

Etiology of autoimmune disease: past, present and future

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Autoimmune disease may be defined as sustained pathology directly caused by a specific self-reactive immune response. This is opposed to the low levels of self-reactivity that are found in most chronic inflammatory diseases and in healthy people. While all true autoimmune diseases are driven by the innate and the adaptive immune response, disease specificity is often defined by the presence of IgG autoantibodies, which may arise as a result of inflammation rather than acting as the causative agent. The etiology of the majority of autoimmune disease is unknown, but because autoantibodies are so strongly associated with their respective diseases, it is reasonable to propose that they are an essential link between the disease phenotypes and the genetic and/or environmental factors that trigger them. Therefore, the keys to understanding autoimmune diseases with unknown etiology are their autoantibodies. Here, we consider progress in unravelling the etiologic triad of genes, environment and autoantibodies with a focus on three key autoimmune diseases: celiac disease (CD), rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). These provide worthy examples that will help decipher the future in the etiology of autoimmune diseases by focusing on evidence from the past and present.

Etiology: past

CD is probably the only autoimmune disease in which there is clear evidence for a specific etiology. Over two millennia ago, the Greeks observed that CD was a disorder of the digestive system, and speculated that it was due to dietary intolerance. The role of dietary gluten was established in the 1950s and a number of T-cell epitopes on gluten were later identified. However,

antibodies characteristic of the disease were not primarily against gluten, but an enzyme present in the endomysium of the gut, namely tissue transglutaminase. It has subsequently been speculated that the complex between the enzyme and its substrate, gluten, results in B-cell maturation after T-cell engagement; thus breaking tolerance to transglutaminase, which became a B-cell autoantigen. Subsequent studies have identified alleles of *HLA-DQ2* and *HLA-DQ8* as the main genetic susceptibility factors. Even though a major etiologic factor in CD was identified long before the autoantibody and susceptibility genes were documented, the disease forms a model of the gene/environment/autoimmunity paradigm [1]. More importantly for clinical practice, identification of the environmental factor has made CD the only curable autoimmune disease to date, simply by removing a critical part of the antigenic complex that drives it: eliminating gluten from the diet.

The last 10 years has been the decade of genomics; ever since the publication of the first human genome sequence in 2001 [2]. This major breakthrough gave birth to genome-wide association studies (GWAS), which were hailed as offering a platform for unbiased, genome-wide searches of susceptibility loci in thousands of patients suffering from any disease of interest. Indeed, among the single nucleotide polymorphisms identified using GWAS of approximately 395 diseases, 375 single nucleotide polymorphisms were identified in eight autoimmune or inflammatory diseases [101]. Although these have been important studies, in some ways the results are disappointing; most of the major susceptibility factors identified in autoimmune diseases had been previously described. The dominant genes were HLA

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class II polymorphisms, and these had already been discovered by tissue typing studies such as the classic study by Stastny of HLA-DR4 in RA over 30 years ago [3]. Likewise, the non-MHC class II genetic polymorphisms, such as PTPN22 and CTLA4, antedated the GWAS. These two genes confer susceptibility to Type 1 diabetes, RA and SLE [4], indicating increased risk of autoimmunity in general rather than any specific disease. While GWAS reports have identified a number of new candidate loci, the relative risk they are generally associated with is small (in the region of 1.1–1.2), and it is now felt that these loci may be of more value in indicating pathogenic pathways rather than identifying etiologic factors. It remains possible that some of these polymorphisms may have a larger role in small subsets of patients, nevertheless, it seems evident that genetics alone cannot predict disease. For example, SLE, which is classically “the queen of autoimmune diseases”, is known to have a strong genetic component, yet the concordance rate between monozygotic twins is only 25%, indicating that environmental factors must play an important role [5].

Etiology: present

The current decade represents a progression of genomics towards the study of gene/environment associations. Unlike genes, which can now be measured with precision by sequencing, environmental factors are notoriously difficult to document with accuracy. One of the most measurable environmental exposures is smoking, often cataloged by pack years or a status of ‘never/ever’. Smoking is associated with a number of chronic inflammatory and malignant diseases, but it is smoking and RA that represent the best examples of the gene/environment/autoantibody triad since the model was exemplified in CD. The first evidence for a gene/environment association was in a study that reported that in twins that were discordant for RA, those with RA were almost invariably those who smoked. It was later established that the risk of smoking was restricted to those that combined the presence of anticitrullinated protein autoantibodies (ACPAs), measured by the anticyclic citrullinated peptide (CCP) assay, and the presence of the HLA risk alleles for RA, termed the shared epitope (reviewed in [6]). The anti-CCP test is a diagnostic test designed to capture the whole family of ACPAs in RA, and approximately half of patients who are positive also carry antibodies to citrullinated α -enolase, measured with a peptide termed citrullinated enolase peptide 1 (CEP-1) [7]. In a large collaborative study of RA patients, the combined effect of shared epitope, PTPN22 and smoking showed the strongest association with the anti-CEP-1-positive subset, odds ratio of 37, compared to an odds ratio of 2 for the corresponding anti-CEP-1-negative, anti-CCP-positive subset. We concluded that citrullinated α -enolase was a specific autoantigen linking smoking to genetic risk factors in the development of RA [8]. Specific ACPA have since shown similarly strong associations [9,10], whereas in other populations this gene/environment association with ACPA appears less notable [11], reflecting differences in genetic and environmental exposure. Nevertheless, our study in support of this association raised the possibility that antibody-defined subsets of patients

with distinctive gene and environment associations may exist even within anti-CCP-positive RA. This remains a subject of active investigation.

Apart from smoking, infection has been the focus of much research in the past, but with the current interest in gene/environmental interactions, has undergone a resurgence of interest for the present, with prospects for the future. Most autoimmune diseases occur in 1% or less of the population, but no single disease has epidemiologic features of a relatively rare infection. It is now thought that if infection was the cause of autoimmunity, it is likely to be an abnormal immune response to a ubiquitous agent. An excellent example of this is Epstein–Barr virus (EBV), which infects over 90% of the population worldwide. EBV has been linked to a number of autoimmune diseases, principally RA, Sjögren’s syndrome, SLE and multiple sclerosis (MS) [12]. In all of these diseases, there are higher titers of antibodies to a number of EBV-associated antigens compared to healthy control serum samples. This was first observed in RA but, although an association with RA was not directly disproven, interest faded in the 1990s alongside evidence that the amount of productive infection could be accounted for by defective T-cell control of latent virus infection, a feature of many autoimmune diseases.

SLE provides the most convincing argument for the involvement of EBV infection to disease etiology [13]. Sequences from Epstein–Barr nuclear antigen-1, a highly immunogenic viral antigen, share similarity with peptides from two major lupus autoantigens, Sm and Ro, and these peptides are immunodominant in the autoantibody response from presymptomatic patients. Thus, EBV in lupus fulfils at least two elements of the gene/environment/autoimmunity hypothesis. However, the ubiquity of infection makes the hypothesis easy to make but difficult to prove. Harley’s group provided compelling evidence in its support by showing that the seroprevalence of EBV infection was almost 100% in patients with SLE compared to the 94% in healthy controls and that this difference was highly significant [13]. This was even greater in children with SLE, in which the seroprevalence of EBV is much lower in controls [13]. Almost identical epidemiologic evidence has been published in MS [14]. It could be argued that the higher prevalence of EBV infection in patients with SLE or MS could be due to increased susceptibility to infection resulting from T-cell abnormalities occurring as a result of these diseases. Nevertheless, the consistency of the epidemiological evidence with the molecular mimicry between lupus autoantigens and Epstein–Barr nuclear antigen-1, makes EBV a compelling candidate for further investigation.

Etiology: future

To date, there has been substantial progress in identifying two of the elements of the etiologic triad, genes and autoantibodies, for a variety of autoimmune diseases. Clearly, the future requires more intensive efforts in identifying the third component; the environment. Sometimes the autoantigen gives a clue. For example, sequence similarities between the reactive epitope of citrullinated enolase and enolase from prokaryotes, suggests a bacterial

component in the etiology for RA. *Porphyromonas gingivalis* is an attractive candidate, because it is the only known bacterium capable of producing a citrullinating enzyme known as PPAD [15]. There is also epidemiologic evidence linking this bacterium to RA, but so far it is relatively soft and much larger studies are awaited. If *P. gingivalis* proves to be important in a subset of RA, the generation of a pathogenic autoimmune response could be prevented by targeting the bacterium or perhaps even PPAD. With the completion of the Human Microbiome Project in 2013, other bacterial candidates may also be targeted for RA or other autoimmune diseases. Thus, removing the inciting antigen – the principle that has made CD curable in a proportion of patients for several decades – may also be the model for

preventing or even treating other autoimmune diseases in the future.

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