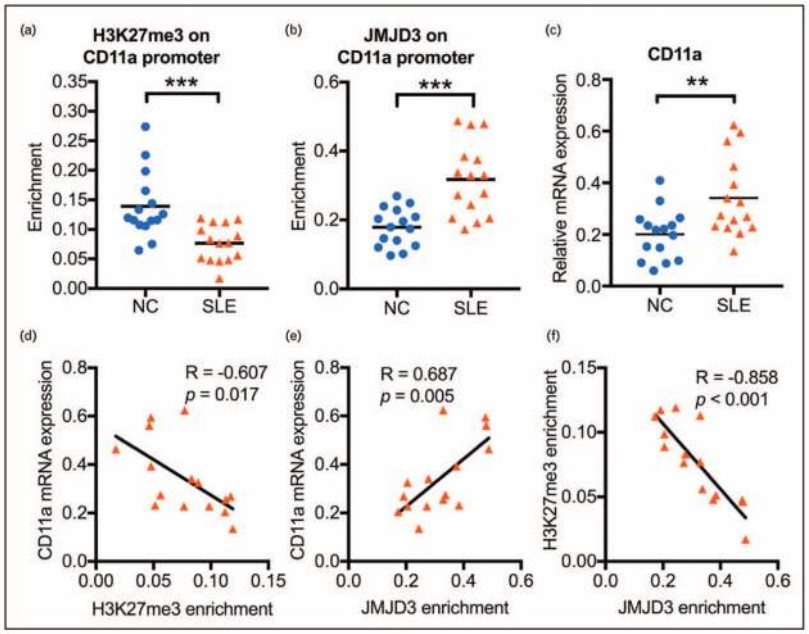

FIGURE 4.

Regulation of CD11a gene expression by loss of the promoter repression mark H3K27me3 and increased JMJD3 in lupus CD4$^+$ T cells. (a, b) Relative enrichment of H3K27me3 and JMJD3 within the CD11a promoter. (c) CD11a gene expression in lupus and normal CD4$^+$ T cells. (d–f) Correlation analysis of H3K27me3 enrichment, JMJD3 enrichment, and CD11a mRNA expression levels. HeK27me3 and JMJD3 appear to have opposite effects on CD11a expression. Source: [64▪].