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Invited critical review

Autoantibodies in pre-clinical autoimmune disease

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ABSTRACT

The presence of autoantibodies is characteristic of autoimmune diseases. It is widely accepted that autoantibodies provide crucial diagnostic and prognostic information for autoimmune diseases. Indeed, numerous studies have demonstrated that the appearance of autoantibodies precedes the clinical onset of autoimmune diseases. We performed a literature review regarding the appearance of autoantibodies that preceded the clinical onset of autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, primary biliary cirrhosis, inflammatory bowel disease, and multiple sclerosis. Herein we review and comment on the major findings of these studies.

Contents

1. Introduction

The onset and development of autoimmune disease (AID) are the consequence of interactions between genetic and environmental factors, which results in dysregulation of the immune system, and is characterized by the presence of autoantibodies and autoreactive T cells. Under these circumstances, immune system antimicrobial defenses react against normal components of the body and result in organ-specific or systemic immunopathology. Thus, one of the most frequent characteristics of AID is the presence of circulating autoantibodies. These autoantibodies provide crucial diagnostic and prognostic information for the management of AID.

Autoantibodies are not necessarily specific for AID, as the autoantibodies can also appear in the blood of healthy individuals or under

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some special situations, such as infections and the pre-clinical phase of AID. Recently, the association between autoantibodies and risk of AID has attracted considerable attention. Numerous studies have shown that detectable autoantibodies precede the clinical onset of AID [1–3], and therefore could be a possible tool for AID screening or early diagnosis. We performed a literature review regarding evidence of autoantibodies during the pre-clinical phase of AIDs and the implications of these findings.

2. Evidence that autoantibodies precede AID

2.1. Rheumatoid arthritis (RA)

Rheumatoid factor (RF) is the most widely used autoantibody to diagnose RA [4]. A positive RF was considered an important criterion by the American Rheumatism Association (AHR) in 1958 [5], the American College of Rheumatology (ACR) in 1987 [6], and the ACR/European League Against Rheumatism (EULAR) in 2010 [7];anti-cyclic citrullinated peptide (anti-CCP) has now been included in the diagnostic criteria of the EULAR [7]. The testing methods used for RF have greatly improved during recent years [4], from the classic Waaler–Rose test (agglutination of sheep red blood cells sensitized with rabbit IgG) and latex particle assays to automated techniques, such as nephelometry and ELISA. This review focuses on published reports that were based on automated RF assays.

Numerous studies have demonstrated that autoantibodies can be detected in the blood of individuals who are free of RA symptoms, but who developed RA years later, including RF [8–17], anti-CCP [9–16,18–21], anti-mutated citrullinated vimentin (anti-MCV) [15], and anti-peptidylarginine deiminase 4 (anti-PAD-4) [14]. Some studies have also shown that RF [22–24], anti-CCP [22–25], and anti-MCV [23] are detectable in the blood of undifferentiated arthritis (UA) patients, with UA defined as an inflammatory arthritis for which no definitive diagnosis can be made [26]. For patients with arthralgias, RF, anti-CCP [27], and anti-carbamylated protein (anti-CarP) antibodies [22] are associated with a higher risk of RA. These studies [8–21], with sample sizes for RA ranging from 49 to 183, and a median follow-up time ranging from 1 to 5 years, all reported that various isotypes of autoantibodies were increased in individuals who were free of RA at the time of blood sampling, but developed RA later, as compared with those who did not develop RA during the follow-up period. The positive rates for RF or anti-CCP antibodies in pre-clinical RA patients range from 10% to 60%, which is higher than healthy controls [9–20].

The prevalence of these antibodies increase at times close to the onset of RA [9–11,13,14,17,19,20,28,29], and these incremental increases remain after the diagnosis of RA was established [14,28]. In addition, the higher the anti-CCP antibody titer and the younger the individual, the shorter the time between a positive autoantibody test and the onset of RA [9,12,18]. The median time between a seropositive result and the onset of RA symptoms was longer for anti-CCP-positive individuals than IgM-RF-positive individuals [12,13]. Thus, the presence of IgM-RF is the consequence of inflammation, whereas the earlier appearance of anti-CCP antibodies suggests a pathophysiologic process [12]. These autoantibodies are also associated with the future clinical characteristics of RA. Anti-CCP antibodies, but not RF, for example, are highly associated with the development of erosive RA [9].

Unlike previous studies that were based on a nested case–control design, Nielsen et al. [30] conducted a general population-based cohort study with a sample size of 9712 and a maximum follow-up period of approximately 28 years to determine the association between detectable RF and future risk of RA; RA occurred in 183 cases. Nielsen et al. [30] found that the cumulative incidence of RA increased as the titer of RF increased. For women 50–69 years of age who smoked and had RF values >100 IU/mL, 1 in 3 developed RA within 10 years from the time of blood sampling.

Taken together, it is clear that the presence of RF and anti-CCP antibodies usually precedes the onset of RA. These results indicate that in apparently healthy individuals, as well as individuals with UA and arthralgias and positive RF or anti-CCP titers, careful follow-up should be provided to aid in an early diagnosis.

2.2. Systemic lupus erythematosus (SLE)

One early study in which 23 asymptomatic pregnant women with positive anti-Ro or anti-La titers were followed for many years reported that four developed SLE, which suggested that anti-Ro or anti-La antibodies preceded the development of SLE [31]. In another study, Aho et al. [32] reported that 10 of 16 SLE patients were positive for antinuclear antibodies (ANA) before the onset of SLE, which was a much higher rate than controls.

The results from the U.S. Department of Defense Serum Repository ($n = 130$; longest follow-up time, 9.4 years) showed that the presence of ANA, anti-Ro, anti-La, anti-dsDNA, anti-Sm, anti-phospholipid (APL), and anti-nRNP antibodies and RF preceded the onset of SLE [33–37]. Among SLE patients, 88% were positive for at least 1 of these autoantibodies, which was a much higher percentage than healthy controls, and the prevalence of these autoantibodies increased after diagnosis [33,34]. Anti-Ro, anti-La, and APL antibodies were the earliest detectable autoantibodies during the pre-clinical phase of RA [33,37]. In addition, the presence of these autoantibodies was associated with incipient severe SLE. For example, patients who were positive for anti-dsDNA antibodies often developed renal disease [34,35], patients who were positive for IgG RF were more likely to develop arthritis [35], and positive APL was associated with malar rash and photosensitivity [36]. In addition, regular patterns exist among these autoantibodies. For example, the majority of La-positive pre-clinical SLE patients were also Ro-positive, and a significant overlap was observed between anti-dsDNA antibody-positive patients and anti-chromatin antibody-positive patients [37].

Additional evidence was reported by Eriksson et al. [38]. Similar to the study performed with the U.S. Department of Defense Serum Repository, Eriksson et al. [38] also found that anti-Ro, anti-RNP, anti-histone, anti-La, and anti-dsDNA antibodies and ANA were detectable in 63% ($n = 38$) of patients' serum samples 4.2 years before the onset of SLE symptoms and a confirmed diagnosis. ANA had the highest sensitivity (45.7%), followed by anti-dsDNA (20%) and anti-Ro antibodies (20%). Anti-Ro antibody was detected first in the serum of these patients, 6.6 years before the onset of SLE symptoms and 8.1 years before a diagnosis was made [38].

2.3. Sjögren's syndrome (SS)

In a study that followed 23 asymptomatic pregnant women who were positive for anti-Ro or anti-La antibodies for 5–9 years reported that 2 patients developed SS, which suggested that seropositivity for anti-Ro or anti-La preceded the development of SS [31]. In another study, which was also based on pregnant women, it was shown that almost all mothers developed SS symptoms during a 9-year follow-up (mean follow-up, 4.5 years) [39].

A recently published nested case–control study ($n = 44$) showed that 66% of SS patients were positive for ANA, RF, and anti-La or anti-Ra antibodies approximately 5 years before the onset of SS [40]. The time that patients were positive for these antibodies persisted for up to 18 years before the onset of SS [40]. The seropositive rate for these antibodies increased nearer the onset of SS [40].

In conclusion, the evidence that autoantibodies are predictors of SS is limited. Additional well-designed studies, particularly general population-based cohort studies, are needed to establish a relationship between other autoantibodies and SS.

2.4. Primary biliary cirrhosis (PBC)

PBC in the early stage is often asymptomatic. One-half of PBC patients will become symptomatic during a 5-year period, and almost all