RESEARCH ARTICLE

MANAGEMENT OF RHUMATOID ARTHRITIS, A LITERATURE REVIEW OF PREVIOUS STUDIES

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ABSTRACT

Rheumatoid arthritis is a common autoimmune disease that is associated with progressive disability, systemic complications, early death, and socioeconomic costs. The cause of rheumatoid arthritis is unknown, and the prognosis is guarded. However, advances in understanding the pathogenesis of the disease have fostered the development of new therapeutics, with improved outcomes. The current treatment strategy, which reflects this progress, is to initiate aggressive therapy soon after diagnosis and to escalate the therapy, guided by an assessment of disease activity, in pursuit of clinical remission. However, several unmet needs remain. Current conventional and biologic disease-modifying therapies sometimes fail or produce only partial responses. Reliable predictive biomarkers of prognosis, therapeutic response, and toxicity are lacking. Sustained remission is rarely achieved and requires ongoing pharmacologic therapy. The mortality rate is higher among patients with rheumatoid arthritis than among healthy persons, and cardiovascular and other systemic complications remain a major challenge. Molecular remission and the capacity to reestablish immunologic tolerance remain elusive. Elucidation of the pathogenic mechanisms that initiate and perpetuate rheumatoid arthritis offers the promise of progress in each of these domains. Rheumatoid arthritis is predominantly classified on the basis of the clinical phenotype**.** This is A literature review of previous studies.

INTRODUCTION

Rheumatoid arthritis is a common autoimmune disease that is associated with progressive disability, systemic complications, early death, and socioeconomic costs (Firestein, 2003). The cause of rheumatoid arthritis is unknown, and the prognosis is guarded. However, advances in understanding the pathogenesis of the disease have fostered the development of new therapeutics, with improved outcomes. The current treatment strategy, which reflects this progress, is to initiate aggressive therapy soon after diagnosis and to escalate the therapy, guided by an assessment of disease activity, in pursuit of clinical remission. However, several unmet needs remain. Current conventional and biologic disease- modifying therapies sometimes fail or produce only partial responses. Reliable predictive biomarkers of prognosis, therapeutic response, and toxicity are lacking. Sustained remission is rarely achieved and requires ongoing pharmacologic therapy. The mortality rate is higher among patients with rheumatoid arthritis than among healthy persons, and cardiovascular and other systemic complications remain a major challenge. Molecular remission and the capacity to reestablish immunologic tolerance remain elusive. Elucidation of the pathogenic mechanisms that initiate and perpetuate rheumatoid arthritis offers the promise of progress in each of these domains.

Rheumatoid arthritis is predominantly classified on the basis of the clinical phenotype (Aletaha, 2010). We believe it is important to make the transition to a new molecular taxonomy that defines discrete disease subgroups with distinct prognostic and therapeutic significance (Klareskog, 2008). Rheumatoid arthritis is characterized by synovial inflammation and hyperplasia ("swelling"), autoantibody production (rheumatoid factor and anti–citrullinated protein antibody [ACPA]), cartilage and bone destruction ("deformity"), and systemic features, including cardiovascular, pulmonary, psychological, and skeletal disorders. These clinical features pose critical mechanistic questions: What genetic–environmental interactions must occur to facilitate autoimmunity a priori, and why does this beget articular localization, Why does synovial inflammation perpetuate, What drives local destruction leading to joint dysfunction, Why does rheumatoid arthritis cause systemic illness, We herein summarize key pathogenetic advances informing these issues. Rheumatoid arthritis involves a complex interplay among genotype, environmental triggers, and chance. Twin studies implicate genetic factors in rheumatoid arthritis, with concordance rates of 15 to 30% among monozygotic twins and 5% among dizygotic twins (MacGregor, 2004). Genomewide analyses make it clear that immune regulatory factors underlie the disease (Wellcome

Trust Case Control Consortium, 2007). The long-established association with the human leukocyte antigen (HLA)–DRB1 locus has been confirmed in patients who are positive for rheumatoid factor or ACPA, alleles that contain a common amino acid motif (QKRAA) in the HLA-DRB1 region, termed the shared epitope, confer particular susceptibility (Gregersen, 1987). These findings suggest that some predisposing T-cell repertoire selection, antigen presentation, or alteration in peptide affinity has a role in promoting autoreactive adaptive immune responses. Other possible explanations for the link between rheumatoid arthritis and the shared epitope include molecular mimicry of the shared epitope by microbial proteins, increased T-cell senescence induced by shared epitope–containing HLA molecules, and a potential proinflammatory signaling function that is unrelated to the role of the shared epitope in antigen recognition (Weyand, 1990; De Almeida, 2010). Many other identified risk alleles in ACPA-positive rheumatoid arthritis consistently aggregate functionally with immune regulation implicating nuclear factor κB (NF-κB)–dependent signaling (e.g., TRAF1–C5 and c-REL) and T-cell stimulation, activation, and functional differentiation (e.g., PTPN22 and CTLA4) (Begovich, 2004; Kurreeman, 2007; Plenge, 2007; Remmers, 2007). Moreover, gene–gene interactions that increase disease risk, as described between HLA-DRB1 and PTPN22, exemplify the complexity of the net risk conferred by any given gene (Kallberg, 2007).

Genetic risk factors for ACPA-negative disease appear to be no less important than those for ACPA-positive disease. However, they are less well established and involve different HLA alleles (e.g., HLA-DRB1*03), interferon regulatory factors (e.g., interferon response factor 5), and lectin-binding proteins (e.g., C-type lectin domain family 4 member A).[3] This fundamental dichotomy in genetic risk on the basis of ACPA expression provides the first clear evidence that a molecular taxonomy for "the rheumatoid arthritis syndrome" is feasible. Patients with ACPA-positive disease have a less favorable prognosis than those with ACPA-negative disease, which suggests that such molecular subsets are clinically useful. Findings from studies of gene–environment interactions complement these observations. Smoking and other forms of bronchial stress (e.g., exposure to silica) increase the risk of rheumatoid arthritis among persons with susceptibility HLA–DR4 alleles.[14] Moreover, smoking and HLA-DRB1 alleles synergistically increase one's risk of having ACPA.[15] Unifying these observations is the finding that environmental stressors of pulmonary and other barrier tissues may promote post-translational modifications, through peptidyl arginine deiminase, type IV (PADI4), that result in quantitative or qualitative alteration in citrullination of mucosal proteins.

Environment–gene interactions described in the text promote loss of tolerance to self-proteins that contain a citrulline residue, which is generated by post-translational modification. This anticitrulline response can be detected in T-cell and B-cell compartments and is probably initiated in secondary lymphoid tissues or bone marrow. Thereafter, localization of the inflammatory response occurs in the joint by virtue of poorly understood mechanisms that probably involve microvascular, neurologic, biomechanical, or other tissue-specific pathways. Synovitis is initiated and perpetuated by positive feedback loops and in turn promotes systemic disorders that make up the syndrome of rheumatoid arthritis.

ACPA denotes anti–citrullinated protein antibody, and RF rheumatoid factor. Loss of tolerance to such neoepitopes elicits an ACPA response (which can be detected with a diagnostic anti–cyclic citrullinated peptide [CCP] assay) (Figure 1) (Vincent et al., 1999; De Rycke, 2004). Several citrullinated self-proteins are recognized in anti-CCP assays, including α-enolase, keratin, fibrinogen, fibronectin, collagen, and vimentin. Characterization of subsets of seropositive patients to elicit true disease autoantigens is ongoing. An estimated 43 to 63% of patients with ACPA-positive rheumatoid arthritis are seropositive for citrullinated α-enolase, which is strongly associated with HLA-DRB1*04, PTPN22, and smoking.[18] Similar interactions are reported for citrullinated vimentin and fibrinogen epitopes (van der Woude, 2010). Infectious agents (e.g., Epstein–Barr virus, cytomegalovirus, proteus species, and Escherichia coli) and their products (e.g., heat-shock proteins) have long been linked with rheumatoid arthritis, and although unifying mechanisms remain elusive, some form of molecular mimicry is postulated (Auger, 1997; Kamphuis, 2005). The formation of immune complexes during infection may trigger the induction of rheumatoid factor, a high-affinity autoantibody against the Fc portion of immunoglobulin, which has long served as a diagnostic marker of rheumatoid arthritis and is implicated in its pathogenesis. Furthermore, rheumatoid arthritis appears to be associated with periodontal disease: Porphyromonas gingivalis expresses PADI4, which is capable of promoting citrullination of mammalian proteins (Wegner, 2010). Finally, the gastrointestinal microbiome is now recognized to influence the development of autoimmunity in articular models, and specific (and potentially tractable) clinical bacterial signatures that are associated with autoantibody-positive rheumatoid arthritis are emerging (Scher, 2010). The greater risk of rheumatoid arthritis among women than among men has long been recognized. The onset of rheumatoid arthritis is also associated with adverse life events. Molecular explanations for such phenomena are emerging from animal models of inflammation, which show a link between the hypothalamic–pituitary–adrenal axis and cytokine production (Capellino, 2010).

The central nervous system is normally involved in immune regulation and homeostasis, and neuroimmunologic interactions regulate disease development in rodent models of arthritis. Such effects may operate locally (several neurotransmitters are expressed in synovitis in rheumatoid arthritis) or centrally (cytokines are rapidly up-regulated in the hypothalamus during peripheral inflammation). Translation of these observations to effective treatment of rheumatoid arthritis is challenging. Critical issues remain unresolved. Autoantibodies, such as rheumatoid factor and ACPA, are often (but not always) detected in patients before the development of arthritis (prearticular phase of rheumatoid arthritis); in some series, autoantibody levels have increased and there has been evidence of epitope spreading as the onset of disease approaches (Rantapaa-Dahlqvist, 2003). Why the systemic loss of tolerance is linked to a localized onset of inflammation in the joint is still unclear (transitional phase of rheumatoid arthritis). It is possible that biologic features of the targeted autoantigen (e.g., regulation of cellular metabolism in the case of α-enolase and glucose-6-phosphatase) may contribute. Other possible factors include local microvascular, neurologic, biomechanical, and microtrauma-related mechanisms (Figure 1). Many other identified risk alleles in ACPA-positive rheumatoid arthritis consistently aggregate functionally with immune regulation, implicating nuclear

factor κB (NF-κB)–dependent signaling (e.g., TRAF1–C5 and c-REL) and T-cell stimulation, activation, and functional differentiation (e.g., PTPN22 and CTLA4) (Begovich, 2004; Kurreeman, 2007; Remmers, 2007). Moreover, gene–gene interactions that increase disease risk, as described between HLA-DRB1 and PTPN22, exemplify the complexity of the net risk conferred by any given gene (Kallberg, 2007). Genetic risk factors for ACPA-negative disease appear to be no less important than those for ACPA-positive disease. However, they are less well established and involve different HLA alleles (e.g., HLA-DRB1*03), interferon regulatory factors (e.g., interferon response factor 5), and lectin-binding proteins (e.g., C-type lectin domain family 4 member A) (Klareskog, 2008). This fundamental dichotomy in genetic risk on the basis of ACPA expression provides the first clear evidence that a molecular taxonomy for "the rheumatoid arthritis syndrome" is feasible. Patients with ACPA-positive disease have a less favorable prognosis than those with ACPA-negative disease, which suggests that such molecular subsets are clinically useful. Findings from studies of gene–environment interactions complement these observations. Smoking and other forms of bronchial stress (e.g., exposure to silica) increase the risk of rheumatoid arthritis among persons with susceptibility HLA–DR4 alleles (Symmons, 1997). Moreover, smoking and HLA-DRB1 alleles synergistically increase one's risk of having ACPA (Klareskog, 2006). Unifying these observations is the finding that environmental stressors of pulmonary and other barrier tissues may promote post-translational modifications, through peptidyl arginine deiminase, type IV (PADI4), that result in quantitative or qualitative alteration in citrullination of mucosal proteins.Environment–gene interactions described in the text promote loss of tolerance to self-proteins that contain a citrulline residue, which is generated by post-translational modification.

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MATERIALS AND METHODS

A literature review of previous studies.

DISCUSSION

Synovitis occurs when leukocytes infiltrate the synovial compartment. Leukocyte accumulation primarily reflects migration rather than local proliferation. Cell migration is enabled by endothelial activation in synovial microvessels, which increases the expression of adhesion molecules (including integrins, selectins, and members of the immunoglobulin superfamily) and chemokines. Accordingly, neoangiogenesis, which is induced by local hypoxic conditions and cytokines, and insufficient lymphangiogenesis, which limits cellular egress, are characteristic features of early and established synovitis (Szekanecz, 2009; Polzer, 2008). These microenvironmental changes, combined with profound synovial architectural reorganization and local fibroblast activation, permit the buildup of synovial inflammatory tissue in rheumatoid arthritis (Figure2).

The genetics of rheumatoid arthritis and the presence of autoantibodies clearly place adaptive immunity at the center of early pathogenesis. However, even though T cells are abundant in the synovial milieu, the functional role of T cells remains insufficiently understood. Direct targeting of T cells by cyclosporine or T-cell–depleting therapeutics has shown limited or no efficacy (Panayi, 2006). This finding may reflect "broad spectrum" deletion of regulatory as well as effector T cells and suggests the need to target T-cell subsets. The synovium in rheumatoid arthritis contains abundant myeloid cells and plasmacytoid dendritic cells that express cytokines (interleukin-12, 15, 18, and 23), HLA class II molecules, and costimulatory molecules that are necessary for T-cell activation and antigen presentation (Lebre, 2008; Schroder, 1996). Moreover, the use of abatacept (a fusion protein containing cytotoxic T-lymphocyte–associated antigen 4 and the FC fragment of IgG1) to disrupt antigen presentation by blocking T-cell costimulation (through the interaction of CD28 with CD80 or CD86) is efficacious in rheumatoid arthritis. Autoreactive T cells against citrullinated self-proteins have been identified. Synovial T-cell oligoclonality, germinal-center reactions, and B-cell hypermutation suggest ongoing local antigen-specific, T-cell–mediated B-cell help (Cantaert, 2009; Humby, 2009). Here are the different medications usually prescribed for rheumatoid arthritis patients: NSAIDs, or non-steroidal anti-inflammatory drugs, are medications meant to relieve pain and reduce inflammation. They are available over-the-counter, and when needed, stronger doses may be prescribed. Many people are already familiar with NSAIDs because they are used to treat headaches, fevers and other common ailments safely at home. Ibuprofen (Advil, Motrin IB) and naproxen (Aleve) are two basic NSAIDs that will reduce pain and inflammation temporarily. Weaker NSAIDs come with little side effects or risks but they also only manage symptoms and pain — they will not help with slowing disease activity. Stronger NSAIDs are available with a prescription and can provide increased pain relief while reducing inflammation throughout the body. NSAIDs with stronger doses come with serious side effects, including:

- Liver damage
- Ringing in the ears
- Heart problems
- Upset stomach
- Kidney damage

There are prescription NSAIDs that are safer or gastrointestinal friendly for people prone to stomach problems. NSAIDs can be taken orally or applied directly to the joint as a patch or cream. Corticosteroid medications or another form of drug used in the treatment of RA. They work in your body similar to hormones as they try to slow the progression of the disease and stop the immune system from attacking healthy tissue. They can be taken as pills, liquids or given as an injection by a provider. Some of the prescribed forms of corticosteroids include Methylprednisolone, Prednisolone, and Prednisone. Corticosteroids offer pain relief, but they also come with the potential for side effects.

Possible side effects include:

- Leg swelling
- Weight gain
- Increased blood pressure
- Mood swings

Studies have shown that using corticosteroids over long periods of time can result in more serious and permanent side effects. These include:

- High blood sugar or even diabetes
- Increased risk of infection
- Calcium deficiency leading to weak bones
- Easy bruising on the skin

For this reason, doctors usually only prescribe corticosteroid medications for a short amount of time to reduce symptoms, and then place patients on less dangerous regimens or over-the-counter drugs once symptoms are better controlled. DMARDs, or disease-modifying antirheumatic drugs, are long-term medications meant to slow or alter the progression of rheumatoid arthritis by stopping the immune system from attacking healthy tissue. These drugs protect joints and tissues from permanent damage and gradually reduce daily pain. DMARDs can be taken with other pain relievers. Examples of traditional DMARDs are:

- Methotrexate (Trexall)
- leflunomide (Arava)
- Hydroxychloroquine (Plaquenil)
- Sulfasalazine (Azulfidine)

Side effects are different for each patient and medication, but the most serious are liver damage and susceptibility to infections. There is a subset of DMARD medications called biologic response modifiers. These drugs target specific parts of the immune system that trigger inflammation that causes joint damage. Blocking TNF inhibitors or the activation of T cells is one method of preventing the joint damage that frequently occurs in patients who suffer from RA. This greatly reduces the risk of further damage or infection. Biologic agents are typically prescribed in combination with other medications to fight RA symptoms.

Common biologic agents are:

- Abatacept (Orencia)
- Adalimumab (Humira)
- Anakinra (Kineret)
- Certolizumab (Cimzia)
- Etanercept (Enbrel)
- Golimumab (Simponi)
- Infliximab (Remicade)
- Rituximab (Rituxan)
- Tocilizumab (Actemra)

JAK Inhibitors (such as Xeljanz) are another type of DMARDs that work against the pathways that increase the body's immune response, known as Janus kinase. JAK inhibitors are helpful because they can be taken by mouth, unlike biologics, and they work well with traditional DMARDs. JAK inhibitors can dramatically decrease inflammation.

Physical Therapy:-Keeping an active, healthy lifestyle is just as important in treating RA symptoms as the right combination of medications. Exercise may seem too painful, but low-risk exercises like walking and yoga can reduce inflammation. A physical therapist can help you design a safe, effective daily workout routine that will keep joints flexible. Life with RA is difficult and not being physically able to complete certain routine tasks may lead to frustration.
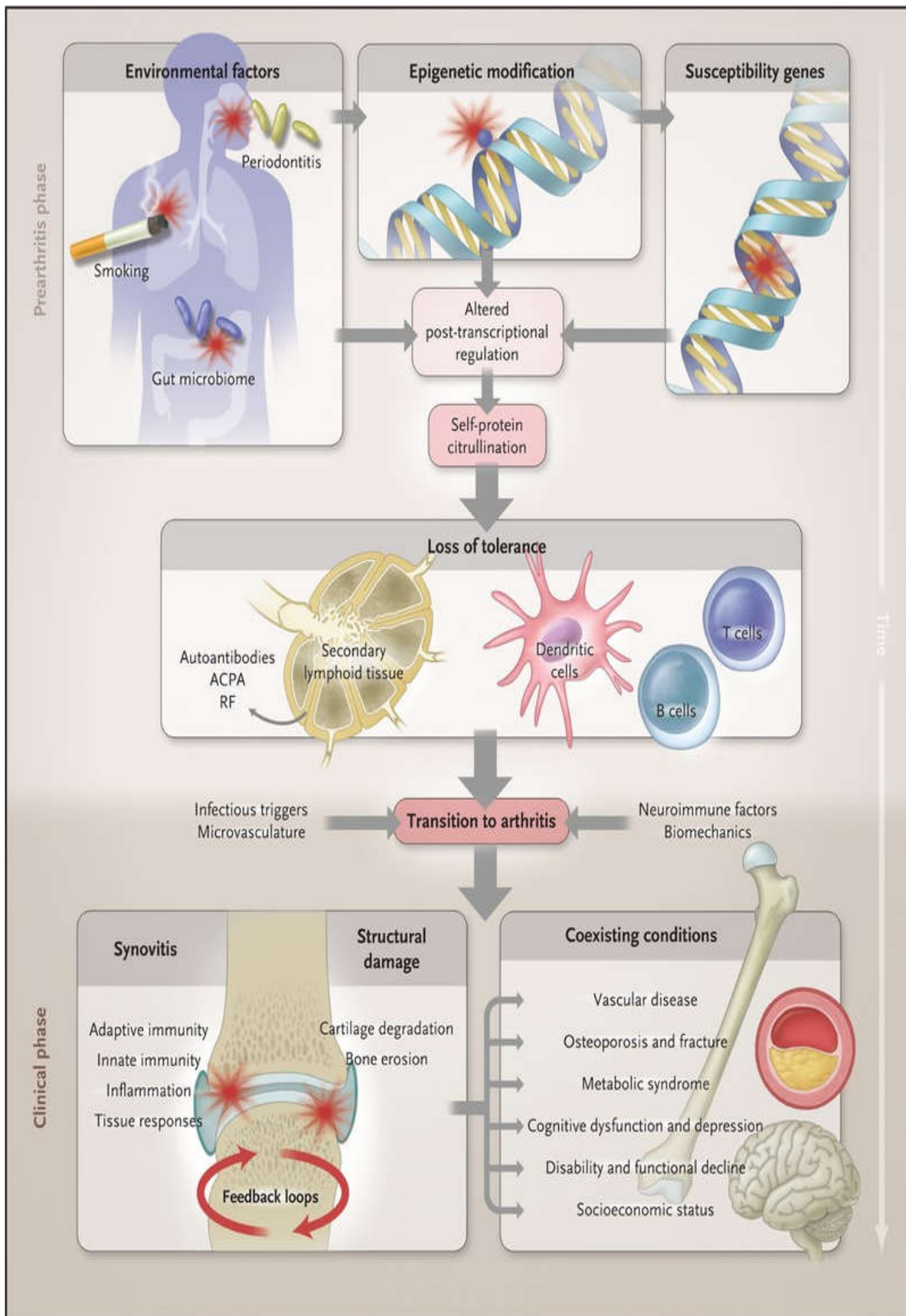
Figure 1. Multistep Progression to the Development of Rheumatoid Arthritis
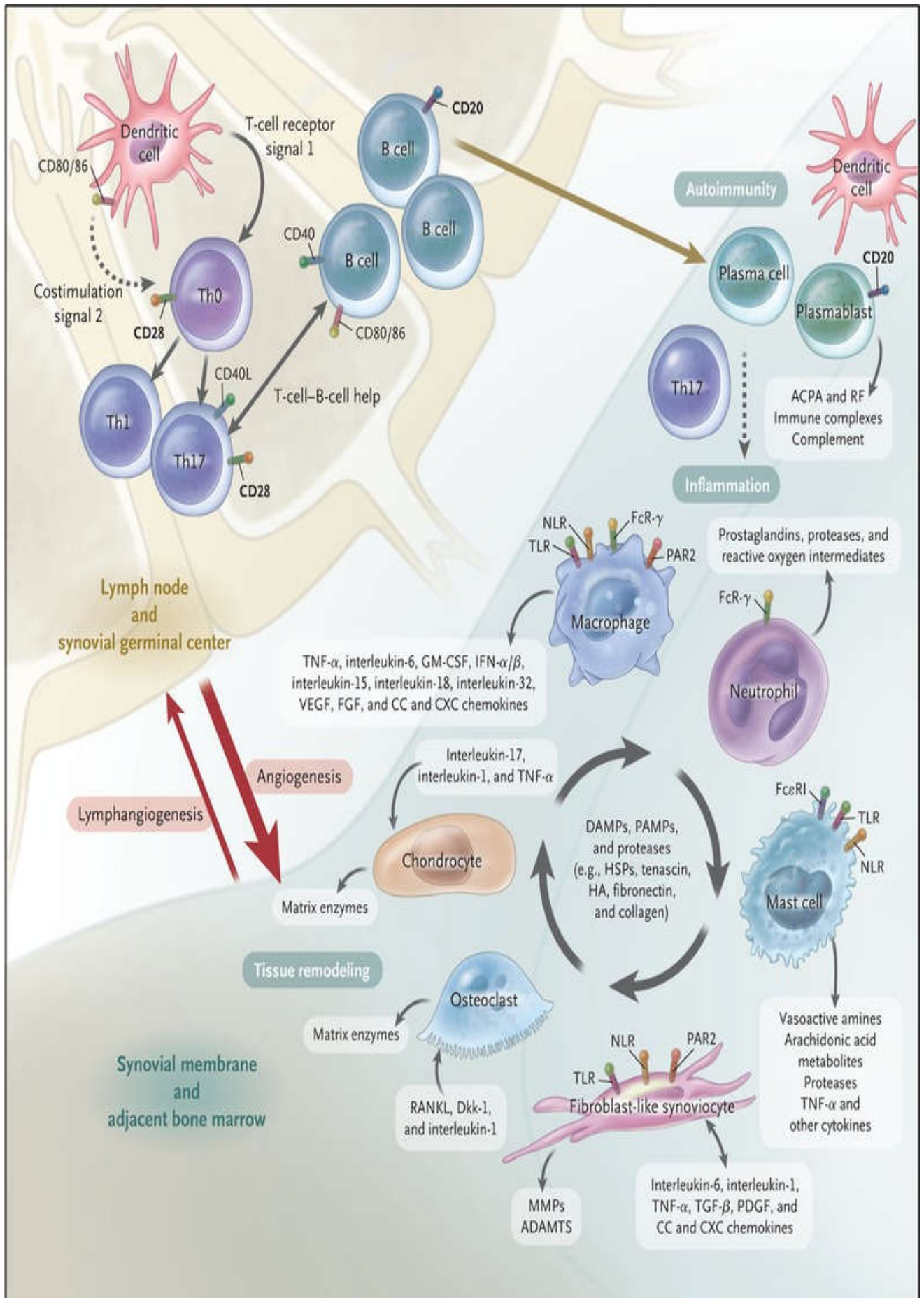
Figure 2. Adaptive and innate immune proceses within the joint in rhumatoid arthritis

Physical therapists can help patients learn appropriate exercises and new ways of approaching tasks that minimize the strain on affected joints while improving overall body strength.

Chiropractic Treatment:-Often, medication alone cannot alleviate all pain associated with RA. One approach to the chronic pain is seeking the care of a chiropractor. Some medical providers advise caution on chiropractic treatment due to the nature of the body manipulations that could potentially worsen RA pain. However, it has been found to be beneficial to certain RA patients. Patients should be cautioned not to receive care from chiropractors when active swelling or RA flare-ups occur, as this could worsen the condition. Make sure to speak with your primary doctor before pursuing any additional, specialized interventions such as chiropractic treatment.

Surgery: Surgery is not the standard of care in the treatment of RA. Surgical management is usually reserved for those with severe joint damage and should always occur in conjunction with the consultation of a rheumatologist. As mentioned before, RA is an inflammatory condition that ultimately leads to joint destruction and is a disease that can accelerate the natural course of joint damage that often occurs with aging. There is no cure, ability to restore damage or fix the deformities caused by RA. However, surgery potentially enables patients to regain function by repairing the joint damage that frequently occurs with this condition. The overall goal of surgery, when deemed appropriate, is to improve the quality of life of those affected. There are three surgical procedures that RA patients typically receive. These are:

- Joint replacement — surgeons remove part of your damaged joint and insert a prosthetic (artificial) replacement
- Joint fusion — when replacements aren't possible, surgeons can fuse and realign joints
- Tendon repair — over time, inflammation can damage tendons. Surgeons can fix these damaged tendons, to enable easier movement.

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