Is Preclinical Autoimmunity Benign?

The Case of Cardiovascular Disease

Darcy S. Majka, MD, MS[a,b,*], Rowland W. Chang, MD, MPH[a,b]

KEYWORDS

• Autoantibodies • Autoimmunity • Preclinical • Cardiovascular disease
• Coronary artery calcification • Intima media thickness

KEY POINTS

- Preclinical rheumatic disease–related autoantibodies have been identified in stored samples before development of systemic lupus erythematosus and rheumatoid arthritis (RA).
- Autoreactive B cells can drive RA pathogenesis through generation of autoantibody-secreting plasma cells, presentation of autoantigens such as citrullinated peptides to T cells, production of proinflammatory cytokines, and formation of ectopic tertiary lymphoid structures, as are found in the RA synovium.
- It has been hypothesized that atherosclerosis might have autoimmune features because of the involvement of autoantigens and their autoantibodies in atherogenesis in both humans and animal models.
- Antiphospholipid antibodies, antinuclear antibodies, and RA–related autoantibodies have been associated with atherosclerosis in clinically active rheumatic diseases as well as in general population study samples.

INTRODUCTION

Preclinical autoimmunity, or the presence of autoantibodies before disease symptoms, has been well described for several autoimmune rheumatic diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren syndrome,

Funding Sources: R01 HL104047, P60AR064464 (Dr D.S. Majka); R21 AR062317, P60 AR064464, R01 AR054155, R01 HL104047 (Dr R.W. Chang).
Disclosures/Conflict of Interest: None.
[a] Division of Rheumatology, Northwestern University Feinberg School of Medicine, 240 East Huron, M300, Chicago, IL 60611, USA; [b] Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, 680 North Lake Shore Drive, Suite 1400, Chicago, IL 60611, USA
* Corresponding author. Northwestern University Feinberg School of Medicine, 240 East Huron, M300, Chicago, IL 60611.
E-mail address: d-majka@northwestern.edu

Rheum Dis Clin N Am 40 (2014) 659–668
http://dx.doi.org/10.1016/j.rdc.2014.07.006 **rheumatic.theclinics.com**
0889-857X/14/$ – see front matter

and antiphospholipid antibody syndrome (APS).[1–7] In studies of preclinical autoantibodies before SLE development, Arbuckle and colleagues[2] noted that autoantibodies less commonly associated with clinical sequelae of SLE such as antinuclear antibodies (ANA), anti-Ro, and antiphospholipid antibodies (APA) were present in the preclinical period more remote to clinical illness, whereas antibodies more specific for pathogenic features of SLE such as anti-Smith, antibodies against double-stranded DNA (dsDNA), and ribonucleoprotein (RNP) developed later, simultaneous to the onset of clinical features of SLE. Thus, benign autoimmunity was used to describe the earlier phase of autoantibody appearance during the preclinical period (**Fig. 1**). Certainly, there are many examples of autoantibodies occurring in disease-free individuals: RA-related autoantibodies and ANA occur in increased number and titer with age-related loss of tolerance[8–11]; healthy relatives of individuals with autoimmune rheumatic diseases also have increased rates of autoantibody positivity.[9,12,13] However, although ANA, rheumatoid factor, and APA may occur in the general population, individuals with such autoantibodies are also at increased risk for development of autoimmune rheumatic disease, with odds estimated as high as 10-fold to 30-fold.[6,7]

Autoantibodies are markers for autoreactive B-cell activation, which can drive disease pathogenesis through a variety of mechanisms. Autoreactive B cells lead to the generation of autoantibody-secreting plasma cells, formation of immune complexes, presentation of autoantigens to T cells and costimulation, as well as the production of proinflammatory cytokines, chemokines, and lymphangiogenic growth factors. But when does benign become pathogenic autoimmunity during disease development? Early on, autoantigens activate self-reactive B cells, leading to the formation of short-lived plasma cells secreting autoantibodies. However, if self-reactive B cells enter germinal centers, they may undergo somatic hypermutation and affinity maturation of B-cell receptors, immunoglobulin class switching, generation of long-lived self-reactive B cells, and differentiation into long-lived plasma cells secreting high-affinity Fc receptor-binding autoantibodies.[14,15] An example of such a transition

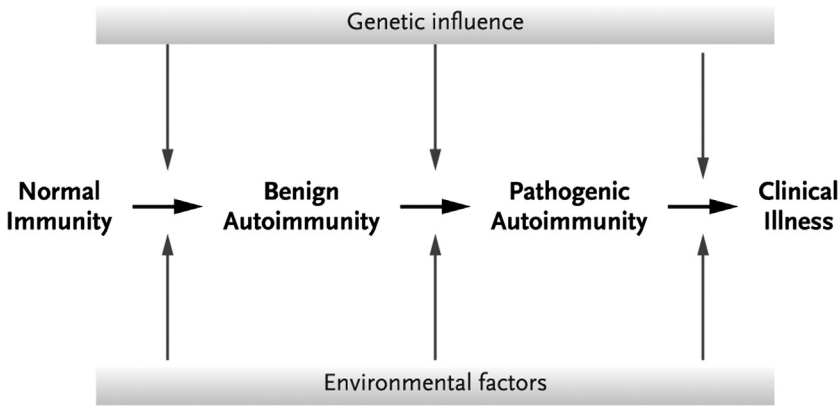

Fig. 1. Phases in the development of pathogenic autoimmunity. Normal immunity progresses to benign autoimmunity through the influence of genetic composition and environment. Later, benign autoimmunity progresses to pathogenic autoimmunity. Symptoms of clinical illness appear soon after pathogenic autoimmunity develops. (*From* Arbuckle MR, McClain MT, Rubertone MV, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. N Engl J Med 2003;349:1532; with permission.)