Review Article

An updated overview of immune complex mediated rheumatoid arthritis

Solai Sophia¹, Mudigere Maligaiah Ramesha²*

¹Associate Professor, College of Medical and Health Sciences, Adigrat University, Adigrat, Ethiopia
²Environment Group, Central Institute of Brackishwater Aquaculture (ICAR), Chennai - 600028, Tamil Nadu, India

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*Correspondence:
Dr. Mudigere Maligaiah Ramesha,
E-mail: dr.rameshamm@gmail.com

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ABSTRACT

Rheumatoid arthritis is a widely known autoimmune disorder which affects the joints and cause major disability in affected population. Even though more emphasis is given in the western world for autoimmune research, people in developing countries are also suffering significantly due to autoimmune arthritis. This review is focused on the updates in rheumatoid arthritis research and developments in therapeutic strategies. The exact cause of this disease is unknown but primary cause for inflammatory changes in the joints are considered due to cytokine network imbalance and correcting this imbalance possibly will cure the disease. Using this knowledge the newer therapeutic approaches to rheumatoid arthritis are being aimed at correcting this imbalance. Recently three most promising therapeutic products appear to be the use of monoclonal antibodies to TNF-α, soluble TNF-α receptors, and IL-1 receptor antagonist. Other therapeutic agents that could regulate the cytokine network are in various stages of laboratory and clinical evaluation. But the need to study the causative factor and prognostic marker along with other approaches is much more important to prevent clinical remission and for the complete cure of the disease. This review highlights the important recent breakthrough in the field and some suggestions for significant basic research.

Keywords: Arthritis, Autoimmune, Cytokines, Prognostic marker

INTRODUCTION

Rheumatoid Arthritis (RA) is a systemic progressive inflammatory autoimmune disease that affects the synovial lining of the peripheral joints characterized by symmetrical inflammation leading to potentially deforming polyarthritis and includes wide spectrum of extra-articular features. Rheumatoid arthritis is the most common of all inflammatory arthritides.¹ The arthritis usually begins in the small joints of the hands and the feet, spreading later to the larger joints. The inflamed joint lining or synovium extends and then erodes the articular cartilage and bone, causing joint deformity and progressive physical disability. Extra-articular features include nodules, pericarditis, pulmonary fibrosis, peripheral neuropathy and amyloidosis. Approximately 1% of the adult population is affected by RA worldwide.² About 0.75 % of adult Indian population is affected by the disease. According to a report by Connelly et al.,³ musculoskeletal disorders contributed 3.4% and 1.7% towards the total disease burden in the developed and developing world respectively, with osteoarthritis being the single largest contributor. The disease is three times more frequent in women than men. Prevalence rises with age and is highest in women older than 65 years, suggesting hormonal factors could have a pathogenic role.⁴ Estimates of the frequency of rheumatoid arthritis vary depending on the methods used to ascertain its presence.⁵,⁶ Rheumatoid arthritis has significant social...
and personal costs. Patient’s life expectancy is reduced by between three and eighteen years.7

CAUSATIVE FACTORS OF RA

While there are many laboratory animal models of autoimmunity, there is currently no general unifying theory to explain how an autoimmune process gets started in the usual clinical setting. Suffice it to say that autoimmunity and autoimmune diseases are multifactorial in origin. Contributory factors are genetic predisposition (as shown by HLA associations, family, and twin studies), host factors (such as weakness of immunoregulatory controls, defects in suppressor T cells, or polyclonal stimulation of B cells resistant to controls), environmental factors (such as certain microbial infections), and antigen-driven mechanisms (sequenced antigen, cross-reacting exogenous antigen, or molecular mimicry) which may bypass self-tolerance in a nominally normal immune system.

EXTRA-ARTICULAR COMPLICATIONS OF RA

The widening in the mortality gap between RA subjects and the general population is mainly in rheumatoid factor positive RA subjects are largely affected by cardiovascular and respiratory deaths.8 Risks of both myocardial infarctions and strokes are amplified in individuals with rheumatoid arthritis.8 A slightly elevated risk of lymphoma and lympho proliferative malignant disease is associated with rheumatoid arthritis activity.9 Prevalence of lung cancer is also raised, potentially due to increased cigarette smoking in patients with rheumatoid arthritis.10 Further, risk of melanotic and non-melanotic skin cancers is raised.11

PATHOPHYSIOLOGY

Pathologically, RA is characterized by chronic inflammatory and proliferative changes in the synovial membrane (interior of joint capsule lined with synoviocytes), accompanied by inflammatory effusion in the joint space and destructive erosion of joint cartilage and adjacent bone cortex. Ultimately, the joint space may become obliterated and the bone ends united by fibrous or bony union (ankylosis). The earliest events in RA might involve activation of the innate immune system, which triggers a T-cell response possibly directed towards citrullinated proteins.13 Infiltrating T-cells in the synovial membrane may, by cell-cell contact, and activation by different cytokines, such as TNF-α, IFN-γ and IL-17, activate monocytes, macrophages and synovial fibroblasts. These cells then produce pro-inflammatory cytokines, mainly TNF-α, IL-1 and IL-6.14 As the disease progresses multiple cytokine networks enter a state of persistent activation, triggering the production of matrix metalloproteinases, ultimately resulting in irreversible damage of cartilage and bone.15 Among several enzymes involved in the process, matrix metalloproteinases (MMPs) have been shown to have an important role in the invasion of the synovial tissue in cartilage, cartilage destruction, and bone erosion formation. Synovial concentrations of matrix metalloproteinases and matrix digesting enzymes are directly responsible for joint destruction.16-18

IMMUNE SYSTEM PATHOGENESIS

Although tremendous progress has been made in disease management over the last decade, cures for these diseases have not yet been found. Consequently, a large research effort is sustained in this field. In addition, autoimmunity has intrigued basic immunologists since the early realization that the ability to discriminate self from non-self was at the core of the immune system’s ability to protect an organism from pathogens while avoiding self-destruction. A failure of this mechanism results in autoimmune reactions that often lead to clinical disease. In spite of massive research efforts, the mechanisms by which autoimmune diseases develop are not clearly understood. Genetic predisposition as well as environmental triggers plays a role, but the identity of these factors has been largely elusive. The identification of the most common genetic and environmental factors that set off autoimmunity may lead to a better understanding of the ensuing pathogenesis, and offers the best hope for improved therapies, and ultimately, cures.19

Analogous to the manner in which hypersensitivity reactions to exogenous antigens initiate tissue injury and inflammation, so also autoantibody, Immune Complex (IC) or cell-mediated reactions to autologous antigens can lead to tissue injury and inflammation, resulting in an autoimmune disease. Adult RA is commonly associated with a peculiar group of anti-IgG autoantibodies called rheumatoid factors which mainly belong to IgM or IgG classes, bind to the Fc portion of other IgG molecules, and form IgG-anti-IgG complexes in the circulation or joint fluid. RFs are detected in serum in up to 80% of adult patients with RA and often at high titer and in repeated tests. Nevertheless, RFs are not specific for RA and occur in other CTDs, such as Sjogren's syndrome, in chronic infectious diseases, such as infective endocarditis, tuberculosis, and hepatitis B and, although usually at low titer, in up to 20% of overtly normal elderly individuals.

In advanced RA, the synovial membrane becomes densely infiltrated with lymphocytes, plasma cells, and macrophages and extends over the articular surface as a membrane, called rheumatoid pannus, which erodes and replaces the underlying articular cartilage. Cell-mediated immune mechanisms and proinflammatory cytokines are now a focus of interest in the study of the pathogenesis of RA. Briefly, T-lymphocytes, mainly T-helper/inducer cells and many of them activated are the most abundant cells in the rheumatoid synovial membrane. Many activated macrophages, macrophage-like synoviocytes, and interdigitating reticular cells (strongly expressing HLA-DR antigen) are intermixed with the recruited T-
cells and B-cells. Among the several inflammatory cytokines released by the activated macrophages are TNF-alpha and IL-1 which are considered to be major mediators of joint inflammation in RA. Recent clinical approaches in the treatment of active RA include the use of new classes of immunomodulatory drugs that inhibit the action of these inflammatory cytokines, for example, that bind to and block TNF-alpha and its interaction with its cell surface receptor.

**MOLECULAR MECHANISM OF IMMUNE COMPLEX MEDIATED INFLAMMATION**

In the past several years, studies have suggested that FcγRs play primary roles in diseases initiated by antibodies. FcγRs are members of the immunoglobulin gene superfamily that binds the Fc binding domain of IgG and are widely expressed in the hematopoietic system. Currently, 2 groups of FcγRs are recognized on cells of the human immune system: the high-affinity FcγRI, which binds monomeric IgG, and the low-affinity receptors FcγRII and FcγRIII, which preferentially bind complexed IgG. The low-affinity FcγRs are present in multiple isoforms, FcγRII (CD32) A and B and FcγRIII (CD16) A and B. The FcγRs are further classified as activating or inhibitory. Signals from these receptors are transmitted via immunoreceptor tyrosine-based activation (ITAM) or inhibitory (ITIM) motifs, respectively. FcγRI, FcγRIIA, and FcγRIIIA are activating receptors, with ITAMs present in the cytoplasmic domain of the α subunit (FcγRIIA) or in an accessory signaling γ chain with which the α subunit associates (FcγRI and FcγRIII). On cross linking of the receptors by ICs, the tyrosine residues in the ITAM motifs are phosphorylated by src family tyrosine kinases, which initiate a cascade of signaling events that trigger neutrophil effector responses. The exception is the uniquely human FcγRIIB, which anchors to the outer leaflet of the neutrophil plasma membrane through a glycosylphosphatidylinositol linkage and does not contain or interact with ITAMs containing adapters. It may signal by associating with FcγRIIA and the integrin complement receptor 3 (Mac-1), which serves as signaling partners, and/or localizing to membrane rafts enriched in signaling molecules like Src protein kinases. The ITIM motif is present in the cytoplasmic domain of the single-chain, inhibitory FcγRIIB. Colligation of activating and inhibitory receptors on the same cell by ICs inhibits ITAM-triggered activation, thus providing a higher threshold for activation of cells.

**ROLE OF COMPLEMENTS IN IC-MEDIATED RESPONSES**

In addition to the strict requirement for FcγRs, complement is required for IC-induced inflammation and subsequent end-organ damage. The 3 major pathways of complement activation are the classic pathway, activated by ICs composed of antibody of certain isotypes: the alternative pathway, triggered by microbial cell surfaces; and the lectin pathway, activated by plasma lectin that binds mannose residues on microbes. Complement activated by all 3 pathways serves the same function. The central event is the generation of complement protein C3, which is then cleaved by C3 convertase to give rise to C3a and C3b. Further binding of C3b to C3 convertase leads to the formation of C5 convertase, which cleaves C5 to generate C5a and initiates the terminal steps of complement activation. C3b covalently attaches to surfaces of cells in which complement is activated to target them for phagocytosis by macrophages. Complement products C3a and C5a are powerful anaphylotoxins that were suspected for a long time to be the primary mechanisms by which IgG ICs trigger inflammation. C5a receptor engagement on mast cells and macrophages increases the expression of activating FcγRs and suppresses the inhibitory FcγRIIB expression. Therefore, C5a, which is a potent chemoattractant, may have a broader role in regulating the relative levels of inhibitory and activating FcγRs on tissue resident cells. A proximal event in the classic pathway of complement activation is the binding of the C1q component of complement C1 to the Fc region of complexed IgG or IgM. This results in the cleavage of C4 and C2 to form an enzyme complex that acts as a C3 convertase and cleaves C3.

More specific treatment approach is needed than the immunosuppression regimens that are currently available for treatment of autoimmune disease. These kinds of treatment are largely nonselective with significant side effects. Cell-specific neutralization of human FcγRs or its downstream signaling partners would offer further specificity for potential therapeutics. At present, the relative contribution of the direct and the cell-derived pathways of complement activation in the recruitment of neutrophils are not known.

**CYTOKINES AND RA**

Although clinical remission is difficult to achieve even with anti-cytokine treatment, these drugs offer the potential to decrease disease activity and improve quality of life in a majority of RA patients, and it is conceivable that combinations of biological therapies may pave the path to even better success, which ultimately is remission or even cure. The first group is pro-inflammatory including interleukin 1 (IL1), tumor necrosis factor alpha (TNF-α), IL-8, IL-12, IL-15, IL-17, and IL-18. The second group, anti-inflammatory cytokines, is represented by soluble factors that down-modulate inflammation, namely IL-4, IL-10, IL-11, and IL-13, and soluble proteins, such as IL-1 receptor antagonist (IL-1Ra), soluble receptors for TNF and IL-1 and IL-18 binding protein. An imbalance between pro-and anti-inflammatory cytokines is believed to play an important role in disease severity and joint damage in RA. The application of molecular biology techniques to design monoclonal antibodies, soluble receptors, or receptor antagonists as therapeutic biologic agents made it...
possible to regulate the cytokine signals for the treatment of the diseases refractory to conventional therapies. Studies of inflammatory process in the inflamed synovium in RA have shown an intricate network of molecules involved in its initiation, perpetuation and regulation that balance the pro- and anti-inflammatory processes. This system is self-regulating through the action of anti-inflammatory and pro-inflammatory cytokines, cytokine receptor antagonists, and naturally occurring antibodies to cytokines. Inflammatory synovitis in RA appears to be the result of an imbalance in the cytokine network with either an excess production of pro-inflammatory cytokines or from inadequacy of the natural anti-inflammatory mechanisms. Using this knowledge the newer therapeutic approaches to RA and other inflammatory arthritides are being aimed at correcting this imbalance. Three most promising products appear to be the use of monoclonal antibodies to TNF-α, soluble TNF-α receptors, and IL-1 receptor antagonist. Other promising therapeutic agents that could regulate the cytokine network are in various stages of laboratory and clinical evaluation. These studies promise to yield therapeutic target that could dramatically change the way inflammatory diseases would be treated in future.

Growing knowledge about cellular interactions in the immune system, including the central role of cytokine networks, has led to new treatments using monoclonal antibodies that block specific components of the immune system. Systemic cytokine concentrations can serve as surrogate outcome parameters of these interventions to study inflammatory pathways operative in patients in vivo. The flow chart (Figure 1) summarizes the integrated steps in immune response that occur in rheumatoid arthritis.

**Figure 1: Schematic representation of integrated immune response in rheumatoid arthritis.**

Keys: TNF-Tumor Necrosis Factor, IL-Interleukin, IFN-Interferon

### CURRENTLY AVAILABLE TREATMENT FOR RA

The primary objective of treatment is to control joint pain and inflammation, slowing or arresting the progression of joint destruction, improve or maintain functional status, thereby improving quality of life. Treatment of rheumatoid arthritis is a multifaceted approach that includes both pharmacologic and non-pharmacologic therapies. Conventional medicines used for RA include non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), biological response modifiers, and corticosteroids. Recent emphasis has been placed on aggressive treatment early in the disease course. The ultimate goal is to achieve complete disease remission, although this goal is seldom achieved. Additional goals of treatment include controlling disease activity and joint pain, maintaining
the ability to function in daily activities or work, improving the quality of life, and slowing destructive joint changes. Rest, occupational therapy, physical therapy, use of assistive devices, weight reduction, and surgery are the most useful types of non-pharmacologic therapy used in patients with rheumatoid arthritis.

CURRENT DEVELOPMENT

Conventional therapeutic approaches are essentially palliative, anti-inflammatory or immunosuppressive; in addition, they are non-specific, unrelated to the antigens involved in disease pathogenesis. This explains the growing attention to modern technologies that made new biological agents and methods available. A few of these are already approved for regular clinical practice; others are still in clinical development but hold great promise. The question is, will these new tools allow us to develop a real cure for autoimmunity, restoring self-tolerance to target auto-antigens? This goal is ambitious, namely harnessing the pathogenic immune response while preserving the host response to exogenous or unrelated antigens.\(^{25}\)

Experiments with gene depletion and antibody neutralization suggest each chemokine and receptor may have a special position on the stage of orchestrated biological responses. It is predictable that the importance of chemokines and receptors will be further appreciated with the enthusiastic participation in the research by scientists from multi-disciplinary backgrounds and the development of new therapeutic agents directed against chemokines or receptors with proven effectiveness in circumventing human diseases.

CONCLUSION

The mechanism involved in initiation, cause of the disease and role of innate immune response during the later stages of the disease is still not clearly understood. Recent research aimed to yield therapeutic target that could dramatically change the way inflammatory diseases would be treated in future. This progression requires improved drugs and biomarkers that accurately predict patients’ status using pathological information. Can biological agents be tapered or stopped? What is the relative effectiveness and cost-effectiveness of DMARD combinations versus biological agents? These unresolved questions are economically relevant because they might reduce the need for ongoing biological treatment. Although substantial progress has been made toward improving diagnosis rates among the Indian population over the last decade, the majority of rural India still suffers from a lack of both specialists and specialty services for autoimmune disease especially Rheumatoid Arthritis.

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