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Epigenetic regulation mediated by methylation in the pathogenesis and precision medicine of rheumatoid arthritis

Shicheng Guo[1,2#*], Lingxia Xu[3,4#], Cen Chang[3,4#], Runrun Zhang[3,4], Yehua Jin[3,4], Dongyi He[3,4,5*]

[1] Department of Medical Genetics, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI, USA

[2] Center for Precision Medicine Research, Marshfield Clinic Research Institute, Marshfield, WI, USA

[3] Shanghai University of Traditional Chinese Medicine, Shanghai, China

[4] Department of Rheumatology, Shanghai Guanghua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China.

[5] Arthritis Institute of Integrated Traditional and Western medicine, Shanghai Chinese Medicine Research Institute, Shanghai, China.

*SG, LX and CC contribute equally to the study.

*** Correspondence:**

Shicheng Guo, Ph.D.

Department of Medical Genetics

School of Medicine and Public Health

University of Wisconsin-Madison, Madison

Tel: 281-685-5882

Email: Shicheng.Guo@wisc.edu

Dongyi He, M.D., Ph.D.

Department of Rheumatology

Shanghai Guanghua Hospital, Shanghai University of Traditional Chinese Medicine

Shanghai, China

Tel: 158-0030-0800

Email: hedongyi1967@shutcm.edu.cn

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Abstract

Rheumatoid arthritis (RA) as a complex disease is thought triggered by interaction between genetics and environment, especially the shared epitope (SE) and cell surface calreticulin (CSC) theory. However, all the evidence shows genetic diversity and environment exposure cannot explain all the clinical characteristics heterogeneity of rheumatoid arthritis. In contrast, recent studies demonstrate that epigenetics play important roles in the pathogenesis of rheumatoid arthritis, especially DNA methylation and histone modification. DNA methylation and histone methylation are involved in innate and adoptive immune cell differentiation and the migration, proliferation, apoptosis, and mesenchymal characteristics of fibroblast-like synoviocytes (FLS). Epigenetic mediated regulation to immune genes and inflammation pathway provides well explanation to dynamic expression network of rheumatoid arthritis. In this review, we summarized the comprehensive evidence to show methylation modification occurred in DNA and histone are significantly involved in the pathogenesis of rheumatoid arthritis and could be applied as the promising biomarker in the disease activity and drug response prediction. We also explained the opportunity and challenge of the current epigenetics research in rheumatoid arthritis. In summary, epigenetic modules provide possible interface through which genetic and environmental risk factors connect together to contribute to the susceptibility and pathogenesis of RA. Meanwhile epigenetic regulators provided promising drug targets to develop novel therapeutic drugs for rheumatoid arthritis. Finally, DNA methylation and histone modification will be important features to provide better rheumatoid arthritis subtype identification to accelerate personalized treatment and precision medicine.

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by synovial hyperplasia and joint destruction(Lee et al., 2017). Its onset is progressive and invasive, which can lead to joint deformity and disability. In the past decades, linkage analysis and genome-wide association study have identified >100 susceptibility genes and shared epitope (SE) in HLA genes and cell surface calreticulin (CSC) mediated by *PTPN22* and *PADI4* have successfully be used to explain the onset of rheumatoid arthritis(Okada et al., 2014). However, at present, the pathogenesis of RA is still not fully understood. What's more, majority of the current rheumatoid arthritis drugs are not developed by GWAS targets but cytokine and inflationary pathways. Rheumatoid arthritis associated genetics neither fully explained heterogeneity of the clinical characteristics nor the treatment differentiation among RA population. Based on the current urgent needs of precision medicine, it is necessary to clarify the pathogenesis of RA, and to identify effective biomarkers and personalized treatment.

In the recent years, more and more studies have focused on the role of epigenetics in RA(Ai et al., 2018; Guo et al., 2019; Tseng et al., 2019a; Guo et al., 2020). Epigenetics includes abnormal DNA methylation and histone modification, which affects the expression of immune genes and inflammation progression, has become a hot spot to explain the

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pathogenesis of RA(Mazzone et al., 2019). DNA methylation and histone methylation modifications specific effect chromatin structure and gene transcription without changing the DNA sequence, leading to gene silencing or over-expression (Meng et al., 2015; Lawrence et al., 2016). Numerous studies have found that DNA methylation and histone modification in immune cells, through coordinated control of immune cell differentiation and function, may lead to the progress of RA(Qiu et al., 2017; Meng et al., 2019). In this review, we systematically summarize the research progress of DNA and histone methylation, aiming to better understand the pathogenesis of RA and provide evidences that methylation modification provided interface to connect genetic and environmental exposures and provided promising biomarkers for diagnosis, treatment and subtype identification. Finally, epigenetic modules also show promising novel drug targets to be developed as the next generation drugs for personalized treatment and precision medicine.

Genome-wide methylation profiling to identify rheumatoid arthritis-associated epigenetic variants

DNA methylation is an important epigenetic modification module which is involved in the regulation of gene expression and transcript splicing. DNA methylation abnormal is found significantly associated with the progress of rheumatoid arthritis from very early stage. In addition, DNA methylation changes are not only occurred in FLS, but also in innate and adopt immune cells including B cells and T-cells. Compared with normal synovial fibroblasts (SF), the CpG island located in the promoter region of *PM20D1*, *EN1*, *SHROOM1* are found hypermethylated in very early RA derived synovial fibroblasts (veRASF). In addition, *MFAP2*, *RIMBP2*, *IRX6*, *DDR1* and HLA-C are found hypermethylated in established, long-standing RA-SF (estRASF). What's more, recent evidenced shows DNA methylation profiles in cadherin, integrin and Wnt cell adhesion signaling pathways, actin cytoskeleton components and antigen presentation pathways (APP) have obviously changed in veRASF and estRASF, compared with nSF(Karouzakis et al., 2018). Compared with early RA (eRA), the global DNA methylation level is lower in the pathways of cell migration, differentiation and adhesion in longstanding RA (LRA)(Ai et al., 2015). DNA methylation changes in these pathway showed similar pattern with human cancer implicates synovial hyperplasia and invasion maybe shared common underlying mechanism with human cancer metastasis(Wang et al., 2015). What's more, extracellular matrix (ECM), cholesterol biosynthesis and immune system pathways also significantly enriched in RA high-risk individuals and RA patients(Karouzakis et al., 2019). Genome-wide methylation levels change was also found in both T and B lymphocytes(Glossop et al., 2013; Rhead et al., 2017; Guderud et al., 2020). Overall methylation levels of LINE-1 are showed up-regulated in B lymphocytes which may be caused by decreased DNA methylation level(Glossop et al., 2014). Further study identifies 150 and 113 CpG loci with unique methylation characteristics in T-lymphocytes and B-lymphocytes of eRA, such as *ARSB* and *DUSP22* are hypermethylation while *GALNT9* and *MGMT* are found hypomethylation in the T lymphocytes. *BARX2*, *ASB1*, *ADAMTS17*, *MGMT* are found hypomethylation in the B lymphocyte cells and is demonstrated can be used to distinguish RA patients from healthy individuals(Glossop et al., 2016).

The methylation difference could explain the different clinical manifestations and mechanisms in autoimmune diseases. Compared with osteoarthritis, *C18orf45, LMO4*,

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MAP3K5, *ODZ4*, *PKNOX2*, *PRDM16*, *SEPT11*, *MSRA*, *MAP3K5* and *MIR155HG* are hypomethylation in RA(Glossop et al., 2015). Abnormal methylation regions maybe overlapped with transcription factors binding sites (TFBS) to activate enhance regulation activities. For example, RA related hypomethylated regions are found overlap with binding motifs of transcription factors such as *GLI1*, *RUNX2*, and *TFAP2A/C*, and these TFs are closely related to the TGF-β pathway(Ham et al., 2019). The hypermethylation genes *CCR6*, *CMTM5*, *IL10RA*, *IL21R* and *IL32* in systemic lupus erythematosus and pSS while hypomethylation in RA(Wang et al., 2018). Although differential methylation regions (DMRs) in different autoimmune diseases are distinct, numerous of DMRs and pathways are found to be shared by different autoimmune diseases. For example, recent study identified 337 differentially methylated genes are shared by RA and Parkinson's Disease (PD) which provides new evidence for the shared biological mechanism between RA and PD (Tang et al., 2018). Further study find mitochondrial L-carnitine shuttle pathway and PTEN signaling pathway are simultaneously differentially expressed in RA, systemic sclerosis, and SLE(Hudson et al., 2017). In another recent studies, genome-wide DNA methylation profiles reveal common epigenetic patterns of interferon-related genes in multiple autoimmune diseases including Graves' disease (GD), rheumatoid arthritis, systemic lupus erythematosus (SLE) and systemic sclerosis (SSc)(Guo et al., 2017; Ding et al., 2018; Chen et al., 2019). In the future research, DNA methylation changes among different autoimmune diseases should be investigated in a parallel style to identify shared and disease-specific epigenetic dysfunctional elements.

DNA methylation mediated disease risk, disease activity and drug response evaluation.

The DNA methylation level of *SHROOM1* is significantly different between eRA and advanced RA which can be applied as an early diagnosis biomarker(Karouzakis et al., 2018). In addition, the MHC region is found hypomethylated(van Steenbergen et al., 2014) in both peripheral blood mononuclear cell (PBMC) and whole blood. What's more, *CD86*, *RAB20*, *XAF1*, *FOLR3*, *LTBR*, *KCNH8*, *DOK7*, *PDGFA*, *PITPNM2*, *CELSR1* in PBMC showed significant methylation differences(Tseng et al., 2019b) in rheumatoid arthritis. In another study, *S100A6* and *EFCAB4B* promoter regions in whole blood(Svendsen et al., 2016),and IFN-related genes (*IFIT1*, *IRF7*, *MX1*, *OAS1*, *USP18*, *RSAD2*, *IFI44L*) in CD4+ T cells are found to be hypomethylated(Chen et al., 2019) indicating these methylation signals might be used as biomarkers for RA diagnosis.

Methylation-derived neutrophil-to-lymphocyte ratio (mNLR) index from peripheral blood DNA is increased during RA onset, but mNLR is not associated with the response to etanercept treatment(Ambatipudi et al., 2018). In contrast, the *LRPAP1* gene encoding low-density lipoprotein receptor-associated protein 1 chaperone is associated with the response of etanercept treatment. Compared with the non-responder, the most significant methylated positions (DMP) for the responder group are located in the *LRPAP* (cg04857395 and cg26401028) indicating the therapeutic role for TNF-i therapy(Plant et al., 2016). Disease modifying antirheumatic drug (DMARD) drugs can reverse the hypomethylation of *RNF5* and *AGPAT1* promoter regions induced by smoking in RA patients therefore could be considered as a therapeutic marker for RA(Svendsen et al., 2016; Glossop et al., 2017). Meanwhile, two methylation loci (cg03018489 and cg14345882) are significantly

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correlated with DMARD treatment response(Svendsen et al., 2016; Glossop et al., 2017). Methylation levels of cg23700278, cg27427581, cg04334751, cg26764200 are found increased significantly after MTX treatment(Nair et al., 2019). In addition, DNA methylation of *LBH*, *CASP8*, *OLIG3*, *IRF5*, *HLA-G*, *ELMO1*, *TRHDE*, *SLCO1C1*, *PLD4*, *AIRE* and *HLA-DQA1* are demonstrated involved in pathogenesis of RA and then are recommended as promising therapeutic markers(Fan et al., 2016). *AZU1*, *LTBR*, *RTEL1* are hypomethylated and related to the trigger of autoimmune signaling cascade indicating the potential roles as epigenetic susceptibility markers(Wang et al., 2018). Hypomethylation of *CYP2E1* is found associated with disease activity and can be used as disease activity marker(Mok et al., 2018). *CD1C*, *TNFSF10*, *C6ORF10* and *UBASH3A* are demonstrated the potential ability to be used as RA risk markers(Julia et al., 2017; Anaparti et al., 2019; Guderud et al., 2020). Overall, numerous evidences demonstrate DNA methylation could be developed as powerful biomarkers for disease risk assessment, disease activity evaluation and drug response prediction.

Epigenetic regulatory roles in the underlying pathogenesis of rheumatoid arthritis

The changes of DNA methylation states in RA-FLS plays important roles in the pathogenesis of RA. Hypomethylation in RA-FLS maybe caused by the down-regulation levels of *DNMT1* and *DNMT3A* after inflammatory environmental stimulation(Nakano et al., 2013). Hypomethylation mediated over-expression of *TBX5* in RA-FLS increases the expression of IL-8, CXCL12 and CCL20 which enhances the inflammatory response in RA(Karouzakis et al., 2014). Hypermethylation of *EBF3* and *IRX1* in RA-FLS mediates the TNF-β pathway and affects the proliferation, apoptosis, and mesenchymal characteristics of RA-FLS(Park et al., 2013). In addition, the methylation level of *LBH* is significantly decreased in RA-FLS, that leads to synovial hyperplasia and joint pathological changes, which may related to FLS cell proliferation(Ekwall et al., 2015; Hammaker et al., 2016). *PTPN2* is upregulated in RA-FLS which can increase IL-6 production, cell death, autophagy and the pathogenesis of RA. Unfortunately the over-expression of *PTPN2* is not related with DNA methylation regulation(Aradi et al., 2015).

The critical role of methylation changes in PBMC during the pathogenesis of RA was also extensively investigated. The demethylation level of *IFNG* gene promoter and *CNS-1* in peripheral blood CD4+ T cells of RA patients is increased which is related to the number of peripheral blood Th1 cells and recruit effector/memory Th1 cells to the inflammation site(Dong et al., 2013). DNA methylation medicated *FOXP3* expression regulation is identified in RA Treg cells(Kennedy et al., 2014). In addition, DNA methylation in the promoter region of *CTLA-4* inhibits *NFAT2* binding and activation of the IDO pathway which results in the defunctionalization of Tregs(Cribbs et al., 2014). There are totaling 90% of de-methylations on TNF gene-promoter in naïve T-cells of RA patients(Pitaksalee et al., 2020). Further evidence shows the activation of *PRLR* can mediate the de-methylation of TNF-α in CD14+ cells and affect the occurrence of RA(Tang et al., 2014). Hypomethylation of *ZBTB38* decrease *IL1R2* expression in B cells of PGIA rat model to participate in the occurrence of RA(Ocsko et al., 2018). Hypermethylation in AHR promoter region is demonstrated associated with the formation of germinal center in B cells(Toth et al., 2019). Evidence shows demethylation in the proximal promoter region of the *ER* mediated increasing expression in peripheral blood lymphocytes (PBL) of RA

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patients is found to induce the occurrence of RA(Liu et al., 2014). Hypomethylation of DNA in activated apoptotic cells (AC) of inflammatory up-regulates the production of *IL-6* in macrophages, and down-regulates the production of TGF-β in DCs and B cells(Notley et al., 2017). Recently, *METTL3* which is the main m6A RNA methylation enzyme is found up-regulated in macrophages which may affect macrophages proliferation and cytokines releasing through NF-κB pathway(Wang et al., 2019). These evidences demonstrated DNA (5mC) and RNA (6mA) methylation might play important roles in the pathogenesis of rheumatoid.

Epigenetic modules medicated by methylation are promising rheumatoid arthritis drug targets

Therapeutic drugs showed significantly epigenetic regulation roles especially to the DNA methylation and histone modifications. Meanwhile, epigenetic modules also provide promising drug targets for rheumatoid arthritis drug development. Recent study shows daurinol induces hypomethylation of FOXP3 promotes Tregs differentiation and stabilization, and inhibits Th17 differentiation through the Nrp1-Pten-Akt-Foxp3 signaling pathway and alleviates the severity of RA(Park et al., 2019). In another study, expansion of Tregs in vitro with rapamycin could improve the function and stability of Tregs, that maintain FOXP3 high expression and strong inhibitory ability(Rossetti et al., 2015) in which TNFR2 is identified to maintain FOXP3 expression by restricting DNA methylation(Tseng et al., 2019c).

Methotrexate can restore the Tregs inhibition function through the demethylation of FOXP3 upstream enhancer, and increases the expression of *FOXP3* and *CTLA-4*, providing a new mechanism for the treatment of methotrexate. Another evidence shows methotrexate can reverse the DNA hypomethylation of T cells and mononuclear in RA patients(de Andres et al., 2015). Furthermore, Patients with higher baseline global DNA methylation levels in eRA are showed with lower methotrexate response(Gosselt et al., 2019). MTX can also reduce *MTR* expression in rheumatoid nodules, affecting re-methylation mediated by *MTR* and *MTRR*(Houlder et al., 2017) indicating multiple roles in the DNA methylation regulation and drug response. Evidence shows methylation inhibitors (Aza-dc, 5-Aza and 5-AzadC) can increase the expression of *PTEN*, decrease the expression of *HOTTIP*, weak the enrichment of Dnmt3b in *SFRP1* promoter region, and down-regulate the expression of β-catenin and *TNF-a*, *IL-6*, *IL-1β*, and *CCLl-2* (Miao et al., 2013; Li et al., 2019b; Hu et al., 2020). These expression changes will regulate AKT signaling pathway and classical Wnt signaling pathway to aids the remission of RA. *miR-152* can also inhibit the activation of classical Wnt signaling pathway and the expression of *DNMT1* to reduce FLS proliferation(Miao et al., 2014). By regulating the expression of methyltransferase and down-regulating the trimethylation of histone in *CCL2* promoter, etanercept and adalimumab play an important immunomodulatory role in mononuclear cells(Lin et al., 2017). Daphnetin can reduce the expression of *DNMT1*, *DNMT3a* and *DNMT3b* in the collagen induced arthritis (CIA) rat synovial cells, leading to demethylation of pro-apoptotic genes *DR3*, *PDCD5*, *FasL* and *p53*, and increased the expression of pro-apoptotic genes and proteins, to achieve the effect of treating RA(Shu et al., 2014). The combination of *SSAT1* inhibitor DA and methyl donor s-adenosyl methionine (SAM) can significantly improve the overall DNA hypomethylation state in RA-FLA and reduce the adhesion of

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RA-FLS(Neidhart et al., 2014). Finally, another interesting study shows hypermethylation of the promoters in *FER1L4*, *GAS5*, and *MEG3* leads to the down-regulation and promotes the release of pro-inflammatory factors which contribute to the pathogenesis of RA, therefore, recovery of hypomethylation of *FER1L4*, *GAS5* and *MEG3* may be a potential therapeutic target for RA(Liu et al., 2019; Yu et al., 2019; Li et al., 2020). In summary, the drugs improve the abnormal methylation could be promising drugs repurposing for the treatment RA and the genes involved in the epigenetic regulation of RA could be considered as the novel drug targets for pharmaceutical companies.

The advance of histone methylation modification research in rheumatoid arthritis

Histone methylation modification is also involved in the pathogenesis of RA. Histone H3 trimethylated at lysine 4 (H3K4me3) in synovial fibroblasts is associated with the opening of arthritis-activated chromatin, thereby making the promoters of pathogenic genes highly active and driving transcription(Ntougkos et al., 2017). Study shows H3K4me3 is increased in the promoter region of MMP positively correlate with the expression of *MMP-1*, *MMP-3*, *MMP-9* and *MMP-13* in RA-FLS(Araki et al., 2016). Peptidylarginine deiminase type-4 (*PADI4*) inhibits p21 transcription by modifying histone H3 arginine in the p21 promoter region which protects FLS from apoptosis and promotes the pathogenesis of RA(Fan et al., 2017). The expression of Jumonji domain-containing protein 3 (*JMJD3*) in RASFs is up-regulate. *JMJD3* specifically demethylates trimethylated lysine, which is directly involved in the activation of *TLR2* gene through the demethylation of H3K27me3 promoter and promotes RA inflammation(Wu et al., 2019). Aiming at the pathogenesis of RA caused by abnormal histone methylation is helpful to improve the inflammation of RA. For example, the application of *JMJD3* inhibitor GSK-J4 inhibits the methylation of H3K27me3 at the *TLR2* promoter, significantly relieved the destruction and inflammation of articular cartilage(Wu et al., 2019). Therefore, histone modification regulators are potential and promising drug targets for RA therapy and drug development.

Challenge and opportunity of the current epigenetics research in rheumatoid arthritis.

Research on epigenetics highlights the role of DNA and histone methylation changes in the pathogenesis, diagnosis, treatment, and prognosis of RA. Methylation in DNA and histones including *TBX5* (Karouzakis et al., 2014), *FOXP3* (Kennedy et al., 2014), *AHR* (Toth et al., 2019), *HKMT* (Araki et al., 2018) and H3K4me3 (Araki et al., 2016) affect the proliferation, migration, apoptosis and inflammation function of immune cells, which can be used to explain the pathogenesis of RA. Pre-clinical differential methylation changes like the ratio of methylation-derived neutrophil-to-lymphocyte ratio contribute to the early diagnosis of RA(Ambatipudi et al., 2018). The identified differential methylation genes can be used as effective biomarkers to predict disease progression and disease severity, and provide potential therapeutic targets for RA. Explaining the target of drug action from the perspective of epigenetic modification could provide the new direction of pharmacological research for the development of new drugs, which is conducive to the development of new drugs and alleviates the clinical pressures of high toxicity, low efficiency, and expensive of current medicine. For example, the status of demethylation of FOXP3 is used as a biomarker to evaluate the therapeutic drugs response, which provides a direction for precision treatment of RA(Tabares et al., 2018). *MALAT1* promotes *CTNNB1* promoter

methylation and inhibits the Wnt signaling pathway, and is showed as an interesting candidate therapeutic target for RA(Li et al., 2019a). In addition, DNA and histone methylation in individual may change the response to drugs, identify the markers to drug response maybe helpful to personalized medication.

Although DNA methylation and histone methylation research have received significant progress in rheumatoid arthritis, the current researches generally have several concerns. For example, there is no comprehensive study to investigate the relationship between differential methylation and disease severity and inflammation indicators. Future research should also strive to extended cohort studies to improve the statistical robustness. Studies of differential methylation and pathways have examined the corresponding sites, but few functional tests have been performed. Different experimental approaches should be integrated to verify the result and to obtain solid conclusion with large sample size. Moreover, further study is needed for the functions and targets of differential methylation to illuminate the pathogenesis and drug discovery for rheumatoid arthritis. We expect multi-omics analysis to be conducted to illustrate the roles of interaction within epigenetic elements (5mC, 6mA and histone modification) as well as the interaction with genetic for the better understanding of pathogenesis of rheumatoid arthritis.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

SG, DH conceived of content. SG, LX and CC drafted the review, which was edited by RZ and YJ.

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