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Prospects for Autoimmune Disease Research Advances in Rheumatoid Arthritis

William J. Koopman, MD

RHEUMATOID ARTHRITIS (RA) IS a chronic systemic inflammatory disease involving diarthrodial joints and other organs. Rheumatoid arthritis occurs worldwide and in all racial groups, and affects females 2 to 4 times more frequently than males, with prevalence estimates from 0.2% to 1.0% in most populations. There appears to have been a recent decline in RA incidence, an increase in the age at onset, and perhaps a diminution in the proportion of patients with severe disabling disease.

Nonetheless, RA causes substantial morbidity and attendant economic burden; approximately 50% of patients are unable to work within 10 years of onset and the lifetime costs of the disease rival those of coronary artery disease or stroke. Mortality rates among persons with RA are increased at least 2-fold and correlate with extent and severity of disease.¹

Major Clinical and Research Advances in the Past 25 Years

Understanding and treatment of RA have been facilitated by development of widely accepted diagnostic criteria, instruments for functional assessment, and criteria for measuring disease activity. Genetic susceptibility to RA is strongly attributable to inheritance of specific HLA alleles (DRB 1) that encode a common 5-amino acid sequence ("shared epitope") in the antigen-binding groove of the DR molecule. Homozygosity for the epitope confers risk for more severe disease.² The synovial membrane in RA (the target organ of the disease) is infiltrated predominantly by CD4 T cells^{3,4}

Rheumatoid arthritis (RA) is a common chronic inflammatory disease associated with progressive destruction of diarthrodial joints, substantial morbidity and economic burden, and a shortened lifespan. Significant progress has been made in understanding the pathogenesis of RA, and increasingly effective therapies have been introduced, including anti-tumor necrosis factor α agents. Advances made in the past quarter century will pale in comparison to those anticipated for the next 25 years, including delineation of the genetic basis of disease susceptibility and severity, genetic definition of disease subtypes that differ in severity and response to therapy, and prompt initiation of effective individualized treatment based on genetic and environmental assessment. Reconstructive surgery will become increasingly unnecessary and the morbidity, economic burden, and mortality due to RA will be reduced substantially.

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that express activation markers⁵; however, cytokines elaborated by the synovium (eg, interleukin 1 [IL-1], IL-6, IL-8, tumor necrosis factor α (TNF- α), granulocyte-macrophage colony-stimulating factor) originate predominantly in macrophages and fibroblasts.⁶ The proinflammatory cytokines TNF- α and IL-1 play a central role in the pathogenesis of inflammation and tissue injury in RA.^{7,8} Fibroblastoid cells in RA synovium exhibit a transformed phenotype and are capable of adhering to and degrading cartilage in the apparent absence of T cells, presumably through expression of metalloproteinases.⁹

Clinical advances include more aggressive treatment of early RA, facilitated by the availability of increasingly effective therapeutic agents including methotrexate, leflunomide, and biologic agents directed against TNF- α .¹⁰ The latter agents are at least as effective as methotrexate and appear to be more active in retarding tissue destruction. Combination therapy,

including concomitant use of methotrexate with anti-TNF- α agents, has enhanced efficacy (vs monotherapy) and caused less than anticipated toxicity.^{11,12} Advances in reconstructive surgery, including use of newer techniques and biomaterials, have improved the quality of life for patients with destructive disease.

Current Theories and Key Issues

While the etiology of RA is as yet unknown, it is presumed that the disease is likely triggered either directly or indirectly (eg, molecular mimicry) by an infectious agent(s) in a genetically predisposed individual. The ensuing pathogenetic events are believed to be driven by T-cell (and B-cell) responses to the inciting antigen(s), self-antigens, or

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both in the synovium with elaboration of proinflammatory cytokines that induce up-regulation of endothelial adhesion molecules, influx of chronic inflammatory cells, induction of protease expression, and subsequent tissue destruction. Non-T-cell dependent mechanisms may contribute to disease perpetuation, including aberrantly regulated cytokine cascades, impaired regulation of growth and programmed death among synovial cells, and cell-cell and cell-matrix interactions that autonomously drive inflammatory mechanisms, destructive pathways, or both.

In addition to addressing the obvious questions regarding the nature of the inciting event(s) in RA, delineation of the genes (and their functions) that contribute to disease susceptibility, phenotype, and response to therapy; elucidation of the specificity (and clonotype) of arthritogenic T cells (if these exist); determination of the molecular and cellular events linking chronic inflammation with tissue destruction; and identification of the cellular and molecular events underlying tissue destruction will be critical for unraveling the sequence of events responsible for the inflammatory and destructive paths of RA.

Forecast for Major Research Advances

Current leading research efforts likely to be most important in paving the way for the major advances in RA during the next quarter century are listed in the TABLE.

At least 10 genes, likely more, will be linked to disease susceptibility and severity and these genes will exhibit distinct patterns of distribution among ethnic groups. While some gene polymorphisms linked to RA susceptibility will influence cytokine/gene factor expression or responsiveness, immune functions, synovial cell growth and programmed cell death of synovial cells, others will act by unanticipated mechanisms to provide fresh insights into disease etiology and pathogenesis.

Research Opportunities and Forecast: Rheumatoid Arthritis
Mapping and Identification of Genes Linked With Disease Susceptibility, Severity, and Response to Therapy in Rheumatoid Arthritis (RA)
Identification of Genes Differentially Expressed in RA Synovium and Relationship to Disease Phenotype
Determination of the Precise Role of Locally Expressed Cytokines, Growth Factors, and Proteases in the Inflammatory and Destructive Manifestations of RA
Identification of Sensitive and Specific Prognostic Markers of Disease Severity
Development of Sensitive Measures for Assessing Disease Progression (ie, Destruction) Including Imaging Techniques
Elucidation of Molecular Mechanisms Regulating Cartilage and Bone Growth, Differentiation, and Maintenance
Characterization of Factors Regulating Growth, Differentiation, and Programmed Cell Death of Synovial Cells in RA
Development of Specific Inhibitors Directed Against Candidate Pathogenetic Cytokines and Growth Factors Elaborated in RA Synovium; Preclinical Investigations and, When Appropriate, Clinical Testing of Such Inhibitors in Patients With RA
Development of Techniques for Selectively Delivering and Expressing Candidate Therapeutic Genes in Synovial Cells With High Efficiency

Individual genotype alone will confer a maximum increased risk of development of RA in the range of 10- to 20-fold greater than the general population frequency; however, with elucidation of gene-environmental interactions, this will increase to 20- to 40-fold. Based on genotype, RA will be classifiable into subgroups that exhibit characteristic differences in phenotype, severity, and response to individual therapies (or combinations thereof).

Diagnosis of RA will be possible earlier and with greater precision and accuracy. In individuals at high risk for developing RA (based on genotype and environmental assessment), blood and imaging diagnostic tests will be developed to detect disease onset prior to overt clinical symptoms.

No single etiologic agent will be identified for RA; rather several reasonably common infectious agents (likely both bacterial and viral) will be demonstrated to trigger the disease in predisposed individuals. While these agents (or their products) will be de-

monstrable in synovial tissue at disease onset, it is likely that they will be transient and that continued presence of the responsible agent(s) will not be required for disease perpetuation. Moreover, the specificity of T-cell (and B-cell) responses in RA synovial tissue will be defined; reactivities to local antigens liberated from damaged joint constituents and neo-antigens generated by posttranslational modification (eg, nitrosylation) will be implicated as important contributors to disease perpetuation.

Therapy for RA will consist of highly individualized combinations of oral cytokine and growth factor antagonists and T-cell-directed antigen-specific tolerance-inducing approaches based on the individual genotype and T-cell repertoire of the patient. Such therapeutic combinations will be instituted promptly after diagnosis, and clinical remissions will occur in a substantial fraction, perhaps half of patients so treated. In addition, reconstructive surgery will rarely be required for pa-

tients with RA after the year 2025. In patients diagnosed prior to this time and requiring reconstructive approaches for

joint damage, techniques will be developed for resurfacing joints with autologously generated cartilage.

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Research Advances in Systemic Lupus Erythematosus

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SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) is a multisystem autoimmune disease involving both humoral and cellular aspects of the innate and acquired immune systems. Lupus is characterized by autoantibodies with a spectrum of specificities that participate in disease pathogenesis. Lupus occurs worldwide and affects females more commonly than males (10:1), and some racial groups, such as blacks and Hispanics, more commonly and severely than others.¹ Autoimmune diseases may currently affect tens of millions of US residents. Lupus, predominantly a disease of younger women, shortens life expectancy, creates significant morbidity, and accounts for substantial total health care expenditures.

Major Clinical and Research Advances

Clinical management of SLE is based on use of nonsteroidal anti-inflammatory drugs (NSAIDs), the addition of hydroxychloroquine and other agents originally developed as antimalarials, targeted and judicious use of glucocorticoids, including large intravenous doses, and aggressive use of other immunosuppressive agents, such as cyclophosphamide. Vigorous management of comorbid conditions, including

Systemic lupus erythematosus is an autoimmune disease with a significant genetic component to susceptibility. Some environmental risks are known, and identification of specific genetic factors promises to define new molecular targets for therapy. Broad immunosuppression will be replaced by early, selective, and individualized intervention. Mortality rates will decline, and insights into therapy may apply to other autoimmune conditions.

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hypertension and infection, has decreased mortality in persons with SLE.^{2,3}

The immune system plays a crucial role in the pathogenesis of both active inflammatory and noninflammatory mechanisms of organ damage in SLE. Autoreactivity encompasses a broad range of specificities that can include inciting antigens and other antigens through spreading of the immune response. Nucleosomes, apoptotic material, and efficient pathways for routine, nonimmunogenic clearance appear pivotal in pathogenesis of SLE. Equally, effector pathways for inflammation are critical for the development of end-organ damage.

Current Scientific Foundation

Lupus involves abnormal activity of the immune system in response to environmental stimuli encountered by the genetically susceptible host. Family studies emphasize the heritability of the SLE diathesis, but susceptibility is polygenic, involving multiple genes with a thresh-

old effect. Deficiencies of complement and other opsonins, genetic variants of IgG and C-reactive protein receptors, and inflammatory cytokine promoter variants have been implicated as components of genetic susceptibility factors.⁴ Breaks in tolerance and immune hyperactivity lead to tissue injury by both myeloid and lymphoid effector cells. The presence of autoantibodies and autoreactive T cells indicates broad involvement of the immune system, and non-inflammatory mechanisms also contribute to vascular and organ injury.

Animal models and clinical observations suggest that different sets of genes can produce similar clinical phenotypes. Consequently, identification of both environmental events and ge-

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