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Editorial

The autoimmune tautology. A summary of evidence

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Autoimmune diseases (ADs) represent a heterogeneous group of chronic conditions that affect specific target organs or multiple organ systems, and are initiated by the loss of immunological tolerance to self-antigens. The chronic nature of these diseases places a significant burden on the utilization of medical care, direct and indirect economic costs, and quality of life.

The "mosaic of autoimmunity" describes the multi-factorial origin and diversity of ADs expression and implies that different combinations of many factors involved in autoimmunity produce several distinct clinical presentations representing the wide spectrum of ADs [1]. The "kaleidoscope of autoimmunity" portrays the fact that more than one disease may coexist in the same individual or family or the possible change from one disease to another [2]. The "mosaic of autoimmunity" concept has evolved from the complex interaction of diverse factors influencing ADs, to the "autoimmune tautology" [3–6] in which factors favoring or protecting against the development of autoimmunity are shared among several autoimmune conditions. Tautology (from Greek tauto, "the same" and logos, "word/idea") is an obvious statement. In logic theory, tautology is a statement that is always true in every possible interpretation. Thus, the autoimmune tautology means that one AD is similar to a second one, to a third one, and so on. ADs are comparable but not equal given the fact the cell and organ targets are different in each case. Ten shared arguments supporting this logically valid propositional theory are discussed below (Table 1).

It is known that approximately 5% of the world population is affected by ADs [7]. Out of this 5%, approximately 80% are women, making ADs the fourth leading cause of disability for them [7]. The more frequent the AD is and the later onset it has, the more women that are affected. Women tend to have a different age at onset and different disease activity than men. The most relevant explanation for this female bias in autoimmunity remains the hormonal theory followed by genetic factors [7].

A plethora of subphenotypes is shared by systemic ADs. These include signs and symptoms, such as arthralgia, arthritis, alopecia, fatigue, photosensitivity, Raynaud's phenomenon and cardiovascular disease. A same phenomenon is observed for non-specific autoantibodies (e.g., antinuclear antibodies, rheumatoid factor, anti-Ro antibodies) and cytokine imbalance (e.g., TNF, IL-1, IL-6, IL-10, IL-17, etc.).

Polyautoimmunity is defined as the presence of more than one AD in a single patient. When three or more ADs coexist, this condition is called multiple autoimmune syndrome [5,8]. Polyautoimmunity represents the effect of a single genotype and similar environmental factors on diverse phenotypes. This condition is observed in about 30% of patients [9], with autoimmune thyroid diseases (AITD) and Sjögren's syndrome (SS) being the most frequent diseases encountered [9]. Factors significantly associated with polyautoimmunity are female gender, familial autoimmunity, Amerindian ancestry and cigarette smoking [9–11].

The main difference between polyautoimmunity and the overlapping syndromes lies in the fact that the former is characterized by the presence of two or more well-defined ADs while the latter is the partial presence of signs and symptoms of diverse ADs. Most of the cases presented with overlapping syndrome have been described in cross-sectional studies. Data has shown that there is a lag in the time interval between the first and the second AD, just as described in the mixed connective tissue disease (MCTD), the classical overlap syndrome, in which some patients will develop systemic lupus erythematosus (SLE), systemic sclerosis (SSc), or rheumatoid arthritis (RA) during the course of the disease, and some will present a longstanding MCTD [12]. In fact, ADs present a heterogeneous spectrum such that disease courses differ from patient to patient and, in addition, the disease goes through different phases within the same patient. Depending on the duration and activity of the disease, these subphenotypes may change. Similarly, the expression of ADs ranges from the incomplete forms or "*forme frustre*" and lenient and slow evolution syndromes to the rapidly progressive and fatal forms. The imbalance between risk and protective factors (i.e., genetics, epigenetics and environmental) would explain the heterogeneity of ADs.

Some authors consider polyautoimmunity as an "overlap syndrome" confined to "connective tissue diseases" [13]. This view reduces the polyautoimmunity spectrum to just the rheumatic diseases and omits several other systemic and organ-specific ADs that are also associated with each other and observed within clusters [9]. Still, some cases may be related to a specific autoantibody which supports the hypothesis that polyautoimmunity could be a well-defined clinical entity with specific clinical characteristics [13]. Two of such cases are:

- anti-t-RNA synthetase syndrome, characterized by the clinical features of SSc, RA, and myositis and the presence of antibodies against aminoacyl-t-RNA synthetase;

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Table 1
Arguments supporting the autoimmune tautology.

Characteristic	Comment
Female predominance	The more frequent the autoimmune disease and the later it appears, the more women are affected
Shared subphenotypes	Autoimmune diseases shared clinical signs and symptoms, even though they have a heterogeneous spectrum and course that varies from patient to patient
Polyautoimmunity	The presence of two or more autoimmune diseases in a single patient. Clustering of autoimmune diseases is not random
Coaggregation	Unlike familial autoimmune disease, which corresponds to the presence of one specific autoimmune disease in various members of a nuclear family, familial autoimmunity uses the term "autoimmune disease" as a trait that encompasses all accepted pathologies for which evidence suggests an autoimmune origin
Age at onset influences severity	Severity of autoimmune diseases is inversely related to the age at onset. Early-onset traits are more sensitive to genetic influence while late-onset ones are to environmental variation
Similar pathophysiology	Induced damage by T, B cells or both, plays an important role in the pathogeny of autoimmune diseases, although the target cells, affected organs and clinical expression differ from one another, similar immunopathological mechanisms have been established
Autoimmune ecology	Similar environmental agents may influence autoimmune diseases
Ancestry	Amerindian ancestry influences the risk of acquiring autoimmune diseases as well as its outcome, including the development of polyautoimmunity
Common genetic factors	Combinations of common and disease-specific alleles in *HLA* and *non-HLA* genes in interaction with epigenetic and environmental factors over time will determine the final phenotype. Epistasis and pleiotropy are crucial in the understanding of the common genetic pathways of autoimmunity
Similar treatment	Similar biological and no biological therapies are used to treat diverse autoimmune diseases

From [3–11].

- scleromyositis, characterized by features of both SSc and polymyositis/dermatomyositis and the presence of anti-PM–Scl antibodies [13].

A primary characteristic of complex diseases is that affected individuals tend to cluster in families (i.e., familial aggregation). Familial autoimmunity is defined as the presence of diverse ADs in multiple members of a nuclear family (i.e., coaggregation). Familial autoimmunity is more frequent than familial autoimmune disease [8,14]. Polyautoimmunity and familial autoimmunity represent extreme phenotypes that are ideal for identifying major genomic variants contributing to autoimmunity [15,16].

The age at onset refers to the time period where an individual experiences the first symptoms of disease. In ADs, these symptoms can be subtle but very relevant for diagnosis; they can appear during childhood, adulthood, or late in life. Early-age of onset is a poor prognostic factor for some ADs, such as SLE and type 1 diabetes mellitus. In other cases, age at onset does not have a significant influence on the course of disease, such as in the case of SS, or no unanimous consensus on its influence exists (e.g., RA and multiple sclerosis) [17].

Damage induced by T cells or B cells, or both, play a major pathogenic role in ADs. Autoimmune phenotype fluctuates depending on the target cell and the affected organ, but still similar immunopathological mechanisms lead to ADs. The predominant infiltrating cells include phagocytic macrophages, neutrophils, self-reactive CD4+ T helper cells, and self-reactive CD8+ cytolytic T cells along with smaller numbers of natural killer cells, mast cells, and dendritic cells. Among the T effector cells Th1, Th17, and Th9 cells contribute to pathogenesis of ADs [18]. A defective regulatory function in both T and B cell compartments and the activation of the type I interferon system are additional mechanisms common to several ADs [18].

Defects in tolerance leading to AD occur in one or multiple tolerance mechanisms. For example, changes in the apoptotic cell death process, which result in inappropriate cell death or survival or disturbances in clearing apoptotic cells, are thought to be involved in the pathogenesis of a number of ADs [18].

Autoantibodies appear long before clinical symptoms, providing a good predictive marker for the potential to develop a disease. In fact, the risk of developing an AD goes from about 10% if one autoantibody is present to around 60–80% if three autoantibodies are present for a particular AD [19].

Ecology (from Greek: οἶκος, "house"; -λογία, "study of") studies the interactions between organisms and their environment. Therefore, the autoimmune ecology corresponds to the effects and relationships between all the environmental factors that may influence the risk and course of ADs [10]. Several environmental factors are common risk factors for ADs. Epstein-Barr virus and cytomegalovirus are notorious as they are consistently associated with multiple ADs [10]. On the other hand, some infections could be protective against AD development [10]. Smoking has also been consistently associated with several ADs including RA and SLE, AITD, primary biliary cirrhosis and multiple sclerosis [10].

Genetic ancestry contributes to the clinical heterogeneity and variation in disease outcomes among AD patients [20]. In addition, latitudinal gradients in allele frequencies due to ancestry may influence the observed effect of genotype on phenotype across populations [20].

The impact of genetic predisposition on susceptibility to ADs was first identified by the analysis of disease concordance rates between monozygotic twins (concordance rates ranged from about 15% to 57%) [21]. Several reports have confirmed that autoimmune phenotypes represent pleiotropic outcomes of non-specific disease genes [3,22]. However, not all ADs share the same genetic susceptibility. Therefore, the genetic risk factors for ADs consist of two forms: those common to many ADs and those specific to a given disorder [3]. Most of the common variants, individually or in combination, confer relatively small increments in risk (1.1- to 1.5-fold) and explain only a small proportion of heritability (i.e., the proportion of phenotypic variation in a population that is attributable to genetic variation among individuals). The influence of heritability depends on the population under study because variations in both additive and non-additive genetic factors and the environmental variance are specific to the population [23]. As a corollary, the genetic influence on any disease should be evaluated or confirmed in different populations.

Last but not least, what we have learned about the etiopathogenesis of ADs, which supports the view that common features of different clinical entities outnumber their differences, makes it possible to use similar treatments for various ADs despite specific variations and regimen tailoring. Indeed, similar biological and non-biological therapies are used to treat diverse ADs.

In conclusion, the heterogeneity of ADs could be due to a collection of diverse disorders based on epidemiology, pathology or diagnostic results, but in fact the underlying physiopathological mechanisms are similar. Identification of such common mechanisms will enhance our understanding of these complexes, frequent and sometimes devastating diseases and will permit us to translate this new knowledge into clinical practice [24].

Disclosure of interest

The author declares that he has no competing interest.

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Juan-Manuel Anaya
Center for Autoimmune Diseases Research (CREA), School of Medicine and Health Sciences, Universidad del Rosario, Carrera 24-63-C-69, Bogota, Colombia
E-mail address: juan.anaya@urosario.edu.co

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