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EDITORIAL

Next Potential Therapeutic Targets in Rheumatoid Arthritis are Molecules Regulating Inflammatory Transition of Synovium

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ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic joint inflammation and destruction. The affected synovium becomes the basis of the inflammatory milieu by recruiting immune cells including T cells, B cells, monocytes, macrophages and granulocytes etc., and activates osteoclasts leading to joint destruction and dysfunction. If this inflammatory environment can be restored, destructive arthritis in RA can be prevented.

With the introduction of molecular-targeted agents (MTAs) at the beginning of this century, RA has become a controllable disease. Nevertheless, effective drugs including MTAs require continuous administration. This is because they are still unable to eliminate the cause of the disease. Patients with refractory RA often show a decreased response to treatment over time, suggesting that there underlie the irreversible traits of cytokine dysregulation. For the treatment aiming a closer-to-cure condition, it is necessary to find new approach to restore such traits.

The RA synovium has two abnormalities: morphological and functional ones. The first is the loss of the single-cell-layer structure surrounding the joint cavity followed by abnormal proliferation to form a tumor-like tissue called pannus which is comparable to epithelial-mesenchymal transition (EMT), and the second is the autonomous activation of inflammation-related genes due to epigenetic changes in DNA and the decrease in immune regulatory response due to metabolic changes, etc. Especially, these functional abnormalities seem to be associated with traits of cytokine dysregulation in RA synovium.

Recent chromatin immunoprecipitation sequencing analysis with synovial fibroblasts has shown that EMT-like changes are linked to changes in cytokine production. In RA, compared to osteoarthritis, non-autoimmune joint disease, there were activating histone modifications at the IL-6 locus. Intriguingly, such activation changes were observed also in the loci of EMT marker genes, SNAI1 and COL1A1. These epigenetic changes in the RA synovium seem to be related to irreversible, fixed traits that continue the inflammatory response.

Candidate targets of the trait-restoring therapy for RA include molecules involved in epigenetic plasticity that can restore irreversible changes toward inflammatory nature in the RA synovium.

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic joint inflammation and destruction. In RA, inflammation arising from synovial tissue activates osteoclasts, causing bone destruction and breakdown of joint structures. Without treatment, patients are left to have their joint destroyed and become disabled.

In the 1950s, glucocorticoids (GCs) were introduced to treat RA and could relieve arthritis as well as symptoms [1]. However, GCs cannot be used in high doses for long periods of time due to side effects, and cannot stop disease progression. In the 1980s, with the introduction of methotrexate, known as the anchor drug of RA, the disease can be controlled stably in the long term [2]. Nevertheless, it is not effective in all cases. In this century, the advent of molecular-targeted agents (MTAs) including biological or synthetic disease-modifying antirheumatic drugs (DMARDs) targeted to tumor necrosis factor, interleukin 6 receptor, T-cell co-stimulatory molecules (CD80/86) and Janus kinases has made rheumatoid arthritis a truly controllable, if not curable, disease that can go into remission [2].

DMARDs including MTAs developed so far require continuous administration. They can be withdrawn, but most are resumed. This is because they are pathological treatments (disease-modifying treatments) and not etiological treatments (treatments to eliminate the cause of the disease). Since the etiology of RA is unknown, the next candidate approach would be to recover and normalize the cytokine dysregulation that may be responsible for relapse from remission. This review will discuss new therapeutic targets and methods for such trait-restoring treatments of RA aiming for a closer-to-cure condition.

The problem of treatment-resistant cases in rheumatoid arthritis

Despite the use of multiple MTAs, at least about 40 percent of patients still do not achieve remission and some suffer from difficult-to-treat rheumatoid arthritis (D2T RA) [3,4]. Rheumatologists have the impression that many of these D2T RA cases are in a vicious cycle of poor response due to prolonged periods of high disease activity that seems to make cytokine dysregulation permanent and free from plasticity, although there may be other reasons such as complications.

D2T RA cases may be effectively treated with a combination of the temporary anti-inflammatory treatments such as short-term GC administration and the methods to restore plasticity and correct abnormal cytokine production. Here is another indication of exploring new targets for the trait-restoring treatment that can be combined with present therapies.

Applying the "Seed and Soil" theory to rheumatoid arthritis

In cancer research, it is commonly believed that metastasis is due to specific interactions between tumor cells and tissues, a notion derived from Stephen Paget's original “Seed and Soil” theory (1889) (tumor cells = ‘Seed’, tissue = ‘Soil’) [5]. Until relative recently, there had been prevailed the Seed-oriented view by Virchow (1858) and Ewing (1929) that metastasis is merely a physical capture of tumor cells by the vascular system [6].

In recent years, the “Seed and Soil” theory has been attracting attention in autoimmune diseases as well. In other words, not only immune cells that damage tissues such as T cells (Seeds), but also tissues that create the environment for damage (Soil) contribute to autoimmune reactions. In RA,

synovial tissue corresponds to the Soil. The main lesions are in the synovial tissue, and in the pathogenesis of RA, inflammation does not basically occur in organs without synovium. For reference, spondyloarthritis is an analogous disease of RA in which the tendon attachments and sheaths are mainly involved [7].

Inflammatory transition of synovial tissue observed in rheumatoid arthritis

The synovium is a single-cell layer of tissue surrounding the joint cavity that supplies hyaluronic acid to the synovial fluid, removes waste products from the joint cavity, and regulates the immune response [8]. The synovium is morphologically similar to the epithelium, but lacks tight junctions and desmosomes, and is therefore described as mesenchymal tissue.

In the synovium of RA, the specific inflammation causes synovial cells to transform in a certain way, proliferate and form pannus, which infiltrates the surrounding tissues and destroys joints and bones. Steenvoorden et al. reported that the synovial membrane undergoes hyperplasia in a process corresponding to an epithelial-to-mesenchymal transition (EMT) [9]. They used EMT markers such as type I collagen, alpha-smooth muscle actin, and telopeptide lysylhydroxylase. The actual pathology may be primarily functional changes rather than morphologically typical EMT. Through this functionally EMT-like change, the altered RA synovium attracts T cells, B cells, monocytes/ macrophages and granulocytes to form an inflammatory milieu.

Synovial dysfunction following epigenetic changes

The transformations of synovial cells were also revealed by the analysis of epigenesis. Analysis of chromatin immunoprecipitation-sequencing (ChIP-seq) data of synovial cells published by Ai et al. (GSE112655) revealed activating histone modifications of lysine-4 trimethylation on histone H3 (H3K4me3) and lysine-27 acetylation on histone H3 (H3K27ac) at the interleukin-6 (IL-6) locus in RA compared to osteoarthritis as a control disease, and IL-6 secretion appeared to be autonomous rather than induced (Figure 1) [10]. Such changes were observed in the EMT markers SNAI1 and COL1A1, as well as in the DNA methyltransferase DNMT3A, indicating that EMT changes and cytokine production changes are linked (Figure 1).

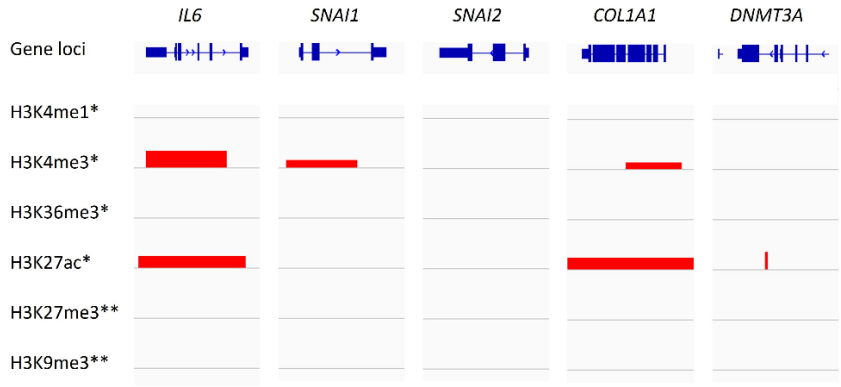

Figure 1: Chromatin immunoprecipitation-sequencing data of synovial cells. More activating histone modifications of H3K4me3 or H3K27ac were observed at the gene loci of interleukin-6, SNAI1, COL1A1 and DNMT3A in rheumatoid arthritis (red in upward positive direction) than osteoarthritis (blue in downward negative direction). The data processed by the authors is provided in the Supplementary Data 1 (41467_2018_4310_MOESM3_ESM.txt). The data browser is an Integrative Genomics Viewer software. *Activation histone modification, **Repression histone modification

EMT experiments in vitro have been established with the human lung cancer cell line A549. Intriguingly, similar epigenetic changes were also observed in the A549 cell ChIP-seq data (GSE42374) by Cieślik et al. with increased IL-6, SNAI1/2 and COL1A1 activated histone modifications after EMT (Figure 2) [11]. There was almost no change in DNMT3A, probably because the cells were already cancerous. This suggests that EMT changes in A549 cells may also be useful for molecular analysis of RA synovial changes.

On the other hand, a distinctive DNA methylation pattern has also been reported as an epigenetic feature of RA synovial cells [12]. Genes in hypomethylated regions are upregulated and those in hypermethylated regions are suppressed, which may contribute to irreversible activation of inflammation-related genes. In cancer cells, DNA methylation-driven EMT is known to be a common mechanism of resistance to therapeutic agents [13]. Besides, it has recently become apparent that DNA methylation and histone modification pathways can be dependent on one another [14]. Anyway, the molecules involved in the regulation of epigenesis in RA synovium can be potential targets for the trait-restoring drugs for RA [15].

It is also important to consider metabolic changes that affect the molecular interactions involved in the epigenetic changes as well as in the immune response [16].

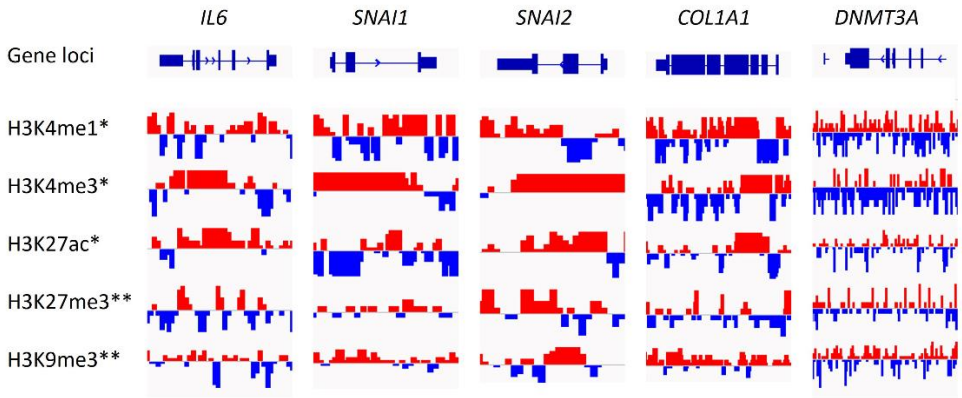

Figure 2: Chromatin immunoprecipitation-sequencing data of A549 cells. More activating histone modifications of H3K4me1, H3K4me3 or H3K27ac were observed at the gene loci of interleukin-6, SNAI1/2, COL1A1 and DNMT3A after EMT (red in upward positive direction) than before EMT (blue in downward negative direction). The data browser is an Integrative Genomics Viewer software. Data provided in the TDF format can be read after processing. *Activation histone modification, **Repression histone modification

Histone deacetylase inhibitors in the treatment of RA

Acetylation and deacetylation of histone proteins are important processes in the regulation of genes involved in cancer and autoimmune diseases [17]. Histone acetylation relaxes the chromatin structure, allowing transcription factors to bind and facilitating gene expression, while histone deacetylation causes chromatin to aggregate, preventing transcription factors from binding to the gene regulatory elements.

Such histone acetylation is regulated by two opposing classes of enzymes: histone acetyl transferases (HATs) and histone deacetylases (HDACs). In the regulation of gene expression, these coordinated balances are considered important. Surprisingly, 'inhibitors' not of HATs but of HDACs (HDACis) have shown efficacy in leukemia and solid tumors and are already being used in clinical practice. Most of HDACis exert their efficacy by

inducing cell cycle arrest and apoptosis, where not histones but transcription factors such as cyclin-dependent kinase inhibitor 1 (p21/WAF1) are the direct substrates of HDACs [17]. In RA, HDACis may be particularly effective in targeting synovial cell proliferation or survival at inflammatory sites. In fact, an HDACi givinostat (ITF2357) has been reported to be effective in clinical trials for systemic juvenile idiopathic arthritis, but further reports are awaited [18]. The concern with HDACis is that they have multiple target molecules including non-histone proteins, cytocidal nature and unresolved complex mechanism of action. First and foremost, it remains clarified whether HDACis have trait-restoring effects.

Conclusions

The details of the pathogenesis of RA remain unclear. Although other immune cells including monocytes/macrophages and granulocytes may be involved, B cells and T cells are considered to be the essential members of 'Seed', and synovial tissue is thought to be the main 'Soil' where B cells and T cells are primed with RA-specific antigens, citrullinated proteins and sheared epitopes, respectively. When the inflammation becomes chronic, secondary and tertiary immune dysregulated cells may reside in the joint and form 'Soil' together with synovial cells. Without therapeutic intervention, the 'Soil' undergoes EMT, takes on an autoinflammatory character, prolongs inflammation, and disrupts peripheral tolerance. In the case of systemic lupus erythematosus and many other autoimmune diseases, the disease activity can be generally suppressed with GC alone, but not in RA. DMARDs are necessary for the treatment of RA. Is it because 'Soil' acquires irreversible and fixed autoinflammatory traits?

Like GCs, MTAs are unable to correct this transformation. Elucidating the molecular mechanisms of the series of EMT changes that lead to these transformations may provide insight into the molecules that confer plasticity to synovial cell epigenetics. In addition to improving the inflammatory environment with effective DMARDs, trait-restoring therapy giving plasticity to 'Soil' and restoring it to its pre-transformation state may be a potential treatment approach.

Conflicts of Interest

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