REVIEW ARTICLE

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Rheumatoid Arthritis — Common Origins, Divergent Mechanisms

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RHEUMATOID ARTHRITIS IS ONE OF THE MOST COMMON IMMUNE-MEDIated diseases. Its primary manifestation is inflammatory arthritis characterized by symmetric, polyarticular pain and swelling, typically involving the small joints of the hands and feet. However, rheumatoid arthritis is a systemic disease associated with multiple coexisting conditions and extraarticular manifestations. Onset of inflammatory synovitis results from the interactions of genetic factors and specific environmental exposures. The disease process begins years before clinically apparent arthritis and manifests as a continuum that originates with asymptomatic immune dysfunction and progresses through various stages before the disease can be classified as rheumatoid arthritis.

This review focuses on seropositive rheumatoid arthritis, marked by the presence of autoantibodies to post-translationally modified proteins, including anti–citrullinated protein antibodies (ACPAs, measured as anti–cyclic citrullinated peptide antibodies); less specific autoantibodies, known as rheumatoid factors, that bind the Fc portion of immunoglobulin; or both antibody types. Seronegative rheumatoid arthritis is a separate entity marked by polyarthritis but with poorly defined pathogenetic mechanisms. The course of seronegative rheumatoid arthritis is typically less destructive to joints,[1] but the approach to treatment is similar to that of seropositive disease.

In contrast to an immune disease such as psoriasis, which largely depends on the dominant interleukin-23–interleukin-17 pathway, rheumatoid arthritis has multiple potential paths to a common clinical presentation. The disease progresses from preclinical rheumatoid arthritis through chronic disease and involves pathogenic pathways and cell lineages that can differ among patients, complicating therapeutic efforts. The predominance of certain pathways over others in individual patients is underscored by the diversity of clinical responses to targeted therapies, despite a remarkably similar clinical phenotype. There have been revolutionary changes in the treatment of rheumatoid arthritis in the past three decades, but many patients still have persistent disease. The ability to identify the specific pathogenic mechanisms in individual patients would improve outcomes by directing therapy to those targets.

The preclinical stages of seropositive rheumatoid arthritis are characterized by disordered immunity, often associated with mucosal surfaces, including the oral cavity, lungs, and gastrointestinal tract, and by local and systemic generation of ACPAs. These autoantibodies can be detected in the blood a median of 4.5 years before the onset of arthritis.[2] The risk of rheumatoid arthritis increases over time as autoantibody levels increase. As this preclinical phase progresses, ACPAs directed against an expanding array of protein epitopes ensue, along with a rise in proinflammatory proteins in blood, ultimately resulting in joint inflammation.[3] Immune responses to altered peptides are not limited to citrullination; carbamylation, malondialdehyde–acetaldehyde adduct formation, and other protein modifi-

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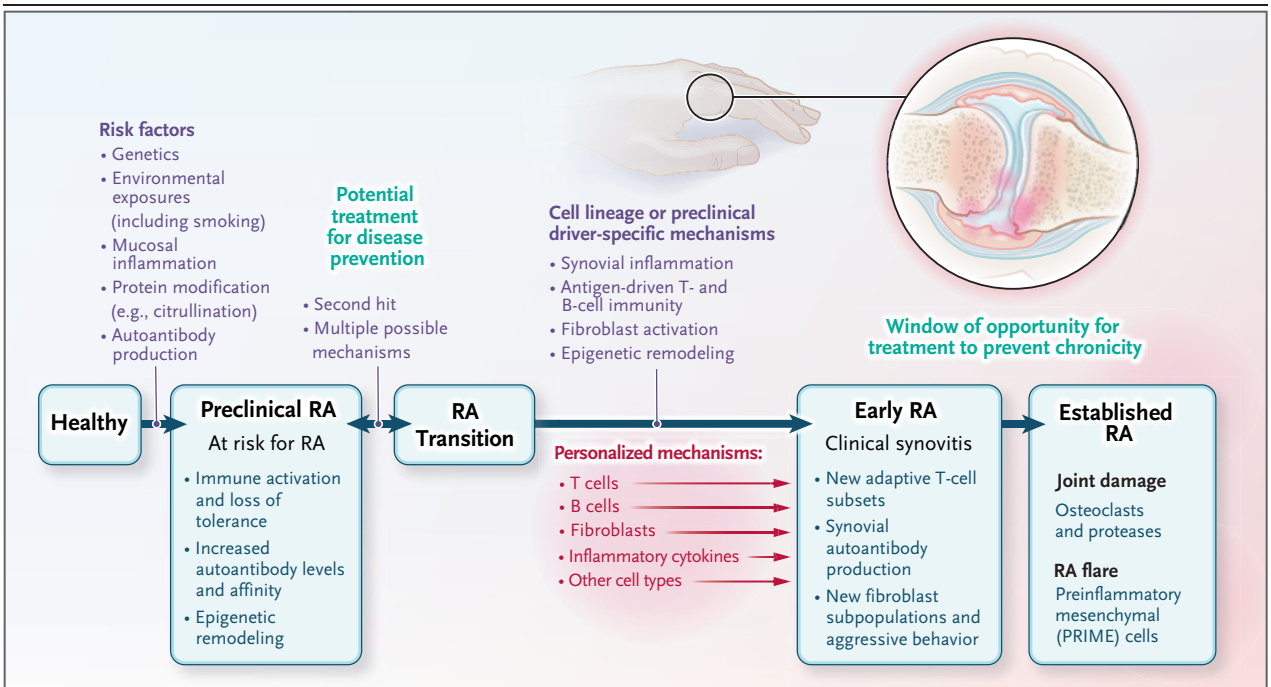

Figure 1. Initiation and Progression of Rheumatoid Arthritis (RA).

The boxes show various stages of the disease continuum and the pathogenic features of each stage. The purple text shows characteristics that affect the transition between disease stages. RA progresses from a healthy state to preclinical RA (at risk for RA) to the RA transition to early synovitis and finally to established, destructive disease. The pathway is not unidirectional, since persons in the disease stage before synovitis who are positive for antibodies against citrullinated peptides (ACPAs) can become ACPA-negative, and in some ACPA-positive persons, disease never develops. The continuum of disease evolution offers potential opportunities for the prevention of RA. Although each disease state has a characteristic clinical phenotype, multiple pathways and mechanisms can contribute to pathogenesis for an individual patient. This is depicted by the red text and arrows, which indicate disease that is dependent on a particular cell type or mediator. Therapeutic approaches should ideally be targeted to address the particular pathogenic mechanism in an individual patient. Some patients may have disease that is characterized by multiple mechanisms, resulting in a partial response or a lack of response to a given targeted therapy.

cations can induce recognition of neoantigens, with the production of antibodies to these modified protein antigens.[4]

Treatments are designed to induce clinical remission in patients with established rheumatoid arthritis. In addition, disease prevention strategies are being developed for persons considered to be at risk for the disease on the basis of family history, autoantibody status, genetic risk factors, or a combination of these findings, as well as for persons with very early stages of joint pain or inflammation, before rheumatoid arthritis has been definitively diagnosed (Fig. 1).

EPIDEMIOLOGY AND DISEASE CLASSIFICATION

The prevalence of rheumatoid arthritis is remarkably consistent worldwide, at about 0.5 to 1.0%, although the prevalence is higher in certain populations, such as Indigenous North Americans. Rheumatoid arthritis can occur at any age, but the incidence peaks in the third through fifth decades of life, and the disease is 2 to 3 times as common among women as it is among men. The effects of estrogen on immune function probably play a part in the female predominance of the disease,[5] although additional sex-related factors are also likely to be involved. Several infectious agents have been proposed as etiologic or contributing agents, including Epstein–Barr virus, retroviruses, bacterial superantigens, and mycoplasma species, as well as organisms such as oral *Porphyromonas gingivalis* and gut prevotella species.[6,7] However, a single microorganism that accounts for all patients is unlikely to be causal. The most prominent behavioral risk factor for the development of rheumatoid arthritis is cigarette smoking. Additional

factors marginally increase the risk of rheumatoid arthritis, including obesity, low vitamin D levels, and use of oral contraceptives. Factors that decrease the risk include a Mediterranean diet, n–3 fatty acid intake, fish oil supplementation, and alcohol consumption.[8,9]

Although rheumatoid arthritis is characteristically marked by symmetric arthritis in the small joints of the hands and feet, as the disease progresses, any synovial joint can be involved. The 2010 American College of Rheumatology–European League against Rheumatism classification criteria[10] focus on earlier disease manifestations than did previous classification criteria, with the introduction of a composite scoring system that includes the number and site of clinically involved joints, the duration of symptoms, and the status with respect to rheumatoid factor, ACPAs, and acute-phase reactants. ACPAs are increasingly used to support the diagnosis because of their high specificity.

GENETIC RISK AND EPIGENETIC FACTORS

The most prominent risk factor for rheumatoid arthritis is genetic. For first-degree relatives of patients with rheumatoid arthritis, the risk of disease is increased by a factor of 2 to 5. The HLA-DR locus is the most important genetic association. Well-characterized sequences in the hypervariable region of the HLA-DRβ chain (amino acids 70–74), known as the "shared epitope," are associated with an increased risk. HLA-DR is involved in antigen presentation to CD4+ T cells and could increase susceptibility through its ability to bind and present specific arthritogenic peptides. HLA-DR genes associated with rheumatoid arthritis can bind peptides modified by citrullination more avidly than native peptides, inducing T-cell activation and cytokine production. In addition, these HLA molecules may influence T-cell receptor selection toward a more autoimmune repertoire.[11] Informatics analysis of major histocompatibility complex (MHC) data indicates that three amino acid positions in HLA-DRβ1 and a single amino acid in HLA-B and HLA-DPβ1 that modify the peptide-binding groove explain most of the MHC association with disease risk.[12] HLA-DRB1 is associated not only with susceptibility but also with disease severity and possibly with varying treatment responses to certain biologic agents.[13,14]

More than 100 additional alleles have been identified that contribute to the risk of disease and overwhelmingly implicate immune pathways. Many are located in gene regulatory or intronic regions, but some involve the coding region and affect gene function. For example, a polymorphism in PTPN22, a phosphatase involved in T-cell receptor signaling, is one of the best-characterized alleles associated with rheumatoid arthritis. R620W, a gain-of-function amino acid change in PTPN22, increases disease risk by a factor of more than 2.[15] Many other risk alleles are also associated with immune processes, including the coding region of the interleukin-6 receptor and noncoding regions near the TRAF1–C5 locus. Most of these alleles marginally increase the odds ratio for rheumatoid arthritis, by a factor of approximately 1.1 to 1.2.

The relatively low concordance of rheumatoid arthritis in monozygotic twins (approximately 15%), as compared with the concordance of monogenic diseases, suggests that noncoding DNA epigenetic marks, possibly induced by environmental or stochastic factors, are also important. DNA methylation might contribute to disease susceptibility, as suggested by distinct methylation patterns in twins who are discordant for rheumatoid arthritis.[16] Furthermore, in at-risk persons without synovitis who have high blood levels of rheumatoid factor or ACPAs, peripheral-blood mononuclear cells are characterized by abnormal DNA methylation in immune-related genes years before the onset of symptoms.[17] Later, T cells with aberrant epigenetic marks in immunologic pathways accumulate in the inflamed synovium.[18] In contrast, patients with osteoarthritis have fewer differentially marked genes in synovial T cells, and they are randomly distributed. Thus, remodeling of the disease-associated epigenome in synovium could be driven by processes that contribute to the transition from preclinical to clinical rheumatoid arthritis.

FROM MUCOSAL INFLAMMATION TO ALTERED PEPTIDES TO CLINICAL DISEASE

Environmental and behavioral influences play a major role in susceptibility to rheumatoid arthritis and disease severity. Cigarette smoking and genetic risk can be synergistic: for ACPA-positive smokers with two copies of the susceptibility shared epitope, the risk of rheumatoid arthritis

is 20 times that for nonsmokers.[19] The risk gradually abates after smoking cessation, approaching the risk for nonsmokers within two to three decades.[20] Inflammation and stress at mucosal surfaces, induced by environmental exposures such as cigarette smoke, contribute to disease initiation in persons with risk alleles for rheumatoid arthritis, and the link between mucosal inflammation and rheumatoid arthritis is strongest for the airway. The mammalian genome includes enzymes known as peptidyl arginine deiminases, which convert arginine to citrulline. These enzymes are induced by cell stress and lead to post-translational citrullination of many proteins. Citrullination is quite active in the airways of smokers, where modified peptides have been detected in macrophages.[21]

Bronchiolar thickening and local neutrophil extracellular trap formation occur in asymptomatic at-risk persons with high ACPA titers, as well as in first-degree relatives of patients with rheumatoid arthritis.[22] The extruded DNA in neutrophil extracellular traps forms a scaffold for citrullinated peptides and amplifies immune responses that can generate ACPAs.[23] In at-risk persons, the combination of peptide citrullination and HLA-DR haplotypes that bind citrullinated peptides more avidly than native peptides[24] can lead to a local immune response and further ACPA production. However, ACPAs produced at sites of mucosal damage might also serve as a mechanism to clear citrullinated proteins.[25] The evolving ACPAs arise from B cells and plasmablasts through affinity maturation, which is driven by specific citrullinated proteins and oligoclonal expansion of antigen-specific cells.[26] Concomitant increases in serum cytokines and chemokines provide evidence of early systemic inflammation that ultimately culminates in symptomatic joint inflammation.

Production of ACPAs and other autoantibodies represents a break in tolerance. Such breaks can be facilitated by the selective introduction of N-linked glycosylation sites in the B-cell receptor antigen-binding pocket, which alters the antigen-binding site and enhances B-cell activation.[27] ACPAs (IgA or IgG) can bind to an array of citrullinated proteins, including fibronectin, enolase, histones, and fibrinogen. The mere presence of ACPAs is not sufficient to induce arthritis, and a consistent pattern of citrullinated proteins or antibody levels that precede or coincide with synovitis has not been identified in patients with rheumatoid arthritis. Synovial-biopsy specimens from persons with preclinical rheumatoid arthritis and arthralgias show little or no evidence of inflammation or local immune responses despite high levels of circulating ACPAs.[28] In preclinical models, the administration of ACPA autoantibodies does not cause arthritis[29] but can exacerbate existing synovitis. Even so, rising ACPA titers in humans are a harbinger of clinical disease. When the titers in at-risk persons reach 3 times the upper limit of the normal range, there is a 30 to 50% chance that rheumatoid arthritis will be diagnosed within 3 to 5 years.[30]

These observations raise the possibility that progression from preclinical rheumatoid arthritis to established disease might be prevented through therapeutic intervention or mitigation of environmental stress. Several clinical trials unsuccessfully attempted to intercede in this transition, including treatment with atorvastatin[31] and B-cell depletion with a single course of rituximab.[32] The latter delayed, but did not prevent, conversion to clinical rheumatoid arthritis in ACPA-positive persons presenting with arthralgias. In at-risk persons with arthralgias and imaging evidence of synovitis, 1 year of treatment with methotrexate, a nonadaptive immune-system intervention, did not prevent rheumatoid arthritis, as assessed after 2 years. However, the disease was less severe in the treated cohort.[33] Although proinflammatory processes have been emphasized in the transition to clinical disease, inadequate production of antiinflammatory cytokines, such as interleukin-1 receptor antagonist (interleukin-1Ra) and interleukin-10, or defective synovial apoptosis[34] could also contribute to the onset and perpetuation of disease.

HETEROGENEITY OF SYNOVITIS IN RHEUMATOID ARTHRITIS

Synovitis is a hallmark of rheumatoid arthritis, with an influx of inflammatory cells leading to multiple villous projections within the joint cavity. Typical histologic features include synovial hyperplasia, neovascularization, and a heterogeneous inflammatory infiltrate that can include lymphoid aggregates and germinal center–like structures. Infiltrating cells include T and B cells, plasma cells, plasmablasts, macrophages, den-

dritic cells, and occasional mast cells and natural killer cells. Neutrophils are sparse in rheumatoid synovium but pass through tissues into synovial fluid rapidly.

Synovial histologic and transcriptional analyses show marked heterogeneity among patients with established rheumatoid arthritis,[35] perhaps providing clues to pathogenic pathways that are active in a given patient. Synovial assessments, however, can be complicated by sampling bias and by distinct epigenetic marks and transcriptomes that depend on joint location.[36] For example, fibroblasts derived from hip and knee synovia can be distinguished from each other on the basis of DNA methylation and transcriptome patterns. Noncoding RNAs also vary according to joint location and could help shape stromal cell phenotypes and function.[37] Although classification systems have been proposed on the basis of histologic features or the most prominent cell types in a given patient's synovial tissue on biopsy,[38] meaningful correlations between histopathological patterns and clinical disease activity or outcomes are thus far limited. Tissue analyses performed with RNA sequencing methods and stratification by cell lineage signatures may have the potential for predicting the response to a given therapy.[39] Data from synovial biopsies in patients with rheumatoid arthritis suggest that molecular and histologic profiling might provide insights into the response to the B-cell–directed agent rituximab as compared with blockade of the interleukin-6 receptor with tocilizumab.[40] These approaches continue to be promising research tools but have not yet defined specific pathways driving disease in a given patient.

Approaches based on systems biology might also help stratify patients according to shared pathogenic pathways. A recent study integrated transcription factor–binding site accessibility with the transcriptome in fibroblasts.[41] At least two clusters of patients were identified on the basis of divergent transcription factor functions in cultured fibroblast-like synoviocytes. For example, the transcription factor retinoic acid receptor alpha had proproliferative effects in the transforming growth factor β pathway in one cluster but antiproliferative effects in the other cluster. Similar unbiased systems approaches could provide insight into how biologic features vary among patients with similar clinical phenotypes.

NEW INSIGHTS INTO PATHOGENESIS

Studies of specimens from ultrasound-guided synovial biopsy in patients with rheumatoid arthritis offer new insights into pathogenesis. Evaluation of synovial cell surface markers with cytometry by time-of-flight and single-cell RNA sequencing has provided data on the large array of cell lineages in rheumatoid synovium, including more than 20 transcription-defined T-cell subtypes.[42] T cells are central in the pathogenesis of rheumatoid arthritis, and one important remaining question is whether some of these cell phenotypes are responsible for the disease, represent a response to the synovial microenvironment, or are merely "spectators at a fire," recruited by the rich chemoattractant milieu. Several novel and important T-cell subsets have been identified, however, including peripheral helper T (Tph) cells, located within synovial B-cell clusters and in the circulation, which promote B-cell production of interleukin-21, supporting immunoglobulin affinity maturation, among other functions (Table 1). Tph cells also promote B-cell proliferation and differentiation into antibody-producing plasma cells.[43] Oligoclonal expansion of synovial B cells with somatic mutations, indicating local ACPA affinity maturation, is also prominent in rheumatoid synovium.[26]

Studies using fate mapping systems have identified novel macrophage subsets, including CX3CR1+ tissue-resident macrophages that form an immunologic barrier on the synovial surface, restricting the flux of proteins across the normal synovial lining.[48] Identification of additional macrophage subsets, including resident macrophages[47] with an antiinflammatory phenotype and inflammatory macrophages that contribute to the production of proinflammatory factors, also provides insights into pathogenesis. In addition, dendritic cells, which are present in rheumatoid synovium, play a part in local antigen presentation and activation of autoreactive T cells.[56] Extensive work with synovial biopsy specimens from patients with rheumatoid arthritis has highlighted the importance of several novel fibroblast phenotypes that promote inflammation, including those with proinflammatory functions whose differentiation is regulated by endothelial cells.[51] In addition, the transcription factor ETS1 defines a fibroblast phenotype that regulates bone damage through the production of RANKL

Table 1. Recently Identified Cell Lineages and Cell Phenotypes Contributing to Rheumatoid Arthritis (RA).*

Cell Class	Comments	Study
T cells		
CD4+ PD1+ CXCR5– (Tph)	Located in lymphoid aggregates adjacent to B cells; produce interleukin-21, which supports B-cell proliferation and differentiation into plasma cells	Rao et al.[43]
CD8+ GZMK+	Located in RA synovial sublining; source of interferon-γ	Jonsson et al.[44]
B cells		
Mucosal, circulating, and synovial B cells	Oligoclonal expansion with evidence of recirculation and ACPA affinity maturation due to somatic mutation	Kongpachith et al.[26]
NR4A+	Produces lymphotoxins and interleukin-6, which promote lymphoid aggregate formation	Meednu et al.[45]
Macrophages		
MerTK–	Proinflammatory; found in active RA synovium; associated with interleukin-6 and TNF production	Alivernini et al.[46]
MerTK+	Antiinflammatory; associated with lipoxin and resolvin production	Cai et al.[47]
CX3CR1+	Resident cells in RA synovial lining with tight junctions that serve as immunologic barrier; disrupted in RA synovium	Culemann et al.[48]
Alternatively activated	Interleukin-33 reprogrammed with metabolic rewiring that uncouples respiratory chain and enhances inflammation resolution	Faas et al.[49]
HBEGF+	Promotes fibroblast aggressiveness and invasion	Kuo et al.[50]
Fibroblasts		
FAP+ CD90+	Proinflammatory phenotype located in sublining; regulated by NOTCH3	Wei et al.[51]
FAP+ CD90–	Located in intimal lining; produce interleukin-6, metalloproteinases, and prostanoids in RA	Mizoguchi et al.[52]
ETS1	Regulates bone damage through production of RANKL by fibroblasts in synovium	Yan et al.[53]
PRIME cells	Present in circulation of patients with RA (according to transcriptome profile); increase in peripheral-blood PRIME cells precedes RA flares, possibly associated with B-cell activation	Orange et al.[54]
Neutrophils: synovium and lung mucosa	Produce NETs, which bind citrullinated peptides to enhance ACPA production	Corsiero et al.[55]

* ACPA denotes anti–citrullinated protein antibody, NETs neutrophil extracellular traps, PRIME preinflammatory mesenchymal, RANKL receptor activator of nuclear factor-κB ligand, TNF tumor necrosis factor, and Tph peripheral helper T.

(receptor activator of nuclear factor-κB ligand) and activation of osteoclasts.[53]

Murine studies indicate that fibroblasts have the potential to migrate from an inflamed joint through the bloodstream and could thus "spread" synovitis.[57] More recent studies in humans have identified the appearance of preinflammatory mesenchymal (PRIME) cells in peripheral blood obtained just before disease flares in patients with rheumatoid arthritis.[54] Longitudinal transcriptomic data also provide evidence of peripheral-blood B-cell activation before the appearance of PRIME cells and disease flares. Interactions between B cells and PRIME cells could therefore serve as a potential target to abrogate disease flares.

LONG-TERM CONSEQUENCES OF DISEASE

MORBIDITY AND MORTALITY

Patients with rheumatoid arthritis have an increased risk of death. Cardiovascular disease is the most common cause of premature death, and the excess risk of cardiovascular disease in rheumatoid arthritis is attributed to the combination of chronic inflammation and well-documented risk factors for cardiovascular disease such as hypertension and dyslipidemia. Traditional risk factors (e.g., elevated low-density lipoprotein cholesterol levels) have a weaker correlation with cardiovascular risk in rheumatoid arthritis than in the general population.[58] Recent

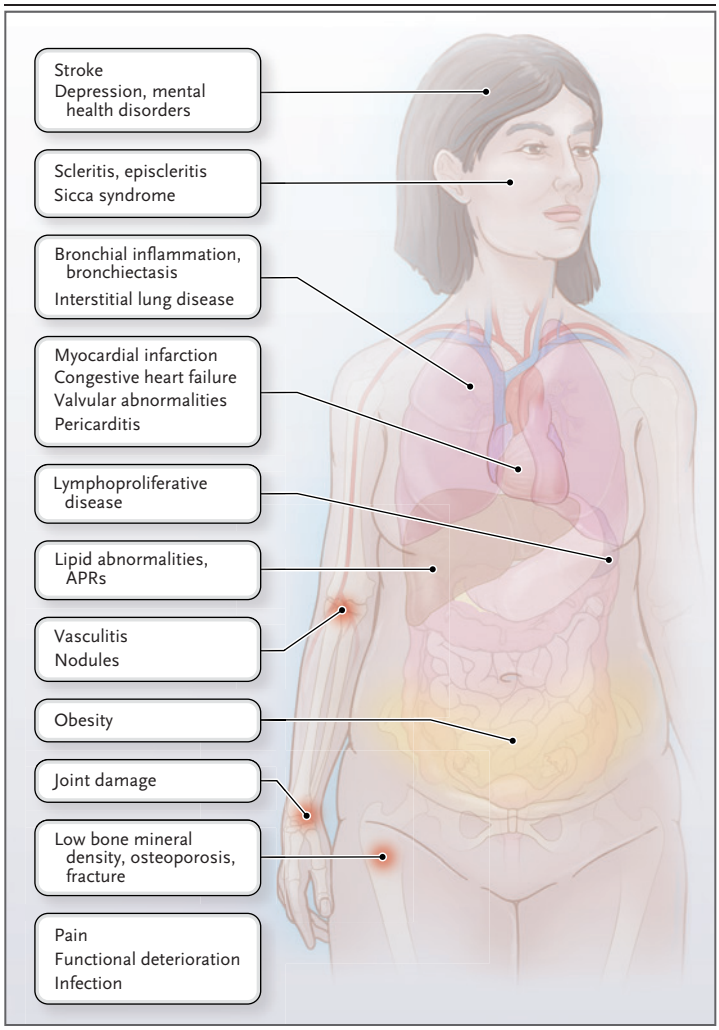

Figure 2. Complications of RA and Coexisting Conditions.

Proinflammatory cytokines, complement activation, and immune complex formation in RA promote systemic inflammation that affects many systems and results in complications and coexisting conditions, along with the production of acute-phase reactants (APRs) mediated in large part by interleukin-6. Designation as a complication or coexisting condition is not exact, and the two categories can overlap. Altered lipid metabolism and cytokines, including tumor necrosis factor and interleukin-6, contribute to atherogenesis, myocardial infarction, and stroke. Pulmonary complications occur through multiple mechanisms. Rheumatoid nodules and vasculitis are seen less commonly with current treatment approaches. Chronic inflammation contributes to metabolic and other coexisting conditions and can result in depression and altered coping behaviors. Possible mechanisms affecting the immune status of the central nervous system (CNS) include effects of proinflammatory cytokines on activation of blood–brain barrier endothelium, leading to the transport of cytokines into the CNS, and effects on neural circuits and plasticity.[62] Proinflammatory cytokines synergize with RANKL (receptor activator of nuclear factor-κB ligand) to promote osteoclastogenesis and articular and systemic bone loss, leading to fractures, and inhibitors of the Wnt signaling pathway prevent bone formation and erosion repair by osteoblasts. Joint destruction is mitigated by tight control of inflammation. The inflamed synovium produces multiple algogens that increase pain sensitivity by reducing the firing threshold for local nociceptors. Sensitization of central pain pathways by proinflammatory mediators has also been implicated.[63] The majority of patients with RA have marked fatigue due to pain, sleep disturbance, and other factors.[64] These complications and coexisting conditions combine to result in a multifactorial deterioration of function over time. Susceptibility to infections is increased in RA owing to impaired host defense, and this can be exacerbated by the use of immunosuppressive agents.

studies have shown coronary microvascular dysfunction in patients with rheumatoid arthritis, like that seen in patients with diabetes,[59] which probably contributes to excess cardiovascular mortality. Current treatment strategies that reduce inflammation mitigate the risk of death. The benefit of this approach is particularly well documented with tumor necrosis factor (TNF) blockers.[60]

Complications and coexisting conditions in patients with rheumatoid arthritis, including an increased risk of lymphoproliferative disease,[61] are shown in Figure 2. As rheumatoid arthritis progresses, pulmonary interstitial fibrosis, bronchial inflammation, and bronchiectasis develop and progress in some patients, and are associated with a higher risk of death from respiratory disease.[65] A variant in the promoter region of the gene encoding mucin 5B (*MUC5B*) is associated with idiopathic pulmonary fibrosis, and this variant is also associated with the usual interstitial pneumonia form of interstitial lung disease in patients with rheumatoid arthritis,[66] implicating mucins in the pathogenesis of this complication.

JOINT DESTRUCTION

The rheumatoid synovium is characterized by expansion of tissue at the interface with cartilage and bone. This expanding tissue, known as pannus, resembles a locally invasive tumor and extends over the surface of cartilage. Pannus also invades the bone marrow space directly or through pores in cortical bone. In active rheumatoid arthritis, the extracellular matrix of

Table 2. Agents Approved and in General Use or Not Approved for Use in RA.*

Class and Agent	Mechanism of Action	Comments
Approved and in general use		
Traditional DMARDs		
Methotrexate	Affects multiple cell types; inhibits several pathways, including adenosine metabolism	Used as a single agent or in combination therapy; most common initial agent
Leflunomide	Inhibits dihydroorotate dehydrogenase and pyrimidine metabolism and may inhibit expansion of activated leukocytes	Used as a single agent or in combination therapy
Sulfasalazine	Combination drug (5-aminosalicylic acid and sulfapyridine) that potentially inhibits inflammatory cytokines and chemokines and alters adenosine metabolism	Often used in combination with methotrexate and hydroxychloroquine
Hydroxychloroquine	Possibly stabilizes macrophage lysosomes; modulates TLR7 and TLR9 activity	Used as monotherapy for mild disease; often used in combination with methotrexate and sulfasalazine (triple therapy)
Biologic DMARDs		
Cytokine inhibition	Interruption of cytokine networks	Often used in combination with methotrexate or another traditional DMARD
TNF: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab	Blockade of TNF inhibits activation of leukocytes, FLS, endothelial cells, and osteoclasts, preventing matrix degradation and production of proinflammatory molecules	
Interleukin-6: sarilumab, tocilizumab	Blockade inhibits B-cell differentiation; activation of leukocytes, osteoclasts, and acute-phase reactant elevation; lipid alterations	
Interleukin-1: anakinra	Interleukin-1Ra blocks interleukin-1 binding to receptor; inhibits activation of leukocytes, FLS, endothelial cells, and osteoclasts, preventing matrix degradation	Less effective than other anticytokine agents in RA
T cells: abatacept	Binds CD80 and CD86 and blocks T-cell costimulation, inhibiting naive T-cell activation	Increased efficacy when used in combination with methotrexate
B cells: rituximab	Binds CD20 and depletes B cells, inhibiting antigen presentation and autoantibody production	Often used in combination with methotrexate
Synthetic DMARDs–JAK inhibitors: baricitinib, tofacitinib, upadacitinib	Interrupt cytokine networks through blockade of JAK–STAT pathway, inhibiting FLS activation, leukocyte maturation, and autoantibody production	
Selected biologic DMARD targets tested but agent not approved		
Cytokine inhibition	Interruption of cytokine networks	

GM-CSF	Blockade inhibits differentiation and activation of myeloid cells and granulocytes	Efficacy in phase 2 studies; phase 3 studies in progress
Interleukin-15	Blockade inhibits T-cell–FLS and T-cell–macrophage interactions and TNF production	Modest efficacy in clinical trials
Interleukin-17A	Blockade inhibits synergism with TNF and activation of FLS, osteoclasts, and chondrocytes	Modest efficacy in phase 3 trials
Interleukin-18	Blockade inhibits granulocyte and osteoclast activation and Th1 responses	Minimal efficacy
Interleukin-23	Blockade inhibits Th17 expansion	Modest efficacy in phase 3 studies
Interferon-γ	Blockade inhibits cytokine production and class II MHC antigen induction	Ineffective
Lymphotoxin alpha	Blockade inhibits lymphoid organ architecture	Ineffective
RANKL	Blockade inhibits osteoclast differentiation and systemic and articular bone loss	Effective in phase 2 trials for erosions but not clinical synovitis
Signal transduction		
p38 MAP kinase	Blockade interrupts cytokine networks	Modest, transient efficacy
Bruton's tyrosine kinase	Blockade inhibits B-cell receptor signaling and B-cell activation	Marginal-to-modest efficacy, depending on the compound
PI3 kinase γ or δ	Blockade inhibits cell proliferation, survival, and migration to synovium	Mixed efficacy
Syk tyrosine kinase	Blockade inhibits activation of T cells, B cells, macrophages, and FLS	Modest efficacy
Cell-targeting		
Cadherin-11	Depletes FLS	Ineffective
CD4	Depletes CD4+ T cells	Ineffective
CD52	Depletes CD4+ T cells and several other immune-cell lineages	Ineffective
CD5	Depletes certain T lymphocytes and mantle-zone lymphocytes	Ineffective
Cell recruitment		
ICAM-1	Blocks ICAM–α$_L$β2 integrin interactions, inhibiting cell recruitment to synovium	Ineffective
Multiple chemokines and chemokine receptors	Block cell recruitment to synovium	Limited or no efficacy for antichemokine antibodies and small-molecule chemokine receptor inhibitors

* DMARD denotes disease-modifying antirheumatic drug, FLS fibroblast-like synoviocytes, GM-CSF granulocyte–macrophage colony-stimulating factor, ICAM-1 intercellular adhesion molecule 1, interleukin-1Ra interleukin-1 receptor antagonist, JAK–STAT Janus kinase–signal transducer and activator of transcription, MAP mitogen-activated protein, MHC major histocompatibility complex, PI3 phosphatidylinositol 3, Th1 type 1 helper T cell, Th17 type 17 helper T cell, and TLR toll-like receptor.

cartilage, ligaments, and tendons is destroyed by proteinases that are produced by synovial cells, especially fibroblasts, and by chondrocytes themselves. The inflammatory cytokine milieu — most notably, interleukin-1β and TNF — directly activates these cells to produce matrix metalloproteinases, including collagenases, stromelysins and gelatinases, and ADAMTS5, which contribute to cartilage and joint destruction.[67]

Bone destruction requires the action of osteoclasts, which differentiate through the combined actions of the receptor activator of RANKL,[68] and proinflammatory cytokines, especially TNF and interleukin-6.[69] The most important source of RANKL, promoting bone loss in rheumatoid arthritis, is synovial fibroblasts,[70] but certain T-cell and B-cell subsets also produce RANKL. Inflamed synovial tissues and pannus bring inflammatory cytokines and RANKL-expressing cells to the bone microenvironment, inducing osteoclastogenesis. Osteoclasts attach to bone, forming an acidic environment that leaches mineral from bone, and produce enzymes, including cathepsin K, that degrade the bone matrix. In addition, inhibitors of the Wnt signaling pathway prevent osteoblast differentiation and bone repair.[71,72] RANKL and proinflammatory cytokines enter the circulation, promoting systemic bone loss and osteoporosis and increasing the risk of fractures. Systemic bone loss begins in the preclinical phase of rheumatoid arthritis, since ACPAs can directly promote osteoclastogenesis by triggering Fc receptor activation and cytokine release from macrophages and activating osteoclasts.[73] Improved therapies and an aggressive approach to controlling inflammation in patients have reduced the severity of articular and systemic bone loss in patients with rheumatoid arthritis.[74]

THERAPEUTIC CONSIDERATIONS AND APPROACHES

Therapeutic approaches and outcomes in patients with rheumatoid arthritis have improved dramatically over the past three decades with the advent of targeted therapies (Table 2 and Fig. 3). Early diagnosis and intervention with a disease-modifying antirheumatic drug (DMARD) remain the cornerstone of treatment to control inflammation, prevent joint and organ damage, and reduce the risk of death.[75] Limiting the use of potentially toxic medications such as nonsteroidal antiinflammatory drugs, glucocorticoids, and opioids is also an important focus. The use of composite disease activity measures, often called "treat to target," is a critical component of the treatment strategy.[76] Determining the order in which drugs are used is not as important as selecting one of the many outcome measures for disease activity that can be incorporated into the clinical workflow and changing or adding therapeutic agents as needed to achieve the target of low disease activity or remission.[77] As successful new therapeutic agents have been introduced, guidelines for treatment and evidenced-based approaches have been updated and are available to guide clinicians.[78,79]

Despite the advent of new therapies that target a wide array of mechanisms, the mainstay for the initial treatment of rheumatoid arthritis remains low-dose methotrexate, and 25 to 40% of patients have substantial improvement with methotrexate alone.[80] Inadequate responses to methotrexate require the addition of another agent, typically a biologic agent or a Janus kinase (JAK) inhibitor. Methotrexate improves the clinical response to many targeted agents when used in combination therapy. Combinations of traditional agents (triple therapy) with methotrexate, sulfasalazine, and hydroxychloroquine can achieve adequate responses,[81] but adherence to the regimen may be challenging. Most drug-specific toxic effects have been well described, such as bone marrow suppression and liver enzyme abnormalities (e.g., with methotrexate and leflunomide) or thrombosis and an increase in cardiovascular events (e.g., with the JAK inhibitor tofacitinib, as compared with an anti-TNF agent).[82] Effective drugs typically suppress host defenses and are associated with low rates of serious infections (typically ≤1%).[83] Glucocorticoids are associated with a dose-dependent risk of serious infection[84] and contribute to fracture and other complications over time.

Many targeted agents evaluated in clinical trials have limited or no efficacy or have not been approved for clinical use (Table 2), but we have learned much from these trials. The site of action of available therapeutic agents in the context of pathogenesis is shown in Figure 3. Treatment should not simply suppress inflammation but must also address the specific pathogenic pathway (or pathways) in an individual patient's

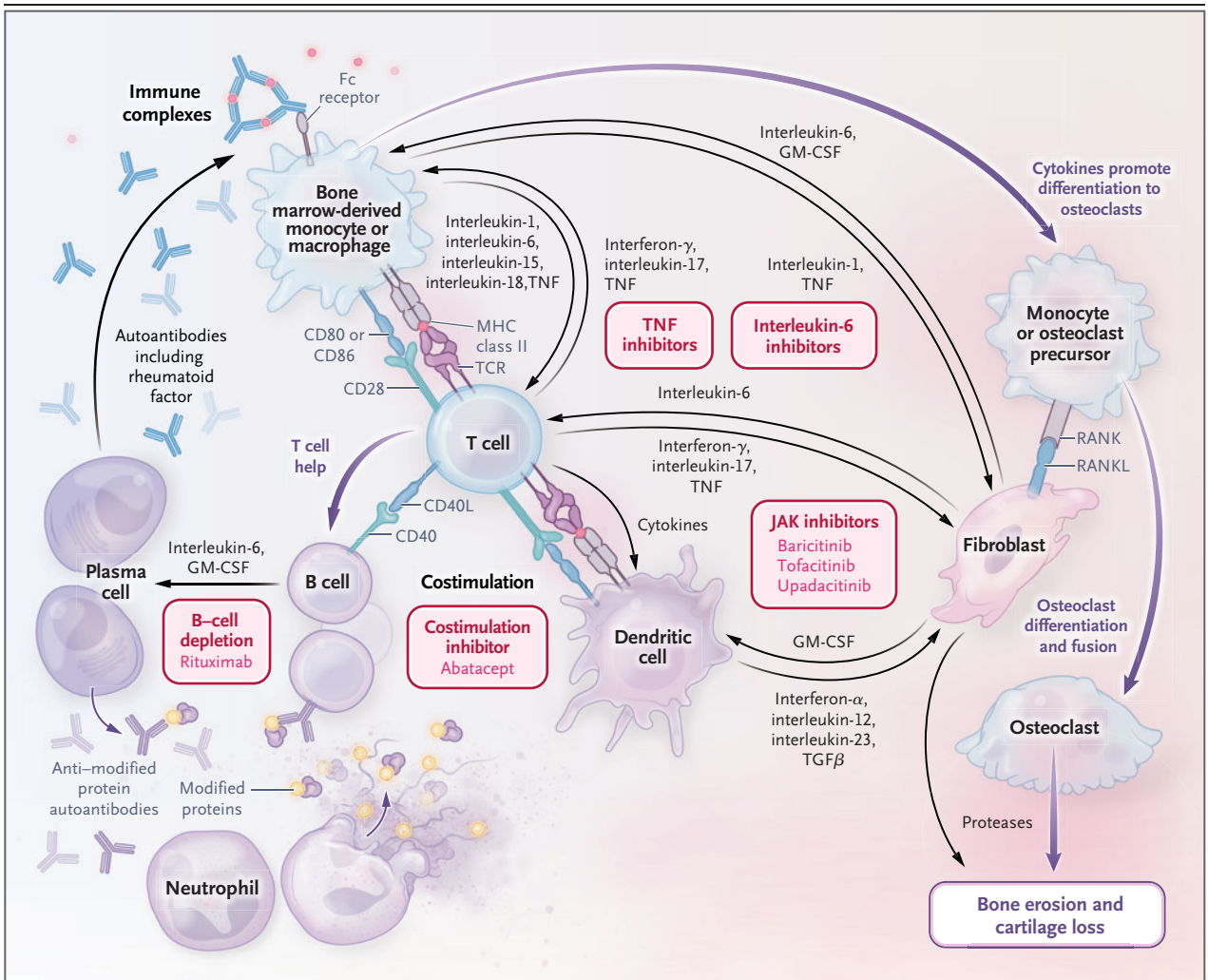

Figure 3. Synovial Cellular Interactions, Cytokine Networks, and Sites of Action of Current Therapeutic Agents.

Cell–cell interactions within the synovium are critical components of RA pathogenesis. Red boxes show effective therapeutic agents. Several cell types (dendritic cells, macrophages, and B cells) can present antigens to T cells, including modified (e.g., citrullinated) proteins, to activate these cells and to induce their differentiation. This results in the production of cytokines that, in turn, activate other, neighboring cells, including monocytes, macrophages, and synovial fibroblasts, to produce additional proinflammatory cytokines and factors. Neutrophil extracellular traps in the lungs form a scaffold for citrullinated proteins and amplify immune responses that can generate ACPAs. Activated B cells differentiate into plasma cells that produce ACPAs and other autoantibodies. RANKL is produced by synovial fibroblasts but also by certain T- and B-cell subsets, inducing the differentiation of monocytes into bone-resorbing osteoclasts. Osteoclastic degradation of bone leads to the joint erosions seen in patients with RA, and proteases induced by inflammatory cytokines lead to cartilage loss and radiographic narrowing of joint spaces. Interleukin-6 inhibitors include tocilizumab and sarilumab. Tumor necrosis factor (TNF) inhibitors include adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab. Rituximab is an anti-CD20, B-cell–depleting agent. Abatacept inhibits T-cell costimulation. Janus kinase (JAK) inhibitors include baricitinib, tofacitinib, and upadacitinib. These are positioned between cells producing cytokines including interleukin-6 and inhibit the JAK–STAT (Janus kinase–signal transducers and activators of transcription) pathway. GM-CSF denotes granulocyte–macrophage colony-stimulating factor, MHC major histocompatibility complex, TCR T-cell receptor, TGF transforming growth factor.

disease. Methods of stratifying patients to identify those who are likely to have a response to a particular treatment, thus improving drug selection, are being investigated. To date, however, no combination of biomarkers (e.g., cytokine levels in the blood), tissue analyses (e.g., histopathological patterns or transcriptome assessments), or genetic markers (e.g., single-nucleotide polymorphisms) has been shown to improve decision making in clinical practice. Rational

drug selection remains a critical unmet need, and the development of alternative taxonomies based on pathogenesis will be essential.

Disease mechanisms may also vary with the stage of disease. Epigenetic marks of synovial fibroblasts in early rheumatoid arthritis are quite different from those in later stages of the disease, and the specificities of ACPAs evolve over time.[85] Thus, individualized therapy might require adjustments for mechanisms that vary as the disease progresses. This concept is supported by the observation that early disease is more responsive to therapy than is late disease[86] and highlights the importance of early control of inflammation.

Clinical remission is the goal of therapy but is not realized in most patients with rheumatoid arthritis. Tapering or even discontinuing therapies in patients with complete responses can be achieved in the short term,[87] but unfortunately, the disease typically recurs. In patients with early rheumatoid arthritis and low disease activity, clinical predictors of disease flare after DMARD discontinuation include measures of the patient's functioning and measures of bone erosion on magnetic resonance imaging.[88,89] Rates of disease flare may also differ on the basis of autoantibody status, as well as the duration of remission once DMARDs are tapered.[90] In a study involving patients with well-controlled seropositive disease in whom anti-TNF agents and methotrexate were tapered and stopped, the cumulative flare rate at 2 years was 61%, and only 15% of patients had a drug-free remission.[91] In addition, therapeutic responses may not be recaptured when a treatment is reinitiated. Disease recurrence is likely because most current therapeutic agents target downstream inflammatory mediators rather than resetting the immune system or inducing pathways that resolve inflammation.

As we increase our understanding of the immunologic continuum from a healthy immune system to preclinical rheumatoid arthritis to early and chronic disease, new opportunities for individualized interventions that treat or prevent disease should emerge. Interceding at the earliest time points to prevent disease will perhaps be as important as identifying new targets for long-standing rheumatoid arthritis. New classification criteria are needed to harmonize data from clinical trials and observational studies involving at-risk persons. At the same time, analyses of multiple streams of genomic, proteomic, metabolomic, and epigenomic data are likely to identify new therapeutic targets and enable clinicians to select the agent that will work best in an individual patient.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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