Rapid review

Autoantibodies as predictors of disease

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Context Many human diseases are the result of autoimmune attack, presumably related to a loss of tolerance to self. Autoimmune disease can be divided into either organ-specific illnesses, such as thyroid disease, type 1 diabetes, and myasthenia gravis, or systemic illnesses, such as rheumatoid arthritis and systemic lupus erythematosus. The pathogenesis of autoimmune damage also segregates autoimmune disease in that some diseases or manifestations are mainly induced by autoantibodies. Pathogenesis may be mainly mediated by autoimmune T lymphocytes. Notwithstanding the underlying mechanism of disease, virtually all autoimmune diseases are associated with circulating autoantibodies, which bind self-protein. Furthermore, for many diseases these autoantibodies are found in serum samples many years before disease onset.

Starting point In the past several years a new autoantibody specificity has been identified in the sera of patients with rheumatoid arthritis. These autoantibodies bind citrulline, a post-translational modification of arginine. Markus Nielen and colleagues recently studied the presence of these autoantibodies and rheumatoid factor in blood donors who later developed rheumatoid arthritis (Arthritis Rheum 2004; 50: 380–86). About half the patients were positive for at least autoantibody at a median of 4-5 years before the onset of the disease. The negative predictive value of these tests was high, while the positive predictive value was very high.

Where next? Autoantibodies might not be directly responsible for many of the manifestations of autoimmune disease, but they are markers of future disease in presently healthy individuals. Long-term large studies of outcome are needed to assess the use of assaying autoantibodies for prediction of disease. Such data could lead to intervention trials to prevent autoimmune disease, as are already underway in type 1 diabetes.

Although the incidence and prevalence of individual autoimmune diseases are not high (table), the population burden of the disease is large and underestimated. Serum autoantibodies, which appear long before onset of clinical disease, are a characteristic feature, as recently emphasised by Markus Nielen and colleagues. Studying patients with rheumatoid arthritis, these researchers found antibodies for IgM rheumatoid factor or anticyclic-citrullinated-peptide (anti-CCP) in serum samples taken a median of 4-5 (range 0-1–13-8) years before disease onset. The negative predictive value of these tests was 75% and the positive predictive value was even higher (100%). Thus the presence of autoantibodies in otherwise healthy individuals might be a marker of future autoimmune disease or, alternatively, certain autoantibodies might predict the course in a person with established disease.

Autoantibodies in rheumatoid arthritis

In another recent study of individuals with stored serum who went on to develop rheumatoid arthritis, Rantapää-Dahlqvist et al showed the predictive ability of anti-CCP, which is highly sensitive for rheumatoid arthritis. In a population-based survey of over 150 000 people in northern Sweden, these investigators found 83 who went on to be diagnosed with rheumatoid arthritis. Anti-CCP was found in a third of these 83, on average several years before onset of disease. The negative predictive value of this test was high, and the positive predictive value in a population with joint symptoms was 62%.

Autoantibodies in pregnancy

Autoantibodies associated with rheumatoid arthritis may also predict disease in healthy individuals in whom hormonal changes might be a trigger for autoimmune disease. In 401 healthy pregnant women followed up for a year, none with a negative rheumatoid factor developed rheumatoid arthritis, whereas two of nine with rheumatoid factor developed the disease. Similar data have been seen for postpartum autoimmune thyroid disease. In 1594 consecutive pregnant women, antithyroid-peroxidase autoantibodies (anti-TPO) were found in 83 (5-2%) when studied within 3 days of delivery, and autoimmune thyroid disease developed in 38 (2-4%) in the year of follow-up. Of the 38 who developed clinical disease, 37 had a titre over 1:1600, whereas of the 33 not developing clinical disease, 30 had a titre under 1:400. Anti-TPO at 1:1600 or higher at delivery had a 97% sensitivity and a 91% specificity for postpartum autoimmune thyroid disease. In another study, 291 pregnant women were tested for anti-TPO at 12 and 32 weeks' gestation and 4 weeks' postpartum. 15 developed autoimmune thyroid disease in the first year postpartum, and ten of these had anti-TPO. Again, the titre of anti-TPO was lower in those that did not develop clinical disease.

The prediction of type 1 diabetes after gestational diabetes by diabetes-associated antibodies at the time of delivery has been studied. 184 women with gestational diabetes were studied for HLA, antiglutamic-acid-decarboxylase (GAD) and antityrosine-phosphatase-like protein.
and islet-cell autoantibodies, and followed up for 5 years. 43 were positive for at least one diabetes-associated autoantibody, and 24 of these developed type 1 diabetes. A combination of HLA typing and autoantibody measurement was highly predictive of future type 1 diabetes. Thus, in pregnancy, future autoimmune diseases can be predicted with autoantibody assay at delivery. Of course, the postpartum woman might be particularly at risk for autoimmune disease. So whether or not such testing can be done in a general population with high positive and negative predictive values is not known.

Another pregnancy-related condition has been studied. Mothers with the autoantibodies associated with systemic lupus erythematosus and Sjögren’s syndrome, anti-Ro (or SSA) and anti-La (or SSB), can give birth to babies with neonatal lupus, which is caused by maternal antibody that crosses the placenta. Most mothers of these babies are healthy at the time of delivery, but several studies have done long-term follow-up. The initial study by McCune et al followed up 21 mothers for an average of 4·5 years after birth of a baby with neonatal lupus. Eight of the 11 who were initially asymptomatic became symptomatic in follow-up, mostly with dry eyes, compared with only one of 37 control mothers. With objective testing of keratoconjunctivitis sicca, another study found that 14 mothers asymptomatic at delivery of a baby with congenital heart block had at least one abnormal test at a mean 10·6 years from delivery. Waltuck and Buyon found that of 22 healthy mothers, 11 remained well, three developed Sjögren’s syndrome, three developed systemic lupus erythematosus, and seven developed an undifferentiated syndrome. So these mothers who have babies with neonatal lupus and anti-Ro/La in their serum subsequently commonly develop symptoms consistent with Sjögren’s syndrome, which is strongly associated with the simultaneous finding of anti-Ro and anti-La.

Autoantibodies in other diseases

Persons serving in the US military have blood drawn and serum stored in the US Armed Services Serum Repository about every 2 years, and the Repository has about 30 million samples from 6 million individuals. My colleagues and I identified 132 military personnel diagnosed with systemic lupus erythematosus who had at least one sample in the Repository before the diagnosis, and two matched controls for each future patient with systemic lupus erythematosus. Antinuclear antibodies and anti-Ro appeared as early as 10 years before first onset of disease, with 47% having anti-Ro and 78% having antinuclear antibody before onset. Thus studies of anti-Ro-La-positive mothers giving birth to babies with neonatal lupus may be of too short a duration. Antibodies binding native (or double-stranded) DNA appeared about 2-5 years before diagnosis in 55% of the cohort, whereas antibodies against nuclear ribonuclear protein and anti-Sm appeared only a few months before disease. Almost no new antibodies appeared after the onset of clinical disease. Furthermore, a few controls had antinuclear antibodies or anti-Ro but no other specific antibody. Thus the presence of lupus-associated antibodies was both sensitive and specific for the subsequent occurrence of systemic lupus erythematosus.

Primary biliary cirrhosis is associated with antimitochondrial antibodies, and the main target of these autoantibodies is the E2 component of the pyruvate dehydrogenase complex (PDC). Kisand and colleagues studied antimitochondrial antibodies in 1461 individuals and antibodies to native purified PDC in a subset of 497. Eight asymptomatic individuals with at least one of these autoantibodies were followed up for 9 years.

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Systemic diseases

- Systemic lupus
- Sjögren’s syndrome
- Addison’s disease
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Three developed abnormal liver-enzyme tests and anti-mitochondrial antibodies by immunofluorescence. The five who did not develop liver-enzyme abnormalities had lower anti-E2-PDC titres, only one immunoglobulin class binding E2-PDC, and antibodies that did not inhibit enzyme activities. Antibody-negative individuals were not followed up.

In Addison’s disease, use of autoantibodies, both anti-adrenal-cortical (ACA) and anti-21-hydroxylase antibodies, has been studied. Organ-specific autoimmune diseases occur together more than expected by chance, so patients with one disease are at higher risk for another autoimmune disease. In the initial study from 1983, one of 284 healthy individuals had ACA and this individual went on to develop Addison’s disease. Meanwhile, eight of 1045 individuals with other organ-specific autoimmune disease had these antibodies, of which five had normal adrenal function. Antibody-negative individuals were not followed up.

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adrenal autoantibodies and similarly mildly impaired adrenal function (increased plasma renin activity, decreased aldosterone, and decreased cortisol response to synthetic adrenocorticotropic hormone), two progressed to overt Addison’s disease and eight showed worsened adrenal function.19 This study was not a randomised trial, but the data suggest that incipient adrenal failure and adrenal autoimmunity can be halted.

Autoantibodies in diabetes

While progress about the prediction of future disease by autoantibodies in the examples above is substantial, this progress pales compared with that made in type 1 diabetes mellitus.22 Many studies have assessed GAD, anti-insulin, anti-islet-cell, and/or anti-IA-2A in non-diabetic siblings of patients with autoimmune diabetes. The presence of two or more of these autoantibodies is highly correlated with patients with autoimmune diabetes. The prediction of diabetes more of these autoantibodies is substantial, this probably cannot be extrapolated to the general population, or those with one organ-specific autoimmune disease, follow-up of special populations, such as pregnant women diseases with widely varying prevalences. Thus testing and probabilities, which will be greatly different in autoimmune diseases. Once natural history of autoimmune diseases. Once natural history is established and predictive values of autoantibodies known, intervention trials in diseases other than diabetes will be ready to start. I have no conflict of interest to declare.

Conclusions

Thus the data indicate that autoimmunity disease is preceded by a long preclinical phase in which individuals can be identified by the presence of autoantibodies. Such identification might allow immunological treatment where by disease is prevented, as is already being studied in diabetes. Alternatively, even if disease cannot be prevented, perhaps life-threatening but treatable conditions could be avoided, such as thyroid storm and Addisonian crisis. For the all diseases, except type 1 diabetes, further work is needed to assess the natural history of disease progression and predictive value of autoantibodies in healthy individuals. Predictive values will vary with pre-test probabilities, which will be greatly different in autoimmune diseases with widely varying prevalences. Thus testing and follow-up of special populations, such as pregnant women or those with one organ-specific autoimmune disease, probably cannot be extrapolated to the general population, which is at lower risk of disease.

Encouragingly, high-throughput protein-array techniques are already available in which hundreds of autoantibody specificities can be analysed simultaneously.23 This technology might allow prospective studies of large numbers of healthy individuals for the development of many autoimmune diseases. Another alternative is to apply this technology to existing databases, such as the US Armed Forces Serum Repository.24 Testing these samples for multiple autoantibodies with protein arrays and correlating the results with diagnosed diseases might answer several important questions about the preclinical natural history of autoimmune diseases. Once natural history is established and predictive values of autoantibodies known, intervention trials in diseases other than diabetes will be ready to start.

References