Discussing modern updated criteria for judging autoimmune disease

By Wan-Chung Hu MD PhD  
Department of Clinical Pathology  
Far Eastern Memorial Hospital  
New Taipei City, Taiwan R.O.C.

About the author:

Wan-Chung Hu got a MD degree from National Taiwan University College of Medicine. Then, he went to Department of International Health, Johns Hopkins University School of Public Health to get a vaccine science PhD. His thesis topic is the host immune response against Plasmodium falciparum by using functional genomics study. He also conducted a SARS-CoV immunopathogenesis study collaborating with Graduate Institute of Immunology, National Taiwan University. After PhD study, he did his postdoctorate in Genomics Research Center of Academia Sinica, Taiwan. His topic was cancer immunotherapy. Then, he is currently doing resident training in Department of Clinical pathology, Far Eastern Memorial Hospital, Taiwan.

Abstract

Witebsky’s criteria for autoimmune diseases were used for decades since 1957. His postulates are: 1. Direct demonstration of free circulating antibodies active at body temperature 2. Recognition of the specific antigen 3. Production of antibodies against same antigen in experimental animals 4. Experimental animal demonstrates same tissue changes in human. More updated and applicable criteria for autoimmune disorders are required due to recent advance in molecular immunology. Here, I propose new criteria. Possible criteria is HLA association. Probable criteria is HLA association plus TH subtype restriction without pathogen. Definite criteria is experimentally reproducible by autoantibody or self reactive T cell transfer. Optional criteria is Clinical or pathology clues. This new criteria is more practical. It should help to explore the actual disease pathophysiology and lead to better diagnosis and treatment strategies.

Main text

Professor Ernst Witebsky proposed a criteria for autoimmune disease in 1957. His
postulates are: 1. Direct demonstration of free circulating antibodies active at body temperature 2. Recognition of the specific antigen 3. Production of antibodies against same antigen in experimental animals 4. Experimental animal demonstrates same tissue changes in human. (1)

Because of the advance in immunology, the original Witebsky criteria are outdated. Dr. Noel Rose and Dr. Constantin Bona proposed a revised Witebsky criteria in 1993. These criteria are: 1. Auto-antibodies detectable in all cases of disease 2. Experimentally reproducible by immunization with antigen 3. Experimental disease must show immunopathological lesions that parallel those in natural disease 4. Transferable by serum or lymphoid cells. (2)

In addition, the modern revisions of Witebsky criteria consider three types of evidences: 1. Direct evidence from transfer of pathogenic antibody or pathogenic T cells 2. Indirect evidence based on reproduction of the autoimmune disease in experimental animals 3. Circumstantial evidence from clinical clues.

According to current immunology research, I think these criteria are not applicable. We should have more updated criteria for autoimmune diseases. Thus, I will introduce my suggested criteria below:

Possible criteria; HLA association

MHC (HLA) molecule is the key molecule to initiate adaptive immunity. If there is a HLA association in a certain disease, it is highly possible that adaptive immune response is triggered in this disease. That is the reason why HLA link was noted in this disease. And, HLA association is the signature of this disease. This host adaptive immunity plays an important role in the pathophysiology of this certain disease. If HLA association is not important, it won’t be a signature for this disease. In addition, adaptive immune activation is due to specific immune response against certain antigens including autoantigens. If the HLA molecule recognizes a specific autoantigen, it will cause subsequent immune reaction to generate effective or memory B or T cells. Thus, a HLA association is a possible criteria for autoimmune diseases.

Probable criteria: HLA association & TH subtype restriction without pathogen

Many host immunological pathways are discovered including acute immunities:
TH1/TH2/THαβ/TH22 and chronic immunities: TH1like/TH9/TH3/TH17. The acute phase of immunity is triggered by THfh and the chronic phase of immunity is triggered by Treg. These findings are due to the contribution of modern molecular immunology. TH1/TH1like links to type 4 delayed type hypersensitivity. TH2/TH9 links to type 1 IgE mediated allergy reaction. THαβ/TH3 links to type 2 antibody cytotoxic hypersensitivity. TH22/TH17 links to type 3 immune complex and complement mediated hypersensitivity. Thus, four types of host immunological pathways perfectly match the four types of hypersensitivities. Certain existence of a specific tract of host immunological pathway stands for a specific activation of a specific type of hypersensitivities. TH1 if a certain immunological pathway continues to exist in a disease, it represents that this specific immunological pathway plays an important role in the pathogenesis of this disease. For example, TH1 immunity in type 1 diabetes is a case. Th1 immunity actually is the cause of pancreatic cell destruction. The specific division of TH1 immunological pathway is the reason to cause type1 diabetes. We can deduct that if there is a persistent activation of a subtype of host immunological pathway, we can infer the autoimmunity plays an important role in pathophysiology of this specific disease. It means adaptive B cells or T cells must exist in the disease for pathogenesis. It will be because the host immunity is not non-specific immune reaction or inflammation. I call this phenomenon “T helper subtype restriction”. It is worth noting that this criteria needs to exclude active infective agent infection. Thus, it can represent that the up-regulation of specific tract of host immunological pathway is due to self autoantigen. How come is there up-regulated specific host immunological pathway without active infection? There should be an autoimmune etiology against self antigens. This probable criteria include HLA association and T helper subtype restriction without pathogen. If this phenomenon exists, we can have more confidence to just this disease is an autoimmune disease. (3-11)

Definite criteria: Experimentally reproducible by autoantibody or self reactive T cell transfer

This criteria is to use animal model to confirm if this disease is an autoimmune disease. We can not direct use patients to let them receive autoantibody or self reactive T cells. It is not applicable for the three above Witebsky criteria. The only thing we can do is to use animal model to see if the pathogenesis of the disease is reproducible after transferring of autoantibody or self reactive T cell from an affected animal to a new animal. Then, this will provide the evidence to prove if this specific disease is an autoimmune disease or not.
Optional criteria: Clinical or pathology clues

Other clinical clues or pathological clues can help to judge if the disease is an autoimmune disease. If a target organ is suffering clear evidence of immune cell infiltration, this disease can be considered in the category of autoimmune disease. Other epidemiological data can also help to judge if this disease is an autoimmune disorder. These further evidences are listed as supporting optional criteria for judging whether this disease is an autoimmune disease.

Bradford Hill criteria for causation include strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy. Autoimmune etiology can fit the above criteria with the help of modern biostatistics methods. Immune mechanism is especially fit the “specificity” criteria because autoantibody or self-reactive T cell can recognize a specific target organ to cause a certain disorder. Because many diseases have HLA association, it is highly possible that more and more diseases will be re-categorized to autoimmune disorders. Immunity is a double-edged sword, it will kill pathogens as well as self. This new criteria can help to explore the real mechanism of disease pathogenesis to find out better diagnosis or treatment strategies.

Reference
2. Rose NR and Bona C. Defining criteria for autoimmune diseases (Witesky’s postulates revisited). 1993;14:426-430
5. Trifari S, Kaplan CD, Tran EH, Crellin NK, Spits H. Identification of a human helper T cell population that has abundant production of interleukin 22 and is distinct from T(H)-17, T(H)1 and T(H)2 cells. Nat Immunol. 2009;10: 864-871.
7. Dominguez-Villar M, Baecher-Allan CM, Hafler DA. Identification of T helper type


