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Review

Molecular and Cellular Contributors of Rheumatoid Arthritis

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Abstract: Rheumatoid arthritis (RA) is a chronic immune-mediated condition affecting about 1% of the world population. Persistent synovial inflammation (synovitis) triggers the hyperplastic transformation of the synovium which eventually destroys juxta-articular bones and articular cartilage. As the disease progresses, RA patients may present systemic and extra-articular manifestations. Particularly, RA patients are at an increased risk of developing cardiovascular events and mortality as compared to individuals without RA. Recent advances in understanding the molecular and cellular mechanisms of RA led to the development of disease-modifying drugs and reliable assessment tools that have significantly improved the management of RA. This review focuses on the current understanding of RA pathogenesis and treatment strategies.

Keywords: Inflammation; autoimmune; Rheumatoid Arthritis; molecular mechanisms; therapeutics

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune and inflammatory condition often affecting symmetrical joints of the body [1]. As the disease progresses, symptoms can spread from smaller joints to weight-bearing joints, such as ankles, knees, and hips [2–4]. Over time, the joints may deform [5] and eventually lose function [6–9]. Besides the articular presentation, around 40% [10] of RA patients also experience systemic manifestations affecting all aspects of patients' organ systems [11–22], and these complications are often more fatal to people with RA than those without [10,23–26]. Cardiovascular disease [27–33] and respiratory disease [34–37] are common causes of death in patients with RA.

The prevalence of RA is around 1% worldwide [26,38]. Most patients are first affected in their thirties to sixties, and the disease prevalence increases with age [39–41]. Like many autoimmune diseases, the sex difference of the incidence, prevalence, disease course, disease activity, and prognosis of RA is well-established [26, 42]. There are many hypotheses for this overrepresentation of women in RA, such as the involvement of x-linked factors and hormonal aspects [43–46].

The primary goal of RA therapy is to minimize disease activity and control joint damage [47]. However, the disease symptom persists in a substantial number of patients despite the active treatment and a variety of side effects have been reported for existing antirheumatic drugs. Therefore, effective management of RA remains elusive.

2. Pathogenesis of RA

RA primarily affects the lining of the joints called synovium, a 1–2 cell thick intimal layer of specialized macrophages and Fibroblast Like Synoviocytes (FLS) [48 – 51]. FLS are mesenchymal-derived cells that express extracellular matrix (ECM) proteins, adhesion molecules, integrin receptors, and surface markers. Under normal conditions, FLS serves to maintain the structural and dynamic integrity of the joint by controlling the composition of the synovial fluid as well as the ECM of the joint lining [49,50,52–55]. In the rheumatoid joint, FLS becomes hyperproliferative [56,57] and contributes to the formation of a highly invasive and destructive phenotype known as pannus [48,55,58 – 62]. The thickened synovium creates a hypoxic environment, which triggers excessive blood vessel formation in an attempt to reduce tissue hypoxia and provide oxygen and nutrients to proliferating FLS. However, these newly formed blood vessels are immature and leaky, therefore, leading to further extravasation of inflammatory cells in the synovium and a vicious cycle of inflammation and tissue damage [63–72]. At the pannus-cartilage interface of the rheumatoid joint, FLS triggers differentiation of bone-resorbing osteoclasts, which produce excessive matrix-degrading molecules leading to progressive cartilage and bone erosion [73 – 77]. The phenotypic transformation of the synovium from a quiescent, relatively acellular structure to a hyperplastic, and invasive tissue filled with immunocompetent cells [78], abnormal vasculatures, and excessive fluid limits the range of motion, causes joint deformities which eventually results in functional deterioration and disability [54,63].

The dysfunctional immune system has been the central place for the pathogenesis of RA. Studies showed that RA synovial microenvironment is highly conducive to the formation of neutrophil extracellular traps (NETs) which serve as a rich source of citrullinated proteins [79,80]. NETs formation activates peptidylarginine deaminase-4 (PAD4) which is a myeloid-specific PAD involved in the process of citrullination and this causes proteins in the NETs to be citrullinated [79]. These citrullinated proteins have been shown to contribute to increased immunogenicity and arthritogenicity and their presence is correlated to RA disease severity [81,82]. They also serve as important RA autoantigens that serve to propagate the spreading of autoimmune response [83, 84]. FLS is in direct contact with synovium-infiltrating neutrophils, endocytoses [79] the citrullinated peptides, acquires antigen-presenting cell capability [85], and presents them via the MHC class II (MHCII) to activate the citrulline-specific CD4+ T cells [79, 86]. The activated T cells perpetuate inflammation by promoting the release of a large amount of pro-inflammatory molecules, MHC-dependent antigen presentation, FLS activation [87], and inflammatory cell recruitment [88,89], survival [90, 91] and retention [92]. Human leukocyte antigen (HLA)-DRB1 is a major MHCII molecule. HLA-DRB1 alleles that code a five-amino acid motif, "shared epitope" (SE), at the positions 70 to 74 of the HLA-DRB1 protein, are strongly associated with RA susceptibility [93–95], severity [96], and penetration [97]. However, the contribution of SE to RA pathophysiology remains equivocal.

Besides the adaptive immune system, the innate immune system also contributes to the pathogenesis of RA, at least partially due to the imbalance between inflammatory and anti-inflammatory macrophages. Inflammatory macrophages secrete cytokines, such as Tumour Necrosis Factor (TNF), and interleukin (IL) 1 and 6 [98,99], which lead to further activation of endothelial cells and excessive growth of new blood vessels, another hallmark of RA [100,101], resulting in further recruitment of inflammatory cells and tissue damages. Anti-inflammatory macrophages serve as immunologic barriers in the synovium and disruption of their function propagates inflammatory signals and further promotes the progression of RA [38,52,53,102–105].

Recently, premature cell senescence has also been implicated in the pathophysiology [106 – 108] and the development of systemic manifestations in RA [109 – 112]. With age, the adaptive immune system is compromised due to the loss of regenerative capacity and develops a senescence-associated secretory phenotype (SASP). A myriad of inflammatory cytokines and chemokines, matrix metalloproteinases (MMPs), microRNAs, growth factors, and small-molecule metabolites [113 – 115] are produced by senescent cells which lead to the recruitment and further activation of immune cells such as macrophages and neutrophils in the synovium [116,117]. However, molecular drivers of premature cell senescence and their impact on changes in other types of cells present in the synovial microenvironment remain to be elucidated.

It is worth highlighting that RA is a multifactorial and heterogeneous disease [118 – 122], which is reflected not only in disease presentation but also in the involvement of numerous pathogenic pathways. Different pathways may contribute to the disease pathophysiology and presentations in individuals with RA

hence requiring different treatment approaches. It is not clear why some pathways are more important than others in certain RA patients [38].

3. Pharmacological Strategies and Challenges

Current guidelines and outcome measures for RA focus on alleviating symptoms control of synovitis and preventing joint injuries. Early diagnosis and interventions before irreversible injury of the joints occurs are critical for the management of RA. Like most autoimmune conditions, RA treatment aims at attaining and maintaining disease remission or low disease activity with Disease Modifying Anti-Rheumatic Drugs (DMARDs) [47,123,124]. Disease-modifying antirheumatic drugs (DMARDs) are often prescribed as soon as the diagnosis is confirmed [125–127]. There are different groups of DMARDs, including conventional synthetic DMARDs (csDMARD), biologic DMARDs (bDMARD), and a newer class of targeted synthetic DMARDs (tsDMARD). Commonly used csDMARD are methotrexate (MTX), sulfasalazine, leflunomide, and hydroxychloroquine. Low-dose MTX is the first-line treatment for RA and is reported to have a faster onset of action, greater efficacy, and better long-term tolerance as compared to the other csDMARDs [128–131]. MTX is a folate antimetabolite that was originally used for the treatment of various cancers as it acts to inhibit DNA synthesis, repair, and cellular replication. However, low-dose MTX is not affected by levels of folic acid, instead, MTX has been reported to dampen the inflammatory environment in RA [132]. Therefore, the MTX likely functions through a folate-independent mechanism in RA. Although MTX is generally well tolerated, significant side effects including bone marrow, lung, and liver toxicity have been reported in RA patients [133–136]. In addition, up to 70% of RA patients do not respond to MTX monotherapy [127,137,138]. MTX when initiated is often used with bridging therapy such as nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids. These drugs act as temporal controls to ease pain and control inflammation while awaiting the response to the slower-acting drugs either in the initiation of treatment or during RA flares. NSAIDs and glucocorticoids although highly effective are not used as monotherapy for a variety of reasons. The use of NSAIDs is associated with unwanted potential side effects, such as heart attack, stroke, stomach irritation, ulcers, and bleeding [139]. Moreover, NSAIDs are merely means of symptom control and areineffective in slowing down the RA progression [125,140]. Glucocorticoids on the other hand are often used only in severe RA not ameliorated by NSAIDs [141]. Glucocorticoids are able to slow down the radiologic progression of RA in the short to medium term [7,142–144]. Recent 2022 EULAR recommendations have called for stricter adherence to the recommendation of discontinuation of glucocorticoids within 3 months of prescription [47].

Advances in understanding the pathogenesis of RA led to the development of multiple bDMARDs that target specific molecules involved in inflammation and joint destruction. The introduction of bDMARDs has revolutionized the treatment of RA [145]. The biologics commonly used in RA include TNF-α inhibitors (adalimumab, etanercept, and infliximab), IL6 inhibitors (tocilizumab, sarilumab), B cell inhibitors (rituximab), and T cell costimulatory inhibitor (abatacept). With regards to the use of bDMARDs, recent 2022 EULAR guidelines recommend the use of bDMARDs in patients with poor prognostic factors who are not responding to csDMARDs treatment [47]. As such, these biologics are mostly used in patients who continue to exhibit symptoms or show disease progression despite the csDMARD treatment [146,147]. In addition, EULAR 2022 recommends that bDMARDs be used in combination with csDMARDs as there is no compelling evidence for monotherapy with bDMARDs [47]. In fact, combinational treatment with bDMARDs and MTX has shown superiority over monotherapy [146,148–152].

As biologics and some DMARDs are often immunosuppressive, latent or opportunistic infections may occur in patients under such treatment [153–156]. For example, anti-TNFα biologics are known to cause severe opportunistic infections [156,157]. In fact, infections account for about 25% of all RA-related deaths [158]. The immune system is also important for cancer surveillance. Immunosuppression thereby can potentially cause an increased risk for malignancy. Indeed, the use of TNF-α inhibitors has been associated with the increased risk of developing non-melanoma skin cancer [153,159,160]. Since these drugs target specific pathways, their efficacy varies greatly between individuals, and not all patients respond to a given treatment regimen [161]. For instance, patients testing positive for Rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA) had a greater likelihood of response to rituximab than those who are

seronegative [162–164]. Given the heterogeneity of the disease process of RA, personalized therapy using pharmacogenomics or certain patient characteristics as a predictor of response could be used to guide the selection of biologic therapy.

tsDMARD is a newer class of DMARD for the treatment of RA. The only tsDMARD available on the market is Janus Kinase (JAK) inhibitors [165–168]. tsDMARD use is generally recommended only after intolerance or inadequate response to at least one TNF-α inhibitor.

4. Future Directions

Advances in understanding the disease pathogenesis lead to the development of more treatment options for RA. Given the heterogeneity of RA pathogenesis among patients, the effectiveness of biologic agents is highly patient-dependent [169]. Some patients remain treatment-resistant or difficult to treat [170,171] which is likely due to the presence of comorbidities [172,173] or adverse side effects. Although much work has been done to investigate the mechanisms leading to RA development, there are areas less explored. Some of the areas that could be investigated include the antibodies generated from citrullinated peptides [174], primary epigenetic changes in FLS [99,175,176], and synovial neovascularization [177–180]. Further insights into RA pathogenesis will also pave the way for personalized therapy, thereby, leading to better treatment outcomes. Delving into the development of personalized medicine, however, would require a clearer understanding of the intricate interplay of compounding factors that could contribute to an individual's propensity to develop RA. Factors include the genetic makeup of an individual, their immunological landscape as well as environmental factors. Only with a clear understanding of the molecular mechanism giving rise to RA would clinicians be able to truly discern why certain groups of patients respond well to certain treatments and not others. This would reduce the need for multiple treatment trials before finding a drug that worked for each individual. A deeper understanding of the molecular mechanism contributing to RA pathogenesis would also allow for the identification of specific biomarkers that could offer early diagnosis, predict treatment responsiveness/adverse outcomes, or predict disease progression which is critical for the effective management of RA.

In essence, the advancement of treatment modalities in RA will depend highly on deepening understanding of RA pathogenesis and uncovering molecular signatures that would allow for personalized therapy and improved patient outcomes.

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