Chapter 6

Autoantibodies and Cytokines in Pathogenesis of Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is an autoimmune disorder in which increased autoantibody production and enhanced secretion of pro-inflammatory cytokines are the hallmark of the disease. A strictly controlled balance of antibody production and proinflammatory cytokines is the key to the healthy state. A slight tilt in this balance causes proinflammatory diseases. In RA there is an increased production of autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA), anti-cartilage type II antibodies, and etc., which have a prominent clinical significance. Furthermore, there is increased secretion of proinflammatory cytokines such as tumor necrosis factor-α (TNFα), interleukin-6 (IL-6), interleukin-1 (IL-1) which have an impact of great magnitude on the RA disease progression and severity. A better understanding of the mechanism of autoantibody production and secretion of cytokines together with crosstalk between immune cells and cytokines can provide us a better insight into the disease pathogenesis as well disease prognosis and management.

Keywords: rheumatoid arthritis, autoantibodies, cytokines, proinflammatory, pathogenesis

1. Introduction

Autoimmunity arises as a result of failure of immune self-tolerance. The condition may involve both T and B cells however it has been found that in most autoimmune diseases, T cells play a pivotal role in both dysregulation and autoimmune aggression, but autoantibodies are also widely produced by B cells. Such autoantibodies play a key pathogenic role in diseases such as autoimmune hemocytopenias, Grave's disease, rheumatoid arthritis, type 1

diabetes and systemic lupus erythemathosus (SLE). Similarly, autoantibodies are also found in other diseases, where although they may play a minor pathogenic role, but can be used as valuable diagnostic markers [1–7].

Furthermore, in addition to T cells and autoantibodies, cytokines also play a pivotal role in development of the autoimmune response. Proinflammatory cytokines have significant involvement in autoimmune associated damage. This chapter aims to discuss the involvement of autoantibodies and cytokines in the pathogenesis of RA.

Immune system has the capacity to mount an immune response against virtually all foreign molecules as well as self. However, several mechanisms exist within the human system that prevent or subdue the response to self-antigens. The immune system has developed a series of checks and balances that enable it to distinguish dangerous signals from harmless ones and allow it to respond to foreign or non-self-antigens. When these mechanisms undergo a breakdown or are overridden, a response directed against self-antigen can occur, resulting in autoimmune reactions and/or autoimmune diseases [8].

RA is a complex chronic disease, primarily affects the lining of the synovial joints and can cause progressive disability, premature death, and socioeconomic burdens. The clinical manifestations of symmetrical joint involvement include arthralgia, swelling, redness, and even limiting the range of motion [9].

Autoantibodies have been associated with human pathologies for a long time, particularly with autoimmune diseases. RA is more frequent in females as compared to males [10]. Organ specific autoimmune diseases involve single or multiple autoantigens. In RA, presence of various autoantibodies such as RF and ACPA, and anti-cartilage type II antibodies in serum and synovial fluid have long been associated with RA severity [11].

The pathological hallmarks of synovitis in rheumatoid arthritis include the proliferation of resident synovial fibroblasts, new blood vessel formation and the recruitment of a wide range of leukocytes including B and T lymphocytes, monocytes/macrophages and mast cells; in turn this leads to synovial hypertrophy and the invasion of cartilage and bone by activated inflammatory tissue. Cytokines are fundamental orchestrators of the development and maintenance of this lesion [12]. RA disorder is a multifactorial disorder other than autoantibodies there are many other important factors involved such as proinflammatory cytokines such as TNF-α, IL-6 and IL-1 are key mediators of cell migration and inflammation in RA [13]. Cartilage degradation in RA occurs when TNF-α, IL-1 and IL-6 activate synoviocytes, resulting in the secretion of matrix metalloproteinases (MMPs), cathepsins and mast cell proteinases into the synovial fluid [14, 15]. Cytokines also activate chondrocytes, leading to the direct release of additional MMPs into the cartilage [14, 15].

Although the availability of advanced drugs and treatment regimes, however the complete remission of the disease is still not achieved. This chapter shed light on the complex network of the autoantibodies and proinflammatory cytokines as immune responses in the RA disease pathogenesis and the development of bio-therapeutics used in RA disorder.

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2. Autoantibodies in RA

Several studies have been demonstrated that levels of disease-related biomarkers (such as RF and antibodies to citrullinated protein antigen, as well as secretory phospholipase A2, C-reactive protein (CRP), glycated HSA, and multiple cytokines/chemokines) may be elevated prior to the onset of symptomatic rheumatoid arthritis [16–24].

These findings suggest that there is a substantial "preclinical" period of RA, during which detectable immunologic and inflammatory changes are occurring that are related to disease development. These increased levels of RA related autoantibodies in preclinical RA may be highly specific for early RA detection [18, 19]. There is a great hope that these autoantibodies may be used to predict which currently asymptomatic individuals are at sufficiently high risk for future RA that they may be targeted with preventive therapies.

2.1. Rheumatoid factors

The RA is associated with systemic autoimmunity as evidenced by the presence of serum and synovial fluid autoantibodies. The first autoantibody to be described in RA was the rheumatoid factor (RF) by Waaler in 1940 [25], and it was later found to be directed to the Fc region of IgG. It is well characterized, although its exact origin still remains unclear. Typically, RF is of IgM isotype, but IgG and IgA may also occur. IgM RFs are the major RF species in RA and are detected in 60–80% of RA patients [26]. In the past, RF levels were determined by classical agglutination reactions; however, sensitivities and specificities depended on the type of test (e.g., latex fixation test, or Waaler-Rose test using sheep erythrocytes). RF levels were also determined by nephelometry [27]. RF has been observed in many other autoimmune diseases, such as, in systemic lupus erythematosus, mixed connective tissue disease and primary Sjogren syndrome, as well as in non-autoimmune conditions, such as in chronic infections and old age [26]. RF specificity to RA is increased at high titers (e.g., IgM RF > 50 IU/ml) and with IgA isotypes [26, 28, 29]. High titer RF and IgA isotypes are also associated with radiologic erosion, extra-articular manifestations and thus, poorer outcomes [26, 28, 30, 31]. The association between high titer RF status and a poor prognosis indicates that RF may have a role in the pathogenesis of RA. The functions of RFs under normal physiological conditions were observed as (i) enhancement of immune complex clearance by increasing its avidity and size, (ii) aiding B cells in uptake of immune complex through efficient antigen presentation to T cells, and (iii) facilitation of complement fixation by binding to IgG containing immune complexes [32–34]. RFs with high affinity and high-titer in synovial fluid of RA patients are considered to exert pathogenic functions and to enhance inflammation and antigen trapping in joints. However, no clear evidence yet suggests that RFs are involved in the initial events triggering the disease process of RA. In fact, it is understood that they may themselves be triggered by RA. Somatic mutations accumulates in RA and the presence of isotype switching indicate that RF production is T-cell driven, although T cells infiltrate RA synovium [35] and contain autoreactive clones [36], which were polyclonal and lack specificity for any particular autoantigen [36, 37]. T-cell clones reactive with autologous IgG were not detected in

RA patients as yet. Additionally, the function of RF expressing B cells to take up immune complexes and present trapped antigens to T cells may allow these cells to bypass the need for specific T cell help and eventually lead to emergence of autoreactive T cells capable of triggering RF synthesis in the absence of an external antigen [38].

2.2. Anti-citrullinated proteins antibodies (ACPA) in RA

Some other names used to describe ACPA are anti-keratin, antiperinuclear factor antibodies, antifilaggrin antibodies, or anti-Sa [39]. ACPA have been associated with human pathology [40] as well as preclinical disease [16, 18, 41]. Latest ELISA assays, exhibited higher specificity (~98%) and sensitivity between 40 and 76% (depending on disease stage) [42]. Recently proved that there is a potential association of ACPA with conditions like psoriatic arthritis [43], periodontitis [44], and osteoarthritis [45]. The key difference between ELISA assays was in the antigens used to detect ACPA. Thus, the diagnostic value of ACAP was established by demonstrating the significance of using appropriate citrullinated peptide [39, 46, 47]. Consequentially, a highly sensitive noncommercial ELISA, based on protein targets identified as reactive with ACPA in synovial tissue such as alpha and beta fibrinogen was therefore developed [48]. The positivity of ACPA for one or both to these two citrullinated peptides covered all reactivity in RA sera [49].

Citrullinated peptides are generated in response to a posttranslational modification mediated by peptidyl-arginine deiminase (PAD) enzymes. Multiple antibody isotypes including IgG, IgA, and IgM directed against these citrullinated peptides are detected in RA [50]. Citrullinated proteins are present in the synovial fluid of inflamed RA joints, exhibiting that ACPA could bind to these antigens in the joint and possibly increase local inflammation [51]. A protein that is commonly targeted by ACPA is Vimentin. In collagen-induced arthritis, mouse models passive transfer of ACPA cannot cause synovitis, although it can worsen preexistent synovitis [52]. Therefore, it is suggested that multiple events are necessary for the development of RA.

ACPA causes inflammation via binding to Fc receptors or complement activation. Autoantibodies are usually glycoproteins that means both Fc and Fab region of the antibody bind to the carbohydrate chains, which is essential for immune effector functions. Compared to IgG antibodies, the Fc region of ACPA has a lower level of galactosylation and sialylation against recall antigens [53]. The decreased sialylation of IgG in immune complexes can drive osteoclastogenesis, both *in vitro* and *in vivo*, through altered FcγR signaling. Moreover, it has been found that RA patients with low levels of ACPA-IgG Fc sialylation displayed lower bone volumes and trabecula numbers [54]. Thus, disease pathophysiology could be influenced by the specific Fc glycan signature of ACPA.

2.3. Autoantibodies against type II collagen

Type II collagen (CII) are abundantly present in joint cartilage [55]. Native CII protein consists of a triple-helix structure containing three identical α chains. The collagen fibrils contribute to cartilage integrity by resisting stretching forces caused by hydrophilic proteoglycan molecules in extracellular matrix of articular cartilage, [56]. The degradation of CII leads to the

degeneration of cartilage and consequent loss of function in RA patients [57]. Denaturation of CII also causes separation of α chains and loss of antigenic sites (epitopes) present in the molecule which are altered due to the disruption of its three dimensional structure [58]. Autoantibodies to both, native and denatured CII, have been reported in RA [59–62]. Varying levels of anti-CII antibodies were detected in the same patient at different times and also between patients, suggesting that these antibodies might be associated with specific events during arthritis development.

Increased anti-CII antibody levels may degrade CII molecules leading to acute inflammation which is mediated by anti-CII antibody containing surface-bound immune complexes (ICs) [60], which activates complement system activation and enhanced the production of proinflammatory cytokines (TNFα, IL-1β and IL-8) [63], which leads to the inflammation of the joints and hence cartilage damage. Antibodies have been detected against major CII epitopes at the site of inflammation, serum and synovial fluid samples from RA patients, supporting the concept of an increased local immune response to CII in the joints [61].

CII is found to be arthritogenic in animals and an injection of native CII in adjuvant induces collagen-induced arthritis (CIA) characterized by antibodies to CII and inflammatory polyarthritis [64]. Variability in expression of arthritis is linked to the expression of particular class II major histocompatibility (MHC) alleles [65] and also depends on an intact immune system. For example, B cell deficient animals [66] or complement deficient ones [67] are protected. Moreover, monoclonal antibodies (mAb) to CII derived from mice with CIA can induce collagen antibody-induced arthritis (CAIA) in naïve mice. CAIA is a condition characterized by inflammation, formation of pannus and erosions of bone similar to that observed in RA [68]. This model disease does not require the help pf T cells and has proven to be an informative model to better understand how antibodies lead to development of arthritis. Not only is arthritis not MHC-restricted, but it can be induced in most strains of mice and represents a model of the effector arm of CIA. However, it depends on the specificity of the antibodies used. A triplet of arginine-glycine-hydrophobic acids, is a common amino acid motif, shared by these arthritogenic mAb, which recognize epitopes on CII. These map to surface-exposed regions on the collagen fibrils that are accessible for antibody binding [68]. These epitopes are conserved, and are also recognized by antibodies from rats [69–71] and from humans with RA [70, 72]. Amino acid arginine molecules are present on the surface of the major epitopes on the collagen fibrils can also become citrullinated [73] and mAb reactive with these citrullinated epitopes may be arthritogenic themselves, or induce more severe arthritis when injected with subclinical doses of anti-CII [74]. Antibodies to major CII epitopes could be useful as markers for the biomonitoring of joint destruction in some patients.

3. Role of cytokines in RA

The network of cytokine in the RA disease is very complex system, with a numerous of cytokines showing pleiotropic actions and many different targets. This network can be divided in two groups, the pro-inflammatory and anti-inflammatory cytokines. Controlling the balance

between these two groups is considered as an important therapeutic goal. This chapter provide an important role of TNF-α in the pathogenesis of RA, leading to the first clinical trials of a biological therapeutic in this disease. Other than TNF-α we address other cytokines such as IL-1, IL-6 and IL-23 that might play a role in the disease, together with selected cytokines that bind a receptor containing the common γ-chain (γc) [75].

3.1. TNF-α

TNF-α is a proinflammaotory cytokine and played a key role in RA with its potential to degrade cartilage [76] and bone [77] *in vitro*. It has been shown in an experiment that dissociated RA synovial mononuclear cell cultures that TNF-α as well as other proinflammatory cytokines (IL-1, IL-6, GM-CSF, and IL-8) [78–81] were produced in a five-day culture [82, 83]. When the activity of TNF-α was blocked in these cultures, the spontaneous production of both IL-1 protein and IL1B mRNA was remarkably decreased and IL-1 bioactivity was neutralized [82]. This is the evidence that the secretion of all these cytokines is a network and controlled by hierarchy of their expressions.

Soluble TNF receptors are found in high concentrations in the synovial fluid and serum of patient with RA [84]. RA patients are found to have high levels of TNF-α in the synovial fluid. This plays an important role in inflammation and joint destruction, both of which are hallmarks of RA. Anti-TNF-α therapy induces a shift in the cytokine equilibrium producing more anti-inflammatory cytokines. Studies have demonstrated dramatic improvement in synovial inflammation in RA patients after treatment with neutralizing anti-TNF-α Abs or soluble TNF receptors. They also suggest decreased joint destruction after treatment with IL-1Ra [85].

In a first clinical trial of a TNF-α blocking agent for the treatment of 20 active RA patients were initiated. Infliximab (Remicade), a chimeric antibody specific for human TNF-α was used. Signs and symptoms of the RA disease were substantially reduced with the treatment with infliximab together with decreased levels of CRP in the serum [86]. Other multicentric placebo-controlled trials were also confirmed the therapeutic efficacy of infliximab when coadministrated with methotrexate. This led eventually to FDA approval of the drug for the treatment of RA [87, 88]. After two-year of clinical trial, it was observed that there was a retardation or arrest of both joint space narrowing and bone erosion due to infliximab and methotrexate therapy [89]. There were two other drugs etanercept (Enbrel) and adalimumab (Humira) which are functioned as TNF-α blockers were used in the treatment of RA.

TNF-α is now considered as controlling a wide variety of effector functions relevant to the pathogenesis of RA, including endothelial cell activation and chemokines production which causes accumulation of leukocytes [90]; osteoclast and chondrocyte activation, promoting articular destruction. These all are RA disease pathogenesis spectrum which explains the broad role of TNF-α blockade in patients. Further, improved therapies targeting TNF-α would be a potential therapeutics for the treatment of RA.

3.2. Interleukin-1

Each member of the IL-1 family binds with high affinity to specific receptors. Binding of IL-1α or IL-1β to type I IL-1 receptors (IL-1RI), can is enhanced by an accessory protein, IL-1R-AcP,

leads to intracellular signal transduction and regulation of gene expression and hence cellular responses [91]. The extent of response of IL-1β in the rheumatoid joint depends on a few factors such as (1) IL-1β and IL-1Rα have similar affinity for IL-1RI on synoviocytes, chondrocytes and other cells and hence, the relative concentrations of IL-1β and IL-1Rα are important in determining the level of cell activation and biological responses, (2) a greater number of IL-1RII reduces the amount of IL-1β and IL-1Rα, that is available for binding to IL-1RI. Similarly, soluble IL-1 receptors found in synovial fluid and in the circulation also decrease the amount of these cytokines available to interact with IL-1RI. The response of IL-1β, as well as to other proinflammatory cytokines, is regulated by various anti-inflammatory and immunomodulatory cytokines, including IL-4, IL-10, IL-11, IL-13 and transforming growth factor-β [91, 92].

IL1 causes inflammatory cells to move into the joints and the synovium in RA patients. An unspecified antigenic trigger is thought to activate the production of IL1 in joints by macrophages (lymphocytes, monocytes and transformed fibroblasts) [54, 93]. These cells secrete proteases and proteoglycans as cellular signals, that may result in pannus formation, which accumulates in the joints. Destructive enzymes can enter and destroy cartilage and ultimately degrade and erode bone. Importantly, specifically blocking IL1 is a targeted, rational treatment against the destructive functions of IL1 in RA [54, 94].

Evidence from experimental studies in animal models of arthritis and from an x randomized controlled trials in patients with RA indicates that IL-1 plays an important role in RA pathogenesis, and that IL-1 inhibition with anakinra is effective in slowing further radiographic progression of the disease and hence models significantly reduces bone erosions and cartilage degradation [14]. It is important to elucidate that, whether slowing radiographic progression with these biological therapies will significantly improve long-term outcomes in RA.

3.3. Interleukin-6

IL-6 is an essential and multifunctional proinflammatory cytokine of the immune system and could be a key mediator for the development of many chronic inflammatory or autoimmune diseases including RA [95, 96].

It is well established that increased levels of autoantibodies are the characteristics of autoimmune RA and hence decreased levels of antibody producing B cells are might have a therapeutic efficacy demonstrates the impact of B-cell activity on synovial inflammation and joint damage. IL-6 stimulates B cells to differentiate into plasma cells to produce immunoglobulins [97]. IL-6 induces B-cell differentiation [98] and it has been established that B-cells induced antibody production [99].

Neutrophils can be directly activated by IL-6 through membrane-bound receptor IL-6R, which in turn help inflammation and joint destruction through the secretion of proteolytic enzymes and reactive oxygen intermediates [100]. An *in vitro* study with fibroblasts from patients with RA showed the role of IL-6 in actively encourage the recruitment of neutrophil by activated fibroblasts. Although untreated fibroblasts were able to recruit neutrophils, it was found that the recruitment was inhibited in the presence of anti-IL-6 antibody [101].

Osteoclasts are multinucleated cells formed by the fusion of mononuclear progenitors of the monocyte and macrophage family. These cells populate the synovial membranes of RA patients and are concentrated in bones [102, 103]. Macrophage derived osteoclastogenesis requires the presence of macrophage colony-stimulating factor. It results from the interaction of the RANK and the RANK ligand (RANKL) [102]. RANKL expression is regulated by pro-inflammatory cytokines such as TNF-α, IL-1, IL-6 and IL-17 [103].

The principal cause of bone erosion is the pannus, which is found at the interface with cartilage and bone. Angiogenesis is an important process in the formation and maintenance of pannus [104]. Vascular endothelial growth factor (VEGF), is an important angiogenic mediator which promotes the migration and proliferation of endothelial cells, as well as inducing vascular permeability and mediating inflammation [105]. Increased levels of VEGF correlate with disease activity in RA patients [106]. IL-6 in the presence of sIL-6R increased VEGF levels in cultured synovial fibroblasts from RA patients and anti-IL-6R antibody significantly reduced VEGF concentration [107].

Blocking antibodies were used with other agents as a combinational therapeutics for the treatment of RA. A humanized anti-IL-6R monoclonal antibody, tocilizumab (TCZ), used in a first clinical trial was conducted in patients with established RA [108]. A total of 45 patients were randomized to receive a single intravenous infusion of TCZ of 0.1, 1, 5, 10 mg/kg or placebo. Patients in the 5 and 10 mg/kg arms showed rapidly improvement in disease activity. CRP normalized after treatment in the 5 and 10 mg/kg treated patients confirming IL-6 as the dominant cytokine in generating the acute-phase response in patients with RA. Another, double-blind, placebo-controlled trial in 164 RA patients was conducted and demonstrates that the clinical response was maintained with repeated dosing of TCZ monotherapy [109]. A European study CHARISMA, examined the combinational effect of TCZ with methotrexate (MTX). In the study of 359 RA patients with partial response to MTX, it was found that TCZ was efficacious as monotherapy or in combination with MTX although the latter appeared to enhance the benefit of TCZ [110]. There were many other clinical trials and studies that ensures the use of TCZ alone or in combinational therapies such as MTX results in sustained improvement in physical function and reduced radiographic joint damage in RA [111–117].

4. Conclusion

RA is a complex disease that develops through a series of events often referred to as disease continuum. It is an autoimmune and inflammatory disease that can be further aggravated with the increased production and secretion of autoantibodies (RF ACPA, anti-cartilage type II antibodies) and the secretion of proinflammatory cytokines (TNF, IL-1, IL-6). With a better knowledge and understanding of the crosstalk between the molecules involved in RA disease pathogenesis, it would be easier to identify better markers for RA disease as well as design and administer specific and efficient therapeutics that can control RA pathogenesis and deliver long term and permanent remission of the disease.

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