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Epigenetic modifications in rheumatoid arthritis, a review

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Rheumatoid arthritis is an autoimmune disease characterized by chronic joint inflammation and progressive destruction of cartilage and bone which leads to ultimately loss of function and pain. Activated synovial fibroblasts are key effector cells in the pathogenesis of rheumatoid arthritis. In the recent years, epigenetic changes including DNA methylation, histone acetylation and other histone modifications were identified that are associated with an intrinsic activation and the aggressive phenotype of these cells. So far, no therapies targeting rheumatoid arthritis synovial fibroblasts exist. This review comprises recent research efforts that propose epigenetic mechanisms behind the activation of rheumatoid arthritis synovial fibroblasts and other cell types.

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Rheumatoid arthritis (RA) is an autoimmune disease characterized by a systemic inflammation, joint destruction, disability and pain. Despite enormous research efforts the underlying cause of the disease is unknown and still no cure exists. Joint resident rheumatoid arthritis synovial fibroblasts (RASF) emerged as key players in the pathogenesis of RA. In addition to macrophages and lymphocytes, RASF are also capable of producing a large set of inflammatory cytokines and chemokines and thereby actively contribute to the inflammatory state in RA. Their intrinsic activation, the inhibition of apoptosis and the recruitment of inflammatory cells including macrophages and lymphocytes, are the major reasons for the excessive hyperplasia of the synovial tissue in RA joints [1•]. The importance of these cells in disease progression was further emphasized by functional studies of RASF in the severe immune deficient (SCID) mouse model; RASF, co-implanted with cartilage under the renal capsule of SCID mice were shown to be capable not only to invade into cartilage in the absence of a functioning immune system but also to migrate [2].

This review comprises recent research efforts that reveal the mechanisms behind the intrinsic activation of RASF by investigating epigenetic changes (Figure 1) and summarizes data available from other cell types.

What is epigenetics?

Originally, epigenetic mechanisms were considered as heritable changes in gene function that were not explainable by changes in the DNA sequence. A more revised definition of epigenetics is the structural adaption of chromosomal regions in order to register, signal or perpetuate altered activity states [3]. Epigenetic modifications including DNA methylation and covalent histone modifications such as acetylation, methylation and ubiquitination alter the accessibility of DNA to the transcription machinery. An increasing amount of proteins that attach (‘writers’) or remove (‘erasers’) modifications to DNA and histones or that bind (‘readers’) to a specific epigenetically modified site have emerged as key players in the regulation of gene expression [4]. Most chromatin marks are highly dynamic and have the capability of influencing transcription by multiple mechanisms; first, they designate chromatin structure and therefore, determine the accessibility of DNA for regulatory proteins; second, they recruit remodeling enzymes that utilize the hydrolysis of ATP to reposition nucleosomes; and third, they mediate the cooperation between pioneer and secondary transcription factors [5].

Most research so far focused on the role of 5-methylcytosine (5-mC) in CpG-rich regions, known as CpG islands. CpG islands are enriched in promoters in vicinity to transcriptional start sites and their methylation has been associated with long-term gene silencing including X-chromosome inactivation. Methylation of DNA is regulated by the activity of DNA methyl transferases (DNMTs) [6].

Histone acetylation on lysines is regulated by the opposing activity of two enzyme families, histone acetyl transferases (HATs) and histone deacetylases (HDACs). Histone acetylation neutralizes lysine’s positive charges, an action that has the potential to weaken the interactions between DNA and histones. HDACs are thought to stabilize the local chromatin structure by restoring the positive charges in lysine residues. Therefore, they are mainly considered as transcriptional repressors [5].

Unlike acetylation, histone methylation does not alter the charge of histone proteins. Histone methylation mainly occurs at lysine and arginine residues of histones H3 and H4 which can be monomethylated, dimethylated (lysines

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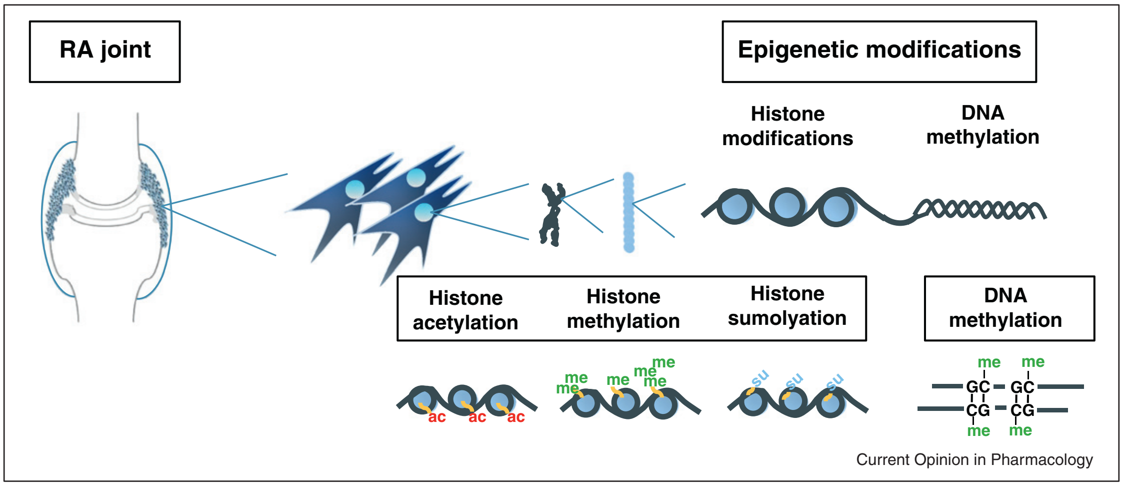
Figure 1



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Epigenetic modifications such as DNA methylation and histone modifications of rheumatoid arthritis synovial fibroblasts (RASF) contribute to their intrinsic activation and aggressive phenotype. ac, acetylation; me; methylation; and su, sumoylation.

and arginines) and trimethylated (lysines) [5]. Depending on the position and the degree of methylation, histone methylation marks can be associated with transcriptional activation or silencing. The polycomb repressive complex 2 with its enzymatic subunit histone methyltransferase enhancer of zeste homologue 2 (EZH2) is responsible for the trimethylation of the repressive mark H3K27me3 (Histone 3 lysine 27 trimethylation) [7]. Today two families of proteins, the lysine-specific demethylase family and the Jumonji C family are known to have histone demethylase activity [8].

In contrast to the above-described histone modifications, histone ubiquitination and sumoylation result in larger covalent modifications of histones. Whereas ubiquitination can be associated not only with transcriptional silencing, but also with transcriptional initiation and elongation, histone sumoylation is associated with repressive functions. Sumoylation targets mainly histone lysines that are modified by the action of E1–E3 enzymes which covalently attach small ubiquitin-like modifier molecules (SUMO) [5].

In the following sections we discuss recent findings on the impact of DNA methylation and histone modifications studied so far in the context of RA (Figure 2 and Table 1).

DNA methylation

RASF display a DNA methylome signature that distinguishes them from osteoarthritis synovial fibroblasts (OASF) and normal SF [9,10•]. Whereas Karouzakis *et al.* described a global hypomethylation in RASF compared to OASF [9], Nakano *et al.* investigated both hypomethylation and hypermethylation patterns in RASF [10•]. A global hypomethylation was also found in peripheral blood mononuclear cells (PBMCs) isolated from RA patients compared to healthy controls [11]. Hypomethylation was identified in key genes relevant for RA and related to multiple pathways including cell migration, adhesion, transendothelial migration and extracellular matrix interactions and was associated with an increased gene expression [10•]. Interestingly, DNMT1, the active enzyme in somatic cells for converting cytosine into 5-methylcytosine (5-MeC) using *S*-adenosyl methionine (SAM) as a methyl-donor, is reduced in RASF compared to OASF [9]. Furthermore, an increased expression of *S*-adenosyl methionine decarboxylase (AMD), spermidine/spermine N1-acetyltransferase (SSAT1) and of polyamine-modulated factor 1-binding protein 1 (PMFBP1) led to an increased recycling of polyamines and a reduced amount of SAM and 5-MeC, and was associated with hypomethylation in RASF [12••]. Beside global changes in methylome signatures in RA, an altered methylation status of single gene promoters, including promoters for DR3 [13], IL6 [14,15], IL10 [16,17], IL1R2 [17] and CXCL12 [18] was described in PBMCs and RASF. Further evidence for the role of DNA methylation in the pathogenesis of RA and a possible explanation for the increased risk of women to develop RA came from studies investigating the pattern of X-chromosome inactivation. Female RA patients exhibited an increased skewed X-chromosome inactivation pattern compared to controls [19] and the promoter of the X chromosome encoded gene CD40L was demethylated in $CD4^+$ T cells from female but not male RA patients [20]. These data clearly show a functional consequence of altered DNA methylation patterns in RA. The results from Karouzakis *et al.* [9,12••] suggested that a supplementation with SAM

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