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EDITORIAL

Epigenetic targets of rheumatoid arthritis

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Abstract

Rheumatoid arthritis (RA) is a systemic, inflammatory and autoimmune disorder, characterized by chronic arthritis with progressive joint destruction. It has a multifactorial aetiology involving both genetic and environmental factors. Epigenetics can be defined as modifications of DNA that result in altered gene expression. The two main epigenetic mechanisms are post translational modifications to histone tails and DNA methylation. Recent evidence has suggested that epigenetic mechanisms may be an important contributor to RA susceptibility. The aim of this editorial is to present evidence for the role of epigenetic mechanisms in the pathogenesis of RA and the potential to therapeutic target. Several studies targeting histone modification and DNA methylation in animal models of inflammatory arthritis will be reviewed and alterations in the epigenetic signature of genes of key RA related pathways such as pro-inflammatory cytokines, proteases and regulators of cellular proliferation.

Key words: Rheumatoid arthritis; Epigenetic; DNA methylation; Histone modification

Core tip: This paper has highlighted the numerous processes involved in the pathogenesis of rheumatoid arthritis (RA) that are modulated by epigenetic mechanisms. This is important hypotheses to explore a novel therapeutic target in RA.

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INTRODUCTION

Rheumatoid arthritis (RA) is a systemic, inflammatory and autoimmune disorder, characterized by chronic arthritis with progressive joint destruction[1]. A typical feature is the over-production of pro-inflammatory cytokines including tumor necrosis factor (TNF) and interleukin-1 (IL-1), which lead to up-regulation of other pro-inflammatory molecules and proteases[2].

RA is a complex disease, and his etiology involves an interaction of both genetic and environmental factors. Genome scans have identified multiple regions

linked to disease[3-5]. Although interesting associations have been reported[6,7], only alleles at the HLA-DRB1 locus have consistently demonstrated both linkage and association[8].

Treatment of RA for most patients involves the administration of disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, leflunomide and sulphasalazine. If DMARDs treatment fails a new drug targets need to be identified to provide therapy for these patients who do not respond to either conventional treatment. Epigenetic mechanisms, which have been implicated in RA, systemic lupus erythematosus and systemic sclerosis[9,10], offers both new targets for therapy but also may help predict the successful outcome of drug treatments in patients.

EPIGENETICS MECHANISMS

Epigenetics can be defined as modifications of DNA or associated proteins without a change in the DNA sequence itself that result in altered gene expression. The two main epigenetic mechanisms are post translational modifications to histone tails and methylation of DNA, which determine the chromatin state and there by access of transcription factors to gene promoter regions. In cells, DNA is packaged by being wound around nucleosome octomers containing two each of histone H2A, H2B, H3 and H4. These histone proteins have N-terminal tails that are susceptible to a number of post-translational alterations including acetylation, methylation, phosphorylation, sumolation, isomerisation of proline and ubiquitination[11,12].

The most widely studied histone modification is the addition of acetyl groups to the lysine residues of the N-terminal tails of histones H3 and H4. Histone acetyltransferases add the acetyl groups to lysine residues within the histone tails from the donor acetyl coenzyme A. In turn the acetylation can be reversed by histone deacetylases (HDAC).

DNA methylation results from the addition of a methyl group to the 5-carbon position ring of cytosine. The methylation blocks binding of transcription factors and other co-activators to the DNA and recruits transcriptional repressors to the promoter[13]. Three active DNA methyltransferases (DNMT) have been identified. De novo methylation is performed by DNMT3A and DNMT3B, whereas methylation is maintained following cell division by DNMT1[14].

EPIGENETIC REGULATION OF IMMUNE CELLS AND PRO-INFLAMMATORY MOLECULES

Both DNA methylation and histone modifications contribute to the expression of a number of T-cell associated cytokines, including interferon gamma (IFN-γ), IL-2 and IL-7Rα[15-21]. At the IFN-γ promoter differential methylation is seen in naïve, effector and memory T-cells being highest in naïve cells. There is rapid loss of methylation upon re-stimulation in memory T-cells that is associated with these cells rapid ability to produce IFN-γ in response to reinfection by a virus[17]. Interestingly, STAT4, which is involved in the stimulation of IFN-γ expression, is also regulated by DNA methylation suggesting that if methylation levels change at both these promoters together there could be a multiplicative effect on the quantity of IFN-γ produced[18]. Protein kinase C activators and phosphatase inhibitors attenuate DNA methylation levels, possibly by altering the activity of DNMT1, correlating with the induction of IFN-γ providing one possible mechanism for changing methylation levels[22]. IL-7 is involved in chronic inflammation in RA, not only does it increase osteoclast formation and thereby enhances bone loss but it is also important in maintaining T-cell homeostasis[23]. Expression of the IL-7 receptor, IL-7Rα, on T-cells is regulated by DNA methylation with T-cells showing only low surface IL-7Rα having higher methylation at the gene promoter[21].

TNF is a major player in the pathology of RA confirmed by the efficacy of anti-TNF treatment in many patients. There is increasing evidence that epigenetic mechanisms play a role in regulating TNF expression. Phosphorylation of Serine $(S)^{10}$ of histone H3 and demethylation of Lysine $(K)^{7}$ has been observed at the TNF promoter in THP-1 cells, following LPS stimulation[24]. These changes to the histone code occur in conjunction with loss of heterochromatin binding protein 1α (HP1α) from the TNF promoter[12]. The role of histone acetylation in the regulation of TNF production remains unclear. In animal models of arthritis it appears that HDAC inhibitors attenuate the expression of TNF whereas treatment of monocyte or macrophages with various inhibitors including sodium butyrate, Chlamydocin and HC-toxin generally increased TNF production with sodium butyrate increasing expression levels by 22 fold in THP-1 cells[24].

Epigenetic regulation has been implicated in the modulation of both IL-1α and IL-1β. Methylation of the proximal promoter regulates the expression of IL-1α and this methylation is responsible for the allele specific expression of this cytokine in $CD4^{+}$ T cells[25,26]. Histone modifications appear the major epigenetic mechanism regulating IL-1β. Inhibiting HDAC activity with fibroblasts trichostatin A (TSA) caused an increase in LPS-induced IL-1β expression in choriodecidual explants[27]. Interestingly DNA methylation appears to have a role in regulating *IL-6* gene expression[2].

IL-6 is another important pro-inflammatory cytokine involved in the hepatic acute phase of RA and with its role confirmed by the success of the IL-6 receptor antibody, tocilizumab, in reducing disease activity and bone erosions[2]. Interestingly DNA methylation appears to have a role in regulating *IL-6* gene expression. In RA patients reduced DNA methylation at a single CpG site within the promoter (-1099) in comparison to healthy for controls has been identified[28]. Reduced

methylation at this site was associated with increased IL-6 mRNA production in response to LPS. In addition to the role of epigenetics in regulating expression of pro-inflammatory cytokines, these molecules once produced may also have a role in epigenetic regulation. IL-6 has been shown to modulate the expression and activity of DNMTs leading to increased DNA methylation at the tumour suppressor gene p53 and Foxp3[29,30]. Methylation induced by IL-6 at the p53 promoter could be playing a role in silencing pro-apoptotic genes in the rheumatoid synovium[29].

Numerous HDAC inhibitors have been developed mainly to target histone acetylation in RA models. Various studies using topical application of suberoylanilide hydroxamic acid (SAHA), MS-275 and FK228 established their potential to decrease serum IL-6, IL-1β and TNF levels suggesting an important role for HDAC in regulating production of pro-inflammatory cytokines[31,32].

EPIGENETIC MECHANISMS AND REGULATION OF THE HOMEOSTASIS IN THE SYNOVIAL JOINT

Increasing evidence suggests that histone tail modifications have an important role in regulating synovial hyperplasia in the RA joint. HDAC inhibitors have been tested in several models of RA in both rats and mice. These studies demonstrated the efficacy of TSA, phenylbutyrate FK228, SAHA and MS275 in ameliorating joint swelling and inflammation associated with inflammatory arthritis[31-34]. Treatment of RA synovial fibroblasts (RASF) with phenylbutyrate, TSA and FK228 causes histone hyperacetylation at $p16^{INK4}$ and $p21^{CIP1}$ promoters associated with expression of these two proteins which involved in the reduction of RASF numbers[35]. Interestingly, treatment with TSA and phenyl butyrate established the potential of HDAC inhibitors to reduce paw swelling in an adjuvant arthritis model in rats. It was reported that treatment had to start early for the inhibitors to prevent pannus formation and associated joint damage. In addition, TSA was found to have a greater ability to suppress synovial hyperplasia than phenylbutyrate[31].

Methylation of DNA may also play a role in regulating cartilage integrity. Demethylation of specific loci within the MMP-3, MMP-9, MMP-13 and ADAMTS-4 promoters is present in cartilage from patients with osteoarthritis compared to controls which, is seen in conjunction with other expression of these enzymes in osteoarthritis cartilage[36]. Osteogenic protein-1 (OP-1) is a potent anabolic growth factor for articular chondrocytes, an aging-related increase in OP-1 promoter methylation that leads to decreased expression may contribute to cartilage loss seen with aging and in particular with the progression of osteoarthritis in older adults[37]. In addition, when comparing DNA methylation patterns in chondrocytes and mesenchymal stem cells undergoing chrondrogenesis, loss of methylation at two CpG sites within the promoter of type X collagen is associated with the production of this collagen in the latter cell type[38]. These findings demonstrate the importance of DNA methylation in regulating the homeostasis cartilage.

CONCLUSION

This editorial has highlighted the numerous processes involved in the pathogenesis of RA that are modulated by epigenetic mechanisms. Key aspects of the production of pro-inflammatory molecules, inappropriate immune cell responses, and abnormalities in the synovium and cartilage degradation have all been shown to be modulated be histone modifications and DNA methylation. However, the complete picture of how epigenetic mechanisms modulate cellular differentiation and response to activation remains unclear. The success of HDAC inhibitors in ameliorating the symptoms of inflammatory arthritis in animal models is an exciting new development for the treatment of RA. Further development in HDAC inhibitors especially as more complete clinical trials, will lead to further knowledge generation on their mechanisms, targets and ability to treat RA.

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