Autoimmune diseases are numerous and heterogeneous, with a broad spectrum of clinical presentations and unpredictable courses. Treatment options include such medications as analgesics and nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, biological agents, and glucocorticoids. If the disease is diagnosed early, the major treatment goal is remission with no active inflammation and no functional deterioration.

Numerous mouse and human studies have improved our understanding of the contribution of different immune mediators to the pathogenesis of autoimmune diseases. Despite these advances, the main causes of the breakdown of immune tolerance that lead to the development of autoimmune diseases remain largely unknown. A large proportion of the risk for developing an autoimmune disease is attributable to genetic factors. For example, HLA regions contribute to approximately half of the genetic susceptibility for rheumatoid arthritis (RA).

Can you highlight some recent advances that have enhanced our understanding of the pathogenesis of autoimmune diseases?

Walther J. van Venrooij: It is believed that anti-citrullinated peptide antibodies (ACPAs) are involved in the pathology of RA and that antibodies to chemical modifications of proteins are involved in the development of autoimmune diseases. Much evidence for this belief has been obtained in the case of RA. For example, ACPA positivity and small-joint arthritis are consistent predictors of chronic arthritis in patients with very early arthritis. ACPA concentrations, epitope-recognition profiles, and isotype usage increase markedly before onset of disease. Studies performed in experimental animal models have demonstrated the importance of these antibodies in the development of arthritic disease. It has been shown that ACPAs can bind to citrullinated peptides, which are found in the extracellular matrix of joints in RA patients. This binding leads to the activation of rheumatoid factor (RF)-positive B cells, which produce ACPAs. These antibodies can then bind to citrullinated peptides on the surface of synovial cells, leading to the activation of immune cells and the production of pro-inflammatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor (TNF).

The clinical management of autoimmune diseases presents a considerable challenge to healthcare providers. The lack of definition of disease subsets in individuals with early autoimmune disease is one of the key gaps in the field. In this Q&A, 3 experts discuss recent developments in the area of early diagnosis of autoimmune diseases and their implications for improved treatment strategies.
have increased numbers of low-density granulocytes, an important cell in the etiology of SLE. Patients with SLE show evidence that the neutrophil may be a critically important cell mediating inflammation in this disease. Emerging research has triggered a cascade of new discoveries.

The role of antibodies against citrullinated proteins has been particularly striking for RA, a disease in which the central etiology of arthritis is not fully understood. The close association of these antibodies with a particular set of HLA-DPB1 alleles against cytokines such as TNFα and IL-6. These treatments have had an enormous impact on many patients. At the same time, integration of genetic, epidemiologic (e.g., impact of smoking), and basic immunology data have led to completely novel insights into the pathogenesis of some diseases. This is, again, particularly striking for RA, a disease in which the central role of antibodies against citrullinated proteins has triggered a cascade of new discoveries.

Michael M. Ward: In RA, ACPAs have a higher diagnostic specificity compared with rheumatoid factor and also have prognostic importance. The close association of these antibodies with a particular set of HLA-DRB1 MHC loci (the so-called shared epitope) and the increased prevalence in smokers have established a major etiologically distinct subset of RA. This scenario follows the model of autoimmunity developing in a genetically susceptible host in response to an inhaled environmental trigger or chronic respiratory inflammation. Cross-reactivity of ACPAs with enzymes in the oral flora suggests an alternative trigger that may account for the association between RA and periodontitis. In systemic lupus erythematosus (SLE), coordinated expression of several interferon-α–inducible genes has been shown to correlate with the clinical activity of SLE, suggesting that interferon-α is a key cytokine mediating inflammation in this disease. Emerging evidence suggests that the neutrophil may be a critically important cell in the etiology of SLE. Patients with SLE have increased numbers of low-density granulocytes, which have a propensity to undergo NETosis (the killing of various pathogens by neutrophil extracellular traps), exposing nuclear constituents as antigens, promoting release of type I interferons, and causing endothelial damage. In rheumatic diseases more broadly, genomewide association studies have indicated that the Th17 (CD4+ T helper cell) pathway is likely important in the development of Crohn disease, psoriasis, and ankylosing spondylitis, and may underlie the clinical associations among these conditions.

What are currently used criteria, including clinical biomarkers, for the diagnosis and classification of early autoimmune disease? What in your opinion will further improve early diagnosis?

Walther J. van Venrooij: For RA, I refer to the recently published ACR-EULAR (American College of Rheumatology/European League against Rheumatism) 2010 RA classification criteria. These new criteria show clearly that the specific serology of autoimmune diseases becomes more and more important to reach an early diagnosis and, consequently, earlier treatment.

Rik Lories: Novel insights from basic science, epidemiology, and genetics have made it clear to clinical scientists that many classification criteria needed an update. Recently, novel criteria for RA, axial spondyloarthritis, and psoriatic arthritis have been published and, even more importantly, debated. These criteria are in balance with the novel discoveries and include biochemical or imaging biomarkers (e.g., ACPAs or characteristic lesions on magnetic resonance imaging). Good criteria will help but not replace the challenge of early diagnosis. From the clinical perspective, a diagnosis is made at the individual-patient level by the skilled physician. The criteria are important for classification at the group level. Nevertheless, the criteria provide a framework in which clinical observations can be tested and thereby contribute to more-specific diagnoses.

Michael M. Ward: Classification criteria for RA were updated in 2010. The presence of either rheumatoid factor or ACPAs, particularly in high titer, is heavily weighted in these criteria, with seropositivity and arthritis in 4 or more small joints being sufficient for a diagnosis of definite RA. Increased C-reactive protein concentrations or erythrocyte sedimentation rates also contribute but are not weighted as heavily in the classification as the autoantibodies. The original 1982 American College of Rheumatology classification criteria for SLE were updated in 1997 to include antiphospholipid antibodies, among other changes. The Systemic Lupus International Collaborating Clinics group has recently proposed a new revision that was found to...
have higher diagnostic sensitivity than the 1982 criteria, but lower diagnostic specificity (Arthritis Rheum 2012; doi: 10.1002/art.34473). This preliminary proposal requires 4 manifestations, including at least 1 of 11 clinical manifestations and at least 1 of 6 immunologic manifestations (antinuclear antibody, anti-DNA, anti-Sm, antiphospholipid antibody, low complement, direct Coombs test), or lupus nephritis with positivity in either an antinuclear antibody or anti-DNA test. Efforts to update classification criteria for scleroderma have also begun. Biologically active agonistic antibodies to platelet-derived growth factor receptor were reported to be diagnostic for scleroderma, but assay reproducibility has been difficult. Advances in early diagnosis of other autoimmune diseases will require similar breakthroughs in understanding immunopathogenesis. It is unlikely that genetic markers will prove useful for early diagnosis, given the polygenic nature of these conditions and the low positive predictive value of these markers.

The generation of ACPAs is an early event in the course of RA. Can you comment on the clinical utility of tests currently available for detection/quantification of ACPAs and what can be done to standardize them?

Walther J. van Venrooij: According to the literature, the second-generation cyclic citrullinated peptide (CCP2) test is still recognized as the gold standard of testing for ACPAs. The use of different ACPA tests in parallel could enable the differentiation between distinct ACPA-positive subgroups. Standardization can be improved by the use of International Units based on the reactivity of a standardized reference serum. Such a serum has now been approved by the Committee for the Standardization of Autoantibodies in Rheumatic and Related Diseases and is available via the Centers for Disease Control and Prevention. The use of a reference serum may also lead to a better distinction between low and high ACPA concentrations, which is important for the 2010 RA classification criteria.

Rik Lories: Commercial systems to detect ACPAs should be properly validated. From the clinical perspective, a high positive predictive value is of great interest, and tests should recognize as many clinically relevant subtypes as possible. However, from the scientific perspective, further individual analysis of different ACPAs is important for understanding the onset and course of disease. Therefore, the goals for clinical practice and basic research may not be the same.

Michael M. Ward: Depending on the particular ELISA used and cohort studied, ACPAs have a reported diagnostic specificity of 0.86–1.00 and a diagnostic sensitivity of 0.39–0.92 for a diagnosis of RA, with most diagnostic sensitivities above 0.65. Some assays have poor precision, poor linearity, and poor concordance with other assays. Reference reagents and serum banks are being established for use in standardizing assay performance.

The genetic background of autoimmune diseases remains to be clearly depicted. What additional advancements are required before genetic markers gain clinical use in disease risk stratification and/or help guide treatment strategies?

Walther J. van Venrooij: I certainly think that in the near future, relevant genetic backgrounds will be routinely measured when there is a suspicion for an autoimmune disease. Such measurements should, however, be cost-effective.

Rik Lories: Clear progress has been made by the genomewide association studies involving thousands of markers at the same time in large patient cohorts. Although successful, these approaches have also identified new challenges. The relationship between markers and specific genes can be controversial. Only common variants are currently detected, many with a limited impact on disease susceptibility. Further progress may come not only from technology improvement (e.g., next-generation sequencing) but also from more specific phenotyping of patients and controls. Such a phenotyping exercise (ACPAs-positive vs -negative in RA) has been highly successful in the genetics of RA.

Michael M. Ward: For genetic markers to gain use in clinical applications, these markers should provide unique information about prognosis or treatment response not provided by other more readily available and less expensive sources, be it the clinical history or examination, or more commonly used laboratory tests. Observational studies showing the differences in patient outcomes by genotype should be followed by randomized controlled trials showing that a strategy of screening for genetic markers, and clinical management based on the screen, results in patient outcomes superior to those obtained with a strategy of not screening. Ideally, treatment based on screening would also result in more-efficient and cost-effective care, so these outcomes should also be measured. At present, markers of potential drug toxicity (glucose-6-phosphate dehydrogenase and thiopurine-S-methyltransferase) are used, but no genetic markers are used clinically for prognosis or to guide treatment decisions. Heterogeneity in symptoms, signs, and re-
Sponses to treatment among patients of the same genotype will complicate these efforts.

Can you briefly discuss current treatment strategies specific for different stages of autoimmune disease? Are there any markers that are clinically used to assess treatment response and predict outcome?

Walther J. van Venrooij: RA patients can be classified into 2 major subsets: ACPA positive and ACPA negative. These 2 groups show very similar clinical presentations in the early phase of the disease, but ACPA positive patients develop a much more erosive disease. Consequently, ACPA-positive individuals with minor complaints [undifferentiated arthritis (UA)] should be treated. It has been reported that ACPA-positive UA patients responded more positively to treatment with methotrexate (MTX) than ACPA-negative patients. UA patients with low or intermediate ACPA concentrations respond better to MTX than ACPA-positive UA patients with high ACPA concentrations, indicating that in patients with high ACPA concentrations the treatment with only MTX might be insufficient (Ann Rheum Dis 2010;69:1333–7).

Rik Lories: My main expertise is ankylosing spondylitis and related spondyloarthritides. I have learned that besides nonsteroidal antiinflammatory drugs, anti-TNF drugs are now essential in the treatment algorithm. The widespread use of magnetic resonance imaging, a technique that can visualize inflammation, has changed clinical practice. Outcome prediction is still more difficult but increasingly successful in other diseases, such as RA. Studies of other systemic diseases, such as SLE, are currently also exploring the use of biologics, and new clinical discoveries are eagerly awaited.

Michael M. Ward: This is difficult to answer because there are many different autoimmune diseases. In general, the treatment approach is to quickly control symptoms and inflammation to limit the potential for permanent organ damage, whether in the joints, skin, vessel wall, kidney, or other organs, and improve quality of life. Treatment guidelines for RA suggest only slightly more aggressive medications for patients with longer durations of RA, compared with those patients with RA of <6 months’ duration; rather, treatment is guided more by the persistence of active arthritis and the presence of poor prognostic factors, such as poor physical functioning, extra-articular features, bone erosions on radiographs, and presence of high concentrations of rheumatoid factor or ACPAs. In patients with active antineutrophil cytoplasmic antibody–associated vasculitis, a staged concept of treatment has taken the form of an initial 6-month period of more-intensive immunosuppression to achieve remission, followed by a more prolonged period of less-intensive immunosuppression to maintain or “consolidate” remission, in an attempt to lessen toxicity of treatment. A similar remission-induction and remission-maintenance paradigm has been used in recent trials of proliferative lupus nephritis. Although the validity of stages of treatment responsiveness is questionable, the idea of initial aggressive treatment to limit inflammation and then reducing treatment intensity has good clinical merit. In granulomatosis with polyangiitis (Wegener disease), there are conflicting data on the ability of anti–proteinase 3 antibody levels to predict clinical relapses.

Can you speculate on how the diagnosis and clinical management of autoimmune diseases will change in the next 10 years? What will be the main factors driving this change?

Walther J. van Venrooij: The example of RA shows how important early diagnosis is for more-effective treatment to avoid irreparable damage to joints and organs. Unfortunately, most research money is directed toward the discovery of new therapeutics. New and early serologic predictors of autoimmune diseases can possibly be found when detailed studies of aberrant chemical modifications of proteins in disease (e.g., phosphorylation and methylation) are performed.

Rik Lories: Better knowledge will lead to more personalized medicine. Novel strategies, often highly effective, are available. One of the challenges will be to translate this progress seen in patients with RA and spondyloarthritis to other, more-rare systemic diseases. An additional challenge will be the management of the individual patient. Different treatment options are available these days, and switching is common when a patient feels a return of symptoms. However, clinical care should avoid jumping to arms immediately and should carefully assess each question at the individual level. This will improve the long-term outcome and the safety profile of the drugs used.

Michael M. Ward: The trend in the diagnostics in autoimmune diseases is clearly toward “-omics,” including genomics and proteomics. As this technology improves, it may be possible to identify specific autoantibody profiles, for example, that could lead to more accurate or earlier diagnosis. Treatments will increasingly be individualized and chosen on the basis of knowledge of the prime mediators (e.g., cytokines or signaling pathways) of inflammation in a particular patient. It is already clear that among patients with the
same disease, some patients respond to one anticytokine biologic but not to a different anticytokine treatment, likely because different pathways are playing the key role. In the future, perhaps somewhat further in the future than the next 10 years, these differences will be identified prospectively so appropriately targeted treatment can be chosen.

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