

RHEUMATOID ARTHRITIS: A CHRONIC INFLAMMATORY DISEASE AND ITS PATHOPHYSIOLOGY

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ABSTRACT

Rheumatoid arthritis is a systemic inflammatory disorder which mainly affects the diarthrodial joint. It has societal effect in terms of cost, disability, and lost productivity. However the pathogenesis of disease is not well understood. Efforts are being made to understand the cellular and molecular mechanism for the pathogenesis of RA. It has been reported that proinflammatory cytokines such as TNF- α , IL-1 β , and IL-6 are important mediators of the disease perpetuation. Moreover, there are also reports that free radical generation worsens the disease and contribute towards damage to bone and cartilage. Immune cells such as T cells also impart their role in the progress of the disease. Apart from the conventional treatment strategies using NSAIDs, DMARDs and glucocorticoids newer and safer drugs are continuously being searched, as long term usage of these drugs have resulted in the hepatic and gastrointestinal disorders. Alternative medicine is another therapeutic approach for treatment of the disease, which include herbal and folklore medicines. Many plants and plant products are under scientific exploration to develop a novel therapeutic agent. Here we have tried to review traditional medicine for their potential to treat RA.

KEYWORDS: Arthritis, Cytokine, Treatment, Herb, Medicinal plant.

INTRODUCTION

Rheumatoid arthritis (RA) is one of the most serious medical problems affecting approximately 1% of the people worldwide, irrespective of race (1). RA is characterised by chronic polyarticular synovial inflammation and progressive erosion of cartilage and bone (2). It is the most common form of autoimmune and inflammatory arthritis, and has a substantial societal effect in terms of cost, disability, and lost productivity. The disease occurs at any age, but is most common among those aged between 40-70 years. Autoimmune diseases are common, with a prevalence of 10-15% in the general population. Autoimmunity is defined as a loss of tolerance to autoimmune antigens, which the immune system mistakes for foreign antigens. It is known that people who carry specific MHC haplotypes such as HLA-DR4 and DR1 show a higher risk for development of chronic RA than those who carry other molecules (3). Several studies have shown a higher disease prevalence among monozygotic twins (12-15%) than dizygotic twins (4%), implying the influence of genetic factors (4). Standardised mortality rate is higher than normal population and relates to disease activity. Approximately 7,00,000 cases are reported in India. Even children may be affected by this disease, and

then it is commonly called as Juvenile RA, which is defined as a chronic arthritis of unknown etiology appearing in children younger than 16 years of age. The healthcare cost of RA is high (5).

Epidemiology

Epidemiology of RA is still not understood completely. Studies of Chopra and workers (6) revealed the prevalence range from 0.28% to 0.7% for RA in a study population. Another research conducted in the village of Bhigwan (Pune district, Maha-rashtra) using population surveys developed by the World Health Organization-International League of Associations for Rheumatology (WHO-ILAR) Community Oriented Program for Control of Rheumatic Diseases (COPCORD). They reported a prevalence of 0.51% for RA diagnosed with ACR criteria and a prevalence of 0.6% for RA diagnosed clinically among 6000 men and women 16 years or older (6).

Pathophysiology

The cause of RA remains unknown, but several hypotheses, involving autoimmune mechanism, super antigen-driven disease (7), and infectious stimulus have been postulated. The etiology and pathogenesis of RA remain a mystery, despite efforts of a number of investigators over the past 40 years (8). Although the pathogenesis of RA remains poorly understood, much

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attention has been paid for cellular and molecular mechanisms of the disease. The pathology of RA extends throughout the synovial joint (9). Pathogenesis of RA involves infiltration and activation of various cell populations and release of many inflammatory and destructive mediators, including cytokines, prostaglandins, and metalloproteinase. It has been reported that the pathology of RA consists of (i) acute and chronic inflammation, (ii) cell proliferation, and (iii) tissue destruction/ fibrosis. Normal synovium is a delicate tissue lining the joint capsule but, in RA, the synovium transforms into an aggressive, tumor like structure called pannus, which invades and erodes the joint (10).

Histology

An inflamed synovium is central to the pathophysiology of rheumatoid arthritis, and it shows pronounced angiogenesis; cellular hyperplasia; an influx of cell-surface adhesion molecules, proteinase, proteinase inhibitors, and many cytokines (11). The major site of tissue damage originates at the junction of synovium lining the joint capsule with cartilage and bone, a region often termed the pannus. The cells of pannus migrate over cartilage and contribute the activity of matrix metalloproteinases (MMPs), enzymes produced by activated macrophages and fibroblasts in response to proinflammatory cytokines such as IL-1 and TNF- (12). In the later phase, cellular phase is replaced by fibrous pannus comprised of vascularised layer of pannus cells and collagen overlying cartilage. The sublining also undergoes striking alterations in cellular content with prominent infiltration of mononuclear cells. Synovial vessel endothelial cells transform into high endothelial venules (13).

Rheumatoid Factor

Rheumatoid factor was first discovered about 60 years ago by Waaler and Rose (14), who demonstrated that patients with RA had antibodies reactive with antigenic determinants on autologous IgG. RF antibody is present in about 75-80% of RA patients. The presence of RF is now widely used as diagnostic marker for RA. RFs are autoantibodies directed to the crystallizable fragment of IgG molecules (15). RF has a self binding capacity that can result in the formation of very large immune complexes, which are able to activate immune system. RFs recognise several determinants distributed among the four subclasses of human IgG on the two Fc domains, CH2 and CH3 (16).

Immunology

T Cells

Several studies have shown the participation of T cells in RA. T cells account for the mononuclear infiltrate in

synovial sublining. The genetic evidence implicating HLA-DR (MHC-II) alleles suggests role for T lymphocytes. HLA-DR alleles suggest a pathogenic process at the level of antigen presentation by the MHC molecule (17). Further, comparison of CD45 isoforms in synovial T cells with peripheral blood T cells reveals an enrichment of cells expressing CD45 isoform characteristic of memory T cells in RA synovium (18, 19).

B Cells

B cells also play a key role in the pathogenesis of autoimmune diseases. B cells are not only the precursors of antibody-secreting plasma cells, but also remarkably effective antigen-presenting cells (20). This antigen presenting role is clearly crucial to the development and persistence of autoimmunity. Finally, B cells secrete many cytokines, including TNF-, which exacerbate autoimmune and inflammatory responses (21).

Cytokines

The inflammatory response consists of the sequential release of mediators and recruitment of circulating leukocytes, which become activated at the inflammatory site and release further mediators. Cytokines regulate the progression and maintenance of autoimmunity; blocking their action with antibodies can either reduce or exacerbate established disease (22). Cytokines are local protein mediators involved in almost all biological processes, including cell growth and activation, inflammation, immunity and differentiation. These are considered as important mediators for the pathology of RA (23). Although cytokines secreted by both T cells and non- T cells are present, macrophage derived cytokines (such as IL-1, TNF-a, and IL-6) are found in greater abundance than those of T cell origin (IL-4, IL-2 and IFN-g) (24). Inflammatory cytokines, such as TNF- and IL-1, are present in higher quantities in the affected synovial fluid and tissue. These both are potent stimulators of synovial tissue functions mainly proliferation, adhesion molecule expression and prostaglandin production in inflamed joint (25).

Matrix Metalloproteinases

Matrix metalloproteinases are produced at high levels by type B synoviocytes in RA. These are family of enzymes required for remodeling and destruction of extracellular matrix (26). Their activity is regulated by tissue inhibitors of metalloproteinases (TIMPs), serine proteinase inhibitors (SERPINS), and 2-macroglobulin (27). High activity of these enzymes contributes to cartilage and bone destruction. Inflammatory cytokines, such as IL-1 and TNF-, upregulate the production of these metalloproteinase (28).

Mast Cells

A potential role for mast cells in RA has also been highlighted. Mast cells also accumulate in the synovial tissues and fluids of human suffering from RA, reflecting the presence of mast cell chemotactic or survival activities such as SCF and transforming growth factor- α in the synovial fluid (29). The invading mast cells produce several inflammatory mediators notably TNF- α , IL-1 and vascular endothelial growth factor (VEGF). Increased number of mast cells (MCs) are found in the synovial tissues and fluids of patients with rheumatoid arthritis, and at sites of cartilage damage (30). Because the MC contains potent mediators, including histamine, heparin, proteinase, leukotrienes and multifunctional cytokines, its potential contributions to the processes of inflammation and matrix degradation have recently become evident (31).

Transcription Factor NF- κ B

The transcription factor NF- κ B has been well recognised as a pivotal regulator of inflammation in RA, but recent developments revealed a broad involvement of NF- κ B in other aspects of RA pathology also, including development of T helper 1 responses, activation, abnormal apoptosis and proliferation of RA fibroblast-like synovial cells. NF- κ B is a collective name for dimeric transcription factors comprised of the Rel family of proteins that include Rel A, c-Rel B, NF- κ B 1 and NF- κ B2. The most abundant form found in the stimulated cells is the Rel A/ NF- κ B1 heterodimer, often referred to as a 'classic' NF- κ B. NF- κ B can be activated by a variety of pathogenic stimuli, including bacterial products and viral proteins, cytokines, growth factors, radiation, ischemia/reperfusion, and oxidative stress (32). The activation of NF- κ B is required to induce expression of diverse inflammatory and immune response mediators. Activated NF- κ B has been detected in human synovial tissue on the early stage of joint inflammation as well as in the later stages of the disease (33).

Free Radicals And RA

In recent years, lots of evidences suggest the possible role of highly reactive products of oxygen and nitrogen termed as Free Radicals (34), in the pathogenesis of RA. These reactive oxygen species (ROS) and reactive nitrogen species (RNS) are produced endogenously during aerobic metabolism and at the site of chronic inflammation. ROS such as super oxide radical, hydroxyl radical and hypochlorous acid contribute significantly to synovial tissue damage. Several mechanisms are involved in the generation and action of ROS in the joint of RA patient, including increased pressure in synovium cavity, reduced capillary density,

vascular changes and increased metabolic rate of synovial tissue. In addition activated leukocytes also produce ROS (35). Super oxide radical and hydrogen peroxide are converted into the highly reactive hydroxyl radicals. ROS can directly or indirectly damage basic articular constituents and lead to the clinical expression of the inflammatory arthritis. Synovial cavity damage correlation with fluctuating oxygen pressure in the joint, overproduction of ROS, lack of oxygen-processing enzymes and free radical-scavenging molecules have been reported in RA. RA patients have an increased contents of plasma conjugated dienes and significantly decreased vitamins E & A levels, which further increases oxidative stress and damages tissue. Moreover, there is growing evidence that oxidative stress exacerbates inflammation and worsens joint tissue (36).

Treatment

The goal of treatment is to control pain, reduce mortality, improve functioning, prevent joint damage and increase quality of life. On the basis of gained knowledge, new therapies have been developed, and clinical trials have been shown the efficacy of treatment of patients with active disease. Conventional anti-inflammatory and anti-rheumatic drugs include Glucocorticoids, aspirin, sodium salicylate, sulfasalazine, and gold compounds. Disease modifying antirheumatic drugs (DMARDs) are capable of reducing the inflammatory markers of the disease (37). Combination therapy has been the next choice for treatment of RA, prevalent combination are methotrexate with cyclosporine, sulfasalazin and prednisolone etc (38, 39). Another group of drugs known as Non-steroidal anti-inflammatory drugs (NSAIDs) is also now common among the patients, for eg. Celecoxib and Rofecoxib. NSAIDs act by inhibiting the COX-2 enzyme. The other list of therapeutics that inhibits NF- κ B includes numerous natural and synthetic anti-oxidants, immunosuppressants, and natural plant compounds, suggest their ability to suppress NF- κ B activation. Treatment options for this disease have in past decade been revolutionised by the introduction of biological agents such as Etanercept and Infliximab, which demonstrate DMARD activity (40). These therapies do have their limitations: the potential to increase susceptibility to infection; a limited responder rate; and a high cost.

CONCLUSION

Arthritis is a prevalent and debilitating disease that affects articulating joints. All factors involved in innate immunity contribute to the pathophysiology of RA. Autoimmune phenomena is the central pathogenetic principle involved in the induction,

progression and perpetuation of a broad range of diseases. T and B lymphocytes play a major role in the pathogenesis of RA along with the mast cells and transcription factor NF- κ B. Free radicals exacerbate the disease and damage bone and cartilage. However, existing therapies such as DMARDs and NSAIDs are main choice for the treatment; biological modifiers (Infliximab and Etanercept) have also been approved by FDA. A wide array of biologic response modifiers and natural products are presently under pharmaceutical development; which may lead to the development of new therapeutic strategies in future.

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