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Review Article

Molecular Medicine of Rheumatoid Arthritis: From Molecular Pathphysiology to Novel Therapeutics and Evidence-Based Practice

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Abstract

Rheumatoid arthritis (RA) is an inflammatory autoimmune disorder that affects joints as well as other organs and systems. It is one of the most common types of arthritis and associated with progressive disability, systematic complications, premature death, and socioeconomic costs. Although the past several decades have witnessed remarkable improvement in the management of this disease, RA remains incurable and continues to be a significant health problem. This article provides a concise review of the recent advances in the molecular pathophysiology of RA and the development of mechanistically-based novel molecular therapeutics. Special considerations are given to the causal involvement of novel molecular pathways, including cytokines, growth factors, and intracellular signaling cascades in RA pathophysiology, and the emerging role of targeted therapeutic agents in the management of RA. The article also considers the impact of genetic variations on RA therapeutics in the context of molecular medicine and individualized patient care.

ABBREVIATIONS

ACPA: Anti-Citrullinated Protein Antibody; ACR: American College of Rheumatology; APRIL: A Proliferation-Inducing Ligand; BAFFR: B Cell Activating Factor Receptor; BLyS: B-lymphocyte Stimulator; BTK: Bruton's Tyrosine Kinase; CRP: C-Reactive Protein; DMARDs: Disease-Modifying Antirheumatic Drugs; ESR: Erythrocyte Sedimentation Rate; EULAR: European League Against Rheumatism; FDA: Food and Drug Administration; GM-CSF: Granulocyte-Macrophage Colony Stimulating Factor; GWAS: Genome-Wide Association Study; HAQ-DI: Health Assessment Questionnaire-Disability Index; HLA: Human Leukocyte Antigen; HRQOL: Health-Related Quality Of Life; JNK: Janus Kinase; M-CSF: Macrophage Colony Stimulating Factor; MYX: Methotrexate; PI3K: Phosphatidylinositol 3-Kinase; RA: Rheumatoid arthritis; RANKL: Receptor Activator of NF-κB Ligand; RF: Rheumatoid Factor; ROS/RNS: Reactive Oxygen and Nitrogen Species; Syk: Spleen Tyrosine Kinase; TACI: Transmembrane Activator and Calcium-Modulator and Cyclophilin Ligand Interactor; TNF: Tumor Necrosis Factor

DEFINITION AND CLASSIFICATION

Arthritis is a complex family of musculoskeletal disorders with many causes, not yet fully understood, and so far there are no cures. This umbrella term consists of more than 100 different diseases or conditions that destroy joints, bones, muscles, cartilage and other connective tissues, hampering or halting physical movement. It is estimated that in the United States arthritis strikes over 50 million adults (1 in 5) and 300,000 children and is the nation's leading cause of disability, resulting in annual costs estimated at $128 billion in 2003 (the most recent estimate) (http://www.cdc.gov/arthritis/media/quickstats.htm; accessed on December 7, 2013).

Common forms of arthritis include osteoarthritis,

rheumatoid arthritis (RA), juvenile arthritis, gout, systemic lupus erythematosus, and fibromyalgia. Among these common types of arthritis, RA has probably received the greatest attention due to the progressive nature of its pathogenesis and its tremendous impact on public health and socioeconomics.

RA affects 0.5-1% of the world population. In the United States, an estimated 1.5 million people have RA. There are 2.5 times as many women as men with the disease, suggesting the possible involvement of sex hormones in disease genesis. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) define RA as a chronic inflammatory disease characterized by joint swelling, joint tenderness, and destruction of synovial joints, leading to severe disability and premature mortality [1]. Given the presence of auto antibodies, such as rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) (tested as anti-cyclic citrullinated peptide), which can precede the clinical manifestations of RA by many years; RA is considered an autoimmune disease. As described below, the autoimmunity and the overall systemic and particular inflammatory load drive the destructive progression of the disease and accompanied complications. Because of the progressive nature of the disease, early recognition of the disease is crucial for effective management of RA and reduces the accrual of joint damage and disability. In this context, recently, ACR and EULAR jointly released RA classification criteria that allow recognition of the disease at its early stage [1].

Based on the ACR/EULAR classification criteria for RA, a score of >6 is needed for classification of a patient as having definite RA (Table 1). The working group of the ACR/EULAR has deliberately labeled these criteria as "classification criteria" as opposed to "diagnostic criteria". The aim is to provide a standardized approach for discriminating, from a population of individuals presenting with undifferentiated synovitis, the subgroup with the highest probability of persistent or erosive RA, who may be enrolled into clinical trials and other studies through the use of uniform criteria. These individuals are also the ones who may therefore benefit from intervention with disease-modifying anti rheumatic drugs.

MOLECULAR PATHOPHYSIOLOGY

Overview of the pathogenesis of RA

RA is characterized by synovial inflammation and hyperplasia ("swelling"), autoantibody production (RF and ACPA), cartilage and bone destruction ("deformity"), and systemic features, including cardiovascular, pulmonary, psychological, and skeletal disorders [2]. These clinical features pose critical mechanistic questions, especially how interactions between genes and environment initiate and perpetuate both localized inflammatory injury in the joints, leading to joint deformity, and systemic inflammation and autoimmunity, resulting in an increased risk of extra-articular disorders, including cardiovascular diseases [3,4] and depression [5], among many others. Environmental factors, including smoking and pathogens have long been implicated as risk factors of RA [6,7]. Recently, emerging data also implicate the microbiome in RA pathogenesis [8]. Mucosal sites exposed to a high load of bacterial antigens, such as the periodontium, lung, and gut, may represent the initial site of autoimmune generation, leading to the development RA [8], as well as other human diseases [9].

A number of genetic loci have been implicated in the genesis and development of RA. The most notable one is human leukocyte antigen (HLA)-DRB1, which encodes the shared epitome (SE) motif that acts as a signal transduction ligand facilitating inflammatory arthritis [10]. The heritability of RA has been estimated to be about 60%, while the contribution of HLA to heritability has been estimated to be 11-37%. Apart from the well-known SE alleles, such as HLA-DRB1*01 and DRB1*04, other HLA alleles, including HLA-DRB1*13 and DRB1*15 have also been linked to RA susceptibility [11]. Large genome-wide association studies (GWAS) have identified more than 30 loci associated with RA pathogenesis, and many of them are related to cytokines, growth factors, and intracellular signaling cascades [2,11-13].

Although the exact mechanisms triggering autoimmunity in RA remain unclear, substantial evidence points to a crucial role for multiple inflammatory cascades as well as oxidative stress in the pathogenesis of RA and the clinical progression of the disease (Figure 1). The section below highlights our current understanding of the molecular pathophysiology of RA, which serves as a basis for developing novel therapeutic agents for this inflammatory arthritis.

Molecular pathophysiology of RA

McInnes and Schett classified key molecules and signal mediators implicated in the pathogenesis of RA into three categories [2]. They are: (1) cytokines, such as tumor necrosis factor (TNF), interleukin (IL)-1, IL-6, IL-7, IL-15, and IL-17A and F; (2) growth and differentiation factors, including B-lymphocyte stimulator (BLyS), a proliferation-inducing legend (APRIL),

Table 1: The 2010 ACR/EULAR classification criteria for rheumatoid arthritis [1]. According to the ACR/EULAR score-based algorithm, the total score from the four categories (i.e., joint involvement, seriology, acute phase reactants, and duration of symptoms) needs to be ≥6 in order for a patient to be classified as having definite RA. The maximum possible total score from the four categories is 10 (5+3+1+1). Hence, the patient's score of ≥6 is expressed as ≥6/10. CRP denotes C-reactive protein; ESR stands for erythrocyte sedimentation rate.

Classification Category	Classification Criteria	Score
Joint Involvement	One large joint (shoulder, elbow, hip, knee, or ankle)	0
	2-10 large joints	1
	1-3 small joints (metacarpophalangeal joints, proximal interphalangeal joints, second to fifth metatarsophalangeal joints, thumb interphalangeal joints, or wrists)	2
	4-10 small joints	3
	>10 joints (at least 1 small joint)	5
Seriology	Negative RF and negative ACPA	0
	Low-positive RF or low-positive ACPA	2
	High-positive RF or high positive ACPA	3
Acute Phase Reactants	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
Duration of Symptoms	<6 weeks	0
	≥6 weeks	1

granulocyte-macrophage colony stimulating factor (GM-CSF), macrophage colony-stimulating factor (M-CSF), and receptor activator of NF-κB ligand (RANKL); and (3) intracellular signaling molecules and transcription factors, such as Janus kinase (JNK), spleen tyrosine kinase (Syk), phosphatidylinositol 3-kinase (PI3K), Bruton's tyrosine kinase (BTK), and NF-κB. As discussed next, these molecules and signaling mediators are key players of the inflammatory pathophysiology of RA, and as such, they provide rational molecular targets for novel therapeutic modalities. Since inflammation and oxidative stress are two intimately intertwined processes, targeting the oxidative stress component with antoxidative agents might also represent an effective strategy for treating RA (Figure 2).

EVIDENCE-BASED GUIDELINES AND NOVEL THERAPEUTICS

Recent advancement in the knowledge of the molecular pathophysiology of RA has greatly facilitated the development of new therapeutic agents for effective treatment of this inflammatory disorder. The availability of new, effective drugs has revolutionized the management of RA and significantly impacted the development of evidence-based guidelines on the treatment of RA. This section first introduces the current treatment guidelines from ACR and EULAR, and then focuses on discussing the new and emerging novel therapeutic agents that target the specific molecular pathophysiological components of RA. The section also considers the current status with regard to RA pharmacogenomics and individualized medication.

CURRENT TREATMENT GUIDELINES

Overall strategies of treatment

The management of RA includes two overall strategies: (1) drug treatment which comprises disease-modifying anti rheumatic drugs (DMARDs) as well as non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids; and (2) non-pharmacological measures, such as physical, occupational, and psychological therapeutic approaches. Effective treatment of RA rests primarily on the early use of DMARDs. These agents are commonly characterized by their capacity to reduce or reverse signs and symptoms, disability, impairment of quality of life, inability to work, and progression of joint damage, and thus to interfere with the entire disease process [14]. Currently available DMARDs include two major classes: synthetic chemical compounds (sDMARDs) and biological agents (bDMARDs). As many newer members of DMARS have recently become available, it is imperative to have a unified scheme to classify this ever-growing family of RA therapeutic agents.

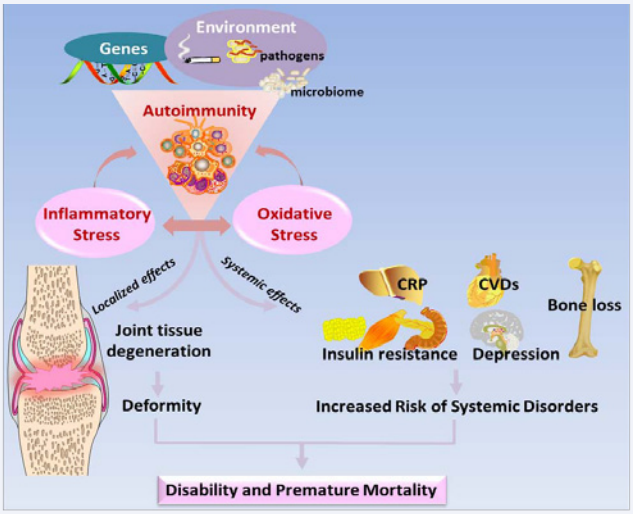

Figure 1 Schematic illustration of key factors involved in the pathogenesis of RA and its systemic complications. See text for detailed description. CVDs denote cardiovascular diseases.

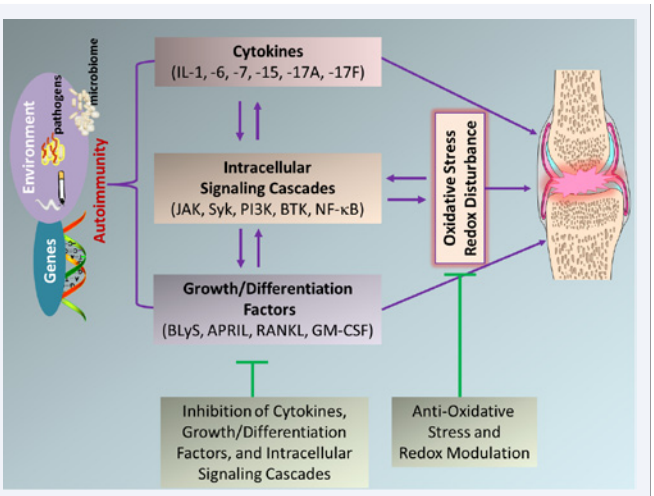

Figure 2 Schematic illustration of the molecular pathophysiology of RA. As depicted, the gene-environment interactions are believed to provoke autoimmunity leading to deregulation of a network of inflammatory pathways consisting of cytokines, growth factors, and intracellular signaling cascades. The involvement of oxidative stress in the pathophysiology is two-fold. On the one hand, inflammatory cells release reactive oxygen/nitrogen species (ROS/RNS), inducing oxidative stress and redox disturbance. On the other hand, oxidative stress and altered cellular redox status cause activation of pro-inflammatory genes via stimulating redox-sensitive transcription factors, such as NF-κB (not shown), thereby amplifying and perpetuating the inflammatory responses. These molecular pathophysiological pathways provide novel targets for RA therapeutics.

New nomenclature for DMARDs

Recently, Smolen et al proposed a new nomenclature for DMARDs [15], which has been utilized for classifying the various DMARDs by EULAR in its current guidelines on the management of RA [14]. According to this new nomenclature, the term conventional sDMARDs (csDMARDs) is used to include chemical agents such as methotrexate, sulfasalazine and leflunomide, whereas tofacitinib, a new sDMARD specifically designed to target Janus kinase (JAK), is designated as a targeted sDMARD (tsDMARD). The five available TNF inhibitors (i.e., adalimumab, certolizumabpegol, etanercept, golimumab, and infliximab), the T cell costimulation inhibitor, abatacept, the anti-B cell agent, rituximab, and the interleukin (IL)-6 receptor-blocking monoclonal antibody, tocilizumab, as well as the IL-1 inhibitor,

anakinra, are designated as biological originator (bo) DMARDs, while biosimilars (bs), such as bs-infliximab, recently approved by the European Medicines Agency (EMA), are classified as sDMARDs (Figure 3) [14].

The U.S. Food and Drug Administration (FDA) defines a biosimilar as a biological product that is highly similar to an already approved biological product, not withstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biosimilar and the approved biological product in terms of the safety, purity, and potency. Biological (also frequently written as biologic) products represent a wide variety of products, including vaccines, blood and blood components, gene therapies, tissues, and proteins. Unlike most prescription drugs made through chemical processes, biological products generally are made from human and/or animal materials.

The ACR current guidelines on the use of DMARDs in the treatment of RA

The ACR most recently published recommendations for the use of DMARDs (both synthetic and biologic DMARDs) in the treatment of RA in 2008 [16]. These recommendations covered indications for use, monitoring of side effects, assessment of the clinical response to DMARDs, screening for tuberculosis (due to increased risk of activation of latent tuberculosis by the use of biologic DMARDs, which cause immunosuppression), and assessment of the roles of cost and patient preference in decision making for biologic DMARDs[16]. In recognition of the rapidly evolving knowledge in RA pathophysiology and management, and the accumulation of new evidence regarding the safety and efficacy of existing and newer therapies, the ACR commissioned an update of the 2008 recommendations in select topic areas and released the update in 2012 [17].

The 2012 revision updated the 2008 ACR recommendations in the following five areas: (1) indications for DMARDs; (2) switching between conventional synthetic DMARD and biologic DMARD therapies; (3) use of biologic DMARDs in high-risk patients (those with hepatitis, congestive heart failure, and malignancy); (4) screening for tuberculosis in patients starting or currently receiving biologic DMARDs; and (5) vaccination in patients starting or currently receiving synthetic DMARDs or biologic DMARDs. The reader is advised to refer to the full ACR guidelines for detailed recommendations on treating RA with DMARDs [16,17].

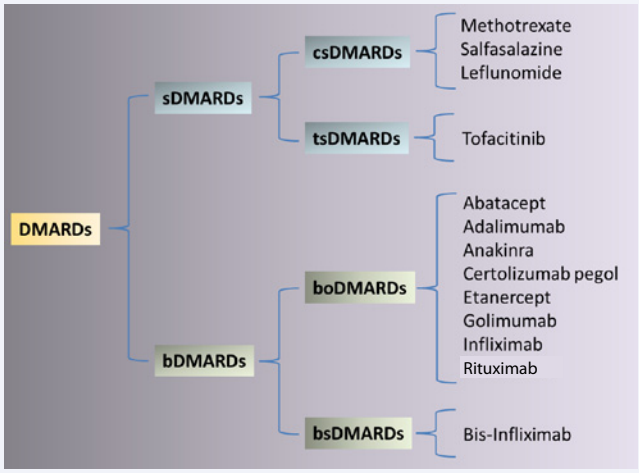

Figure 3 New nomenclature of DMARDs. See text for detailed description of this newly proposed scheme for classification of DMARDs. Tofacitinib is the only U.S. FDA-approved tsDMARD. The bdDMARDbs-in fliximab is currently not a U.S. FDA-approved biosimilar for treating RA.

The EULAR current guidelines on the use of DMARDs in the treatment of RA

The EULAR published its most recent recommendations for the management of RA with synthetic and biologic DMARDs in 2010 [18]. The 2010 recommendations were based on five systematic literature reviews and focused on indications for the use of, and suggestions for, differential and strategic employment of csDMARDs and bDMARDs based on treatment targets, disease risk assessment, safety aspects, and contraindications. While some of the individual recommendations have elicited extensive discussions, all of them were based on the evidence available at that point in time. The EULAR 2010 recommendations have been used and adopted widely, as suggested by their application as a template for many national and regional recommendations after their publication [18]. However, as with most recommendations and especially in a rapidly evolving field such as RA, it was anticipated that the 2010 recommendations would need updating within a few years. Indeed, more experience and additional evidence on agents approved at that time, as well as data on new therapeutic agents, have become available over the past 3 years. This has motivated the EULAR to update the 2010 recommendations, and publish the 2013 update [14].

The EULAR 2013 update provides 14 recommendations on the use of DMARDs in treating RA, including that: (1) therapy with DMARDs should be started as soon as the diagnosis of RA is made; (2) treatment should be aimed at reaching a target of remission or low disease activity in every patient; (3) monitoring should be frequent in active disease (every 1-3 months); if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted; (4) methotrexate should be part of the first treatment strategy in patients with active RA; (5) in cases of methotrexate contraindications (or early intolerance), sulfasalazine or leflunomide should be considered as part of the (first) treatment strategy; (6) in DMARD-naïve patients, irrespective of the addition of glucocorticoids, csDMARD monotherapy or combination therapy of csDMARDs should be used; (7) low-dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more csDMARDs) for up to 6 months, but should be tapered as rapidly as clinically feasible; (8) if the treatment target is not achieved with the first DMARD strategy, in the absence of poor prognostic factors, change to another csDMARD strategy should be considered; when poor prognostic factors are present, addition of a bDMARD should be considered; (9) in patients responding insufficiently to methotrexate and/or other csDMARD strategies, with or without glucocorticoids, bDMARDs (TNF inhibitors, abatacept or tocilizumab, and, under certain circumstances,

rituximab) should be commenced with methotrexate; (10) if a first bDMARD has failed, patients should be treated with another bDMARD; if a first TNF inhibitor therapy has failed, patients may receive another TNF inhibitor or a biological agent with another mode of action; (11) tofacitinib may be considered after biological treatment has failed; (12) if a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs, especially if this treatment is combined with a csDMARD; (13) in cases of sustained long-term remission, cautious reduction of the csDMARD dose could be considered, as a shared decision between patient and physician; and (14) when therapy needs to be adjusted, factors apart from disease activity, such as progression of structural damage, comorbidities and safety issues, should be taken into account [14].

As noted, the EULAR 2013 update has included the recently approved JAK inhibitor, tofacitinib in its Recommendation 11 for treating RA patients who have failed biologic DMARD therapy. It is anticipated that the ever-growing list of newer effective DMARDs will continue impacting the development of science- and evidence-based treatment guidelines for RA.

NEW AND EMERGING NOVEL THERAPEUTIC MODALITIES

Cytokines and molecular targeting of therapeutics

As noted earlier, several biologic agents targeting inflammatory cytokines (e.g., TNF, IL-1 and IL-6) have been approved for treating RA. These include five available TNF inhibitors (i.e., adalimumab, certolizumabpegol, etanercept, golimumab, and infliximab), the IL-6 receptor-blocking monoclonal antibody, tocilizumab, and the IL-1 inhibitor, anakinra. These cytokine-targeting biologic DMARDs have become an important component of RA therapeutics recommended in guidelines from both ACR and EULAR.

Novel inhibitors for other cytokines including IL-7, IL-15, IL-17A, and IL-17F are currently under active investigation in both preclinical and clinical studies. IL-7 and IL-15 play important roles in promoting and maintaining T cell activation and memory, as well as T cell-antigen presenting cell interactions, and T cell response to self-antigen [19,20]. IL-17A and IL-17F, on the other hand, act synergistically to enhance activation of synovial fibroblasts, chondrocytes, and osteoclasts, contributing to particular degeneration in RA [21]. While several clinical trials demonstrated the safety of these newer cytokine inhibitors, their clinical efficacy remains to be established by large-scale randomized trials [22-24].

Lymphocyte anergy/death and molecular targeting of therapeutics

Currently, there are two approved biological DMARDs that target T cells and B cells, respectively, leading to energy and/or apoptosis. Abatacept is a T cell costimulation inhibitor. It complexes with costimulatory B7 molecules (CD80/CD86) on antigen presenting cells, and prevents the delivery of a co stimulatory signal to T cells, leading to T cell energy and apoptosis. Rituximab, on the other hand, is an anti-B cell agent. It is a chimerical marine-human monoclonal antibody that binds to CD20 on B cells, resulting in B cell killing via mechanisms including receptor signaling cascade-induced apoptosis, antibody-dependent cell-medicated cytotoxicity, and activation of complements [25].

Recently, several additional anti-B cell CD20 antibody therapies have been developed for treating RA. In this regard, of atumumab and ocrelizumab are monoclonal antibodies, humanized to reduce immunogenicity, which target extracellular domains of the B cell CD20 antigen. They have enhanced complement- and antibody-dependent cell-mediated cytotoxicity compared to rituximab. Multiple randomized trials demonstrated an efficacy for these newer anti-CD20 agents in various RA populations [26-30]. Ofatumumab and ocrelizumab are currently not approved by the U.S. FDA for clinical use.

GROWTH AND DIFFERENTIATION FACTORS AND MOLECULAR TARGETING OF THERAPEUTICS

BLyS and APRIL

Both BLyS and APRIL are B cell stimulating factors that play an important role in B cell activation, maturation, and production of autoantibodies (Figure 4). As shown in Figure 4, several investigational biologic therapeutic agents, including atacicept, belimumab, and tabalumab have been developed to bind to BLyS or APRIL to block their stimulating effects on B cells. Belimumab

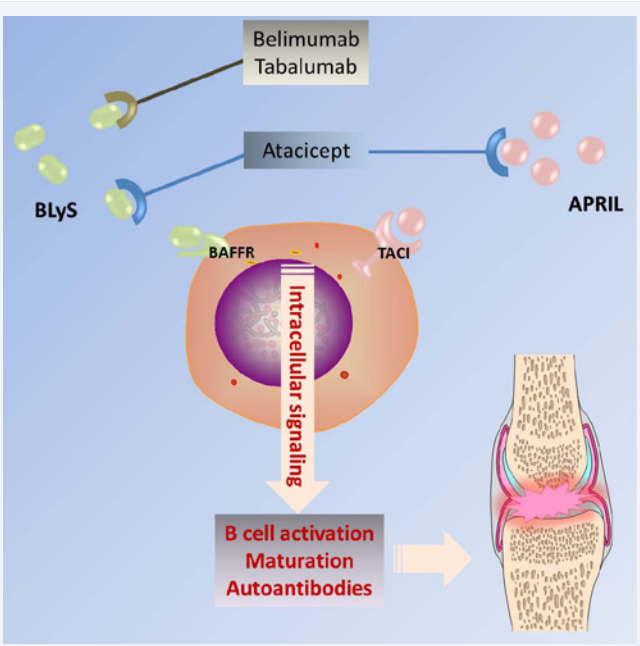

Figure 4 Growth factors BLyS and APRIL as novel molecular targets of emerging new therapeutic agents for RA. As depicted in the scheme, binding of BLyS and APRIL to their corresponding receptors leads to activation and maturation of B cells and the production of auto antibodies, a key molecular pathophysiological process in RA. Via selectively binding to and trapping these growth factors, atacicept, belimumab, and tabalumab reduce B cell activation, maturation, and production of auto antibodies, thereby attenuating the inflammatory pathogenesis and disease progression. BAFFR denotes B cell activating factor receptor. TACI stands for trans membrane activator and calcium-modulator and cyclophilin legend interaction. Please note that this is a simplified scheme, and that BLyS and APRIL also interact with other receptors.

and tabalumab bind to BLyS, whereas atacicept binds to both BLyS and APRIL. A phase II, randomized, placebo-controlled trial involving 311 RA patients reported that treatment with atacicept failed to improve the primary end point (ACR20-CRP response) despite significant biological effects (decreases in serum levels of immunoglobulins, mature B cells, plasma cells, and rheumatoid factor) of atacicept that were consistent with its proposed mechanism of action. Modest effects of atacicept were seen for some secondary efficacy end points. Treatment with atacicept raised no new safety concerns [31]. Another trial reported similar findings [32]. Together, these studies demonstrated the lack of efficacy for atacicept in treating RA. The robust biological effects of atacicept might benefit patients with other autoimmune diseases that involve B cells and auto antibodies. In contrast to the findings with atacicept, multiple recent trials reported clinical efficacy for tabalumab and belimumab in various populations of RA patients [33-36]. These two drugs are currently not approved by the U.S. FDA for treating RA.

RANKL

RANKL promotes maturation and activation of osteoclasts and has been implicated in the bone erosion in RA [37-39]. Denosumab is an investigational human monoclonal antibody to human RANKL, preventing activation of osteoclasts. Its treatment results in a reduction in bone restoration and an increase in bone mineral density. In clinical studies, denosumab has been shown to decrease the risk for vertebral, hip and no vertebral fractures in women with postmenopausal osteoporosis and the risk for new vertebral fractures in men with no metastatic prostate cancer receiving androgen deprivation therapy, with a rate of side effects similar to placebo [40]. A number of clinical trials with denosumab are ongoing to determine its value for other indications including RA [41-43]. Denosumab was approved by the U.S. FDA in 2010 for use in postmenopausal women with risk of osteoporosis and for the prevention of skeleton-related events in patients with bone metastases from solid tumors. It is the first RANKL inhibitor to be approved by the FDA. In June 2013, denosumab was approved by the FDA for treating giant cell tumor of bone. Denosumab is currently not approved by the U.S. FDA for treating RA.

INTRACELLULAR SIGNALING MOLECULES AND MOLECULAR TARGETING OF THERAPEUTICS

JAK

Cytokines bind to their receptors on the cell surface and subsequently activate intracellular signaling cascades, such as the JAK/STAT pathway, resulting in inflammatory responses. Deregulation of the JAK/STAT signaling cascade causes autoimmunity as well as uncontrolled cell growth. Several pharmaceutical companies have recently developed therapeutic agents to inhibit JAK for treating autoimmune disorders and malignancies. In this context, the FDA recently approved two JAK inhibitors, tofacitinib and ruxolitinib for treating RA and intermediate or high-risk myelofibrosis, respectively. Tofacitinib is the first oral JAK inhibitor indicated for the treatment of moderately to severely active RA patients who have not responded adequately to, or are intolerant of, methotrexate. In randomized trials [44-47], tofacitinib demonstrated efficacy and safety comparable to other DMARDs. Tofacitinib was efficacious in RA patients, indicated by achievements of ACR20, ACR50, and ACR70 criteria. Similar improvements were observed in patients who met remission criteria based on the Disease Activity Scores 28 criteria and quality of life as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI) [48]. In addition to tofacitinib, several other JAK inhibitors are currently under development, which include baricitinib, VX509, and GLPG0634 [49].

Syk

Syk is a tyrosine kinase that regulates immune complex-mediated and antigen-mediated activation of B and T cells as well as other Fc receptor-bearing leukocytes. The role of Syk in the initiation or pathogenesis of rheumatoid arthritis is not well understood. However, Syk is present in the fibroblast-like synoviocytes of patients with RA, and phosphor - Syk (a potential indicator of active Syk) is seen in significantly greater amounts in the synovial tissues of patients with RA than in those of patients with osteoarthritis [50]. The possible importance of Syk in RA may be linked to its role as a signaling component of Fc receptors, which bind to immunoglobulin's, including auto antibodies [50].

Two initial randomized trials reported by Weinblatt and associates suggested that R788, an orally administered inhibitor of Syk, was effective in patients who have active RA despite treatment with methotrexate [51,52].More recently, Weinblatt and coworkers further reported that treatment with R788 (now known as fostamatinib) at 100 mg bid also showed significant improvement in health-related quality of life (HRQOL) outcomes in patients with active RA taking background methotrexate [53]. While R788 is efficacious in RA patients taking background methotrexate, a recent phase II study in patients with active RA that did not respond to biologic DMARDs, found no differences in the primary end point between the R788 and placebo groups. Differences were, however, observed between the R788 and placebo groups in secondary end points, particularly in those patients who entered the study with an elevated CRP level [54]. The efficacy of R788 compared with existing biological DMARDs, especially the JAK inhibitor tofacitinib in treating active RA warrants further investigation in randomized trials. Furthermore, as tyrosine kinase cascades are subject to redo modulation, the effects of antioxidants, including those present in normal diet, on the efficacy of the targeted therapeutic agents of RA may also deserve studies. Indeed, as discussed next, targeting oxidative stress and redox modulation by anti oxidative agents may be a promising adjuvant strategy for treating RA.

Oxidative stress and molecular targeting of novel therapeutics

Due to the excessive inflammatory responses in the joint, augmented release of reactive oxygen and nitrogen species (ROS/RNS) from the activated inflammatory cells and the consequent oxidative damage to synovial cells and cartilages are important pathophysiological features of RA [55-57]. Elevated production of ROS/RNS also causes activation of NF-κB, resulting in perpetuation of inflammation in the joint. There is also experimental evidence suggesting a critical role for oxidative stress in bone remodeling in RA [58]. In line with a critical

involvement of oxidative stress in RA, systemic administration or gene delivery of antioxidant enzymes, such as superoxide dismutase protects against experimental RA in animal models [59-61]. In contrast, deficiency of Nrf2, a transcription factor regulating antioxidant gene expression, aggravates inflammatory arthritis and joint degeneration [62]. Similar to antioxidant enzymes, treatment with a variety of non-enzymatic antioxidant compounds, including dietary polyphenols, α-lipoic acid, antioxidant enzyme mimetics, and the antioxidant nanomaterial fullerene also results in attenuation of inflammatory responses and amelioration of joint destruction in animal models of RA.

In human subjects with RA, increased systemic oxidative stress and compromised antioxidant defenses have been reported in multiple studies [63-66]. A number of studies have also investigated the association between polymorphisms of antioxidant genes and altered risk of developing RA. For example, both the low-expressing genotype of paraoxonase-1 (PON1 55MM) and the null allele of glutathione S-transferees M1 are found to be associated with increased susceptibility to developing RA, especially in East Asian populations [67-69]. There have also been observational epidemiological studies suggesting a potential association between dietary intake of antioxidant compounds and decreased risk of developing RA. However, interventional trials on antioxidant supplements (e.g., quercetin plus vitamin C, α-lipoic acid, *N*-acetylcysteine, vitamin E) have mostly failed to show any benefits in the management of patients with RA [70,71].

There are several reasons for the failure of the above interventional studies, including poor design of the trials, non-optimal doses and duration of treatment of the antioxidant compounds, lack of understanding of the detailed pharmacokinetic and dose-response profiles of the antioxidant compounds, as well as the unknown oxidative stress and antioxidant status in the patient populations with RA included in the trials. In addition, the incomplete understanding of the oxidative stress mechanism of human RA and the lack of sensitive and selective biomarkers for assessing oxidative damage in RA have also hampered the development of effective antioxidant-based therapeutic modalities. Hence, future efforts should be directed to the continued elucidation of the role of oxidative stress in the pathophysiology of human RA and the development of reliable oxidative stress biomarkers to assess the disease progression in different populations of RA patients. It is possible that both dietary and genetic factors may affect the oxidative stress and antioxidant status of the RA patients and thereby influence their responses to antioxidant-based therapies. In line with this notion, as discussed next, genetic variations affects both the efficacy and adverse effects of RA therapeutic drugs, especially DMARDs.

PHARMACOGENETICS/PHARMACOGENOMICS AND INDIVIDUALIZED THERAPEUTICS

Overview of pharmacogenetics/pharmacogenomics

The pharmacological effects of drugs are influenced by many factors including the patient's genetic makeup. The terms pharmacogenetics and pharmacogenomics are often used interchangeably to describe a field of research focused on how genetic variations affect individual's responses to pharmacological agents. The convergence of recent advances in genomic science and equally striking advances in molecular pharmacology has resulted in the evolution of pharmacogenetics into pharmacogenomics. In this context, pharmacogenomics is generally considered a broader term referring to a large number of genes affecting drug responses, whereas pharmacogenetics refers to a more limited set of genes. However, the difference between the two is largely arbitrary. As stated above, they are often time used interchangeably. Here PGx is used to denote pharmacogenetics/pharmacogenomics. PGx provides unique methodologies that can lead to DNA-based tests to improve drug selection, identify optimal dosing, maximize drug efficacy, or minimize the risk of toxicity [72]. PGx provides an important path to personalized medicine or patient-centered medicine [73-75]. This is particularly true for RA, a disease showing considerable heterogeneity in all its aspects, especially responses to drug therapies.

PGx and individualized therapeutics of RA

As discussed above, the past decade has seen the rapid development of new therapeutic agents for treating RA as well as the evidence-based guidelines for effective management of this common inflammatory arthritis. However, it has become also evident that a significant subset of RA patients fails to achieve adequate therapeutic response and/or experience significant adverse response to both synthetic and biologic DMARDs. Genetic variations may lead to altered enzymatic pathways involved in the metabolism of DMARDs and/or changes in the molecular targets of the DMARDs, thereby resulting in altered response to drug therapy.

While PGx studies of RA therapies began decades ago, only the past several years have witnessed the major advances in this area, largely due to the availability of large-scale high-throughput methods, including genome-wide association study (GWAS). For example, UmićevićMirkov et al. recently conducted a multistage GWAS with a primary analysis of 2,557,253 single-nucleotide polymorphisms (SNPs) in 882 patients with RA receiving anti-TNF therapy [76]. The authors identified 8 genetic loci associated with response to anti-TNF treatment [76].

With regard to methotrexate (MTX) therapy, Bluett and associates tested the associations between 863 known PGx variants and MTX response in 471 Treatment of Early Aggressive Rheumatoid Arthritis Trial participants with early RA. The strongest genetic associations with efficacy were in CHST11, encoding carbohydrate (chondroitin 4) sulfotransferase 11. Top markers associated with MTX toxicity were in the cytochrome p450 genes CYP20A1 and CYP39A1, solute carrier genes SLC22A2 and SLC7A7, and the mitochondrial aldehyde dehydrogenates gene ALDH2. The selected markers explained a consistently higher proportion of variation in toxicity than efficacy [77].

The findings described above along with many others reported in the literature add to the knowledge base of PGx, which may eventually lead to the development of personalized therapeutic approaches to the effective management of RA. It is beyond the scope of this article to provide an in-depth coverage of this rapidly evolving area of RA therapeutics. The reader may refer to a recent excellent review on PGx of RA and its potential

impact on personalized medicine [78].

CONCLUSION AND PERSPECTIVES

Recent advances in our understanding of the molecular pathophysiology of RA have paralleled the introduction of new effective therapies and dramatic improvement in clinical outcomes, as well as the development of evidence-based recommendations for guiding patient care. As our knowledge in molecular medicine of RA increases, more effective therapies targeting critical molecular pathways will continue to emerge. On the other hand, studies of PGx of RA therapeutics in the post-genomic era will continue to uncover key genetic factors that dictate the individual's response to drug therapies. Such efforts may eventually lead to the development of evidence-based, personalized therapeutic modalities for effective management of RA. This along with available preventive strategies will ultimately transform the notion of RA as a chronic, debilitating disease.

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