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Challenges to the use of autoantibodies as predictors of disease onset, diagnosis and outcomes

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ABSTRACT

Autoantibodies (AA) are a serological hallmark of most autoimmune diseases. In contrast to genetic markers that show a predisposition for disease development, certain AA serve as diagnostic biomarkers and classification criteria for a number of these conditions. The role of AA is still not clearly understood: some are pathogenic, some disease specific and others serve as predictors of disease outcome, but little is known about those that protect against disease or serve as signatures of the inciting agent of autoimmunity. Because of growing evidence that some AA antedate clinical diagnosis, significant effort is being spent on gathering evidence regarding their value as predictors of disease onset and outcome. Although many studies have shown that specific AA are detected in the pre-clinical phase and are biomarkers of increased risk of developing an autoimmune disease, they are currently not widely used to determine risk or as a pre-clinical screen. Additional prospective and retrospective studies are urgently needed to determine the precise risk of developing autoimmune disease in the presence of various AA. Such studies must be attended by the development of strategies for earlier diagnosis and novel therapeutic interventions of early disease.

Contents

Abbreviations: AA, Autantibodies; ALBIA, Addressable laser bead immunoassay; ANA, Antinuclear antibody; CCP, Cyclic citrullinated peptide; dsDNA, Double stranded DNA; ELISA, Enzyme linked immunoassy; IIF, Indirect immunofluorescence; LIA, Line immunoassay; OSAD, Organ specific autoimmune diseases; RA, Rheumatoid arthritis; RNP, Ribonucleoprotein; SARD, Systemic autoimmune rheumatic disease; SjS, Sjögren's syndrome; SLE, Systemic lupus erythematosus; Sm, Smith antigen.

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1. Introduction

The serological hallmark of systemic autoimmune rheumatic diseases (SARD) is the presence of circulating autoantibodies (AA) directed to a variety of intra- and extracellular components. Historically, autoantibodies have been used primarily to assist the clinician in discerning, diagnosing and classifying SARD. Not long after the discovery of the LE cell and antinuclear antibodies (ANA), studies began to determine if AA were also involved in pathogenesis of the disease. In part, these investigations were fuelled by observations that AA in organ specific autoimmune disease (OSAD) such as Grave's disease, pernicious anemia and myasthenia gravis could be linked to the pathogenesis of these conditions [1]. A half century of studies of the pathogenic role of AA in SARD has been marked by considerable progress but, in many cases, the direct pathogenic role of most autoantibodies in SARD remains controversial.

As studies of AA progressed, it became clear that they were also seen in first degree relatives of patients, individuals with *forme fruste* disease and even in normal blood donors. The key question of whether these individuals progressed to develop SARD was prompted by studies of OSAD (reviewed in [1]). The efforts to determine if AA antedated the onset of clinical disease were undertaken with emerging evidence that in some cases they could predict flares, remission, clinical outcome and/or prognosis [1,2].

Most SARD are characterized by a spectrum of AA directed to a wide range of nuclear (ANA), cytoplasmic and extracellular components. The AA targets include proteins, nucleic acids, nucleoproteins, phospholipids, glycoproteins, and glycolipids. In systemic lupus erythematosus (SLE) alone there are now over 150 target autoantigens described [3] and the list continues to grow. In this review, the focus will be the challenges encountered in studying and applying information about AA as predictors of disease onset and flares, and response to therapy.

2. The challenges

Current concepts about the genesis and evolution of SARD is based on substantial evidence that SARD progress through a number of pre-clinical and post-diagnosis stages [1]. The genetic background of the host, including the major histocompatability complex and a growing number of single nucleotide polymorphisms (SNPs), are key to the development of SARD [4,5]. On the background of genetic 'susceptibility', a number of endogenous (stress, metabolic, physiologic) and exogenous (viruses, xenobiotics, toxins) factors may be responsible for triggering the disease [6]. The pre-clinical phase of the disease is manifested by a variety of cellular, mediator and AA changes that set the stage for progression to clinically overt disease. In some individuals, the presence of autoimmunity may be limited to a transient sub-clinical disease, while in others the disease progresses relentlessly, perhaps under the influence of a "second hit" by any number of endogenous or exogenous agents [7,8].

Table 1
Challenges to studies that determine the predictive value of autoantibodies

- Collection of sera before onset of clinical manifestations
- Retrospective cohort studies are difficult
- Meaningful prospective studies take longer than the lifetime of the initiating investigators
- Ethical, legal and insurability implications
- Dynamic nature of autoantibodies
- Myopia: studying restricted sets of antibodies.
- The importance of 'esoteric' autoantibodies
- Serum banks should be established to accommodate a variety of future biomarker studies

Table 2
Candidate cohorts to study

- Birth cohorts
- Children
- Adults and/or senior adults
  - Female, male
  - Ethnicity
- At risk groups
  - First degree relatives
  - Environmental exposure (silica, heavy metals, phytoestrogens, nicotine, etc.)
  - Endogenous risk factors (MHC, SNPs, Vitamin D status, etc.)
  - Autoimmune diseases
  - "False positive" ANA cohort
  - Primary immune deficiencies
    - Selective IgA
    - Common variable immunodeficiency
    - Complement (C1q, C2, C3, C4, etc.)

Serological studies of the induction and pre-clinical phases of SARD have been notoriously challenging (Table 1). First, the sera required for AA and other biomarker analysis is ideally collected before clinical manifestations appear. This is followed by the challenge of identifying the cohort that should be studied (Table 2). Most studies have focussed on adults, but studies of the pre-clinical outcomes of children bearing AA of various specificities have been reported. It is also likely that the rate and frequency of progression from pre-clinical status to overt disease in children is different from adults making studies in children not applicable to adults and vice versa. Although it is widely known that senior adults (>65 years) have both a higher frequency and titer of various AA [9], long term prospective studies of "normal" seniors have been very few. One exception was a remarkable study of Danish centenarians [10]. Although AA are thought to be specific for a certain autoimmune disease, in the induction and pre-clinical phase of the disease the individual bearing these AA may have signs and symptoms that are atypical before they evolve into the predicted clinical condition.

3. How long will meaningful studies take?

Meaningful studies of the predictive value of AA require a long horizon. It is well known that the progression of many SARD to a full clinical picture can take up to three decades. This means that from the pre-clinical phase through to the clinical phase and follow-up, a strategy for long term monitoring and follow-up is required and requires the engagement of at least two generations of investigators for studies that will have the power and applicability required of evidence-based medicine. Given that meaningful studies would cover at least one or two decades, it is very likely changes in diagnostic technologies and standards of care could render some data at considerable risk of becoming outdated or even irrelevant. For example, many laboratories are migrating to multiplexed diagnostic platforms that can provide a robust and rapid analysis of AA and other