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Development of autoantibodies precedes clinical manifestations of autoimmune diseases: A comprehensive review

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ABSTRACT

The etiology of autoimmune diseases is due to a combination of genetic predisposition and environmental factors that alter the expression of immune regulatory genes through various mechanisms including epigenetics. Both humoral and cellular elements of the adaptive immune system play a role in the pathogenesis of autoimmune diseases and the presence of autoantibodies have been detected in most but not all autoimmune diseases before the appearance of clinical symptoms. In some cases, the presence or levels of these autoantibodies portends not only the risk of developing a corresponding autoimmune disease, but occasionally the severity as well. This observation is intriguing because it suggests that we can, to some degree, predict who may or may not develop autoimmune diseases. However, the role of autoantibodies in the pathogenesis of autoimmune diseases, whether they actually affect disease progression or are merely an epiphenomenon is still not completely clear in many autoimmune diseases. Because of these gaps in our knowledge, the ability to accurately predict a future autoimmune disease can only be considered a relative risk factor. Importantly, it raises the critical question of defining other events that may drive a patient from a preclinical to a clinical phase of disease.

Contents

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1. Introduction

The presence of autoantibodies is a hallmark of many autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, primary biliary cirrhosis, multiple sclerosis, autoimmune hepatitis, drug-induced lupus, autoimmune thyroid disease and type 1 diabetes. Clearly genetics and the environment play significant roles in loss of tolerance [1–9]. In this review, we will present the evidence for preclinical disease in several autoimmune diseases and we will speculate on mechanisms that drive the patient from a preclinical to a clinical phase. Because there has not been any reports concerning the appearance of autoantibodies before clinical symptoms of myasthenia gravis and anti-phospholipid syndrome, and genetic factors accounting for these two autoimmune diseases are obscure, these two diseases are not discussed in the present article. The appearance of autoantibodies in specific autoimmune diseases before disease onset is presented below and is summarized in Table 1. The basis for the development of autoimmunity is generally unknown, but consensus appears to indicate that chance plays a significant role. Current knowledge indicates that a combination of genetic predisposition, the environment, and how the environment influences the turning on or turning off of genes is in play, but defining specifically what genes or environmental factors are important has been elusive, although there are many that have been proposed [10,11]. In many autoimmune diseases, the presence of autoreactive T cells and autoantibodies directed against self-tissues suggest that adaptive immunity is required for pathogenesis, but this may only be a small part of the picture [10]. The innate immune system may play a significant and critical role as well. Although the signature autoantibodies of most autoimmune diseases are determined (Table 2), in several autoimmune diseases, such as psoriasis, autoantibodies to a specific protein have yet to be discovered.

2. Autoantibodies preceding clinical presentation in autoimmune diseases

2.1. Primary biliary cholangitis (PBC)

Our laboratory has focused on PBC, whereby the serologic

Table 1
Development of autoantibodies before the clinical onset of autoimmune diseases.

Disease	Latency time	Autoantibodies preceding clinical disease	Ref.
PBC	0.9–19 years [23]	AMAs	[23,400,401]
RA	0.1–13.8 years [54] 1.1–5.9 years [55]	RFs, ACPAs, anti-CarP antibodies	[48,54,55,402]
SLE	0.88–3.68 years [83] 1.1–8.1 years [120]	ANAs Anti-dsDNA antibodies Anti-Ro antibodies Anti-La antibodies Anti-Sm antibodies Anti-nuclear ribonucleoprotein antibodies Anti-phospholipid antibodies Anti- type VII collagen antibodies	[83,119–121]
T1D	Within 10 years [403] 1.7–6 years [165]	IAAs GADAs Anti-pancreatic hsp60 antibodies	[165,167,403]
AITD	Up to 7 years [174]	Anti-TG antibodies Anti-TPO antibodies Anti-TSHR antibodies	[174,178,192–194]
MS	1–3 years [240]	Anti-proteasome antibodies Anti-MBP antibodies Anti-MOG antibodies	[211,215,240,241]
Celiac disease	Not reported	Anti-reticulin antibodies Anti-EMAs, AGAs Anti-tTG antibodies	[246,280–283,404–407]
AAD	3 months to 10 years [309]	Anti- 21-OH antibodies Anti- 17-OH antibodies Anti-SCC antibodies	[290,309,310]
SSc	Not reported	ATAs, ACAs, ARPAs	[340–342]
IBD	UC: 4.4 years [381] CD: 4.5 years [381] or 3 years [380]	ANCAs, ASCAs, Anti-OmpC and flagellin CBir1 antibodies	[380,381]
SS	7 years	ANAs, RFs, anti-SSA and-SSB antibodies	[397]

AbbreviationsAMAs, anti-mitochondrial antibodies; RFs, rheumatoid factors; ACPAs, anti-citrullinated peptide antibodies; anti-CarP antibodies, anti-carbamylated peptide antibodies; ANAs, anti-nuclear antibodies; dsDNA, double stranded DNA; IAAs, insulin autoantibodies; GADAs, the 65-kDa form of glutamic acid decarboxylase autoantibodies; TG, thyroglobulin; TPO, thyroid peroxidase; TSHR, thyroid stimulating hormone receptor; MBP, myelin basic protein; MOG, myelin oligodendrocyte glycoprotein; EMAs, anti-endomysial antibodies; AGAs, Anti-gliadin antibodies; tTG, tissue transglutaminase; OH, hydroxylase; SCC, the cytochrome P450 side chain cleavage enzyme; ATAs, anti-topoisomerase I antibodies; ACAs, anti-centromere antibodies; ARPAs, anti-RNA polymerase III antibodies; ANCAs, anti-neutrophil cytoplasmic antibodies; ASCAs, anti-saccharomyces cerevisiae antibodies; OmpC, outer-membrane porin C; SSA, Sjögren's syndrome A; SSB, Sjögren's syndrome B.