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Cutting-edge Issues in Autoimmunity and Allergy of the Digestive System

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Abstract Autoimmunity and allergy involving the digestive system may be considered as paradigmatic for numerous common themes of complex diseases secondary to tolerance breakdown. Among gastrointestinal autoimmune diseases, for example, we encounter diseases in which a clear environmental trigger is identified (i.e., celiac disease), serum autoantibodies are most specific (i.e., primary biliary cirrhosis), or in which the disease pathophysiology is clearly understood (i.e., autoimmune gastritis). Similarly, it is intriguing that the gastrointestinal tract and the liver circulation represent the crucial environment for the development of immune tolerance. This issue is dedicated to the discussion of recent concepts while identifying two major common issues, i.e., the need for serum biomarkers and the role of vitamin D. Other common themes characterize the etiology and effector mechanisms of these and other autoimmune diseases and are discussed in each cutting-edge overview.

Keywords Tolerance · Vitamin D · Adjuvant · Autoantibody

Our understanding of the pathogenesis and etiology of autoimmune disease has witnessed an enormous improvement over the past decade, paralleling the availability of new high-throughput technical tools [1]. The recent progress is well represented by the numerous genome-wide association studies that investigated several thousand single nucleotide polymorphisms in large cohorts of patients with systemic sclerosis [2–4], systemic lupus erythematosus [5–7], primary biliary cirrhosis [8, 9], rheumatoid arthritis [10–16], celiac disease [12, 17], and other autoimmune diseases sharing a complex etiology [18] with limited overlap of observed associations [19]. One of the paradigmatic features shared by these complex conditions is the widely variable and incomplete concordance rate observed in monozygotic twins which illustrates the role of environmental factors in the initiation of the disease process [20].

One of the areas in which major developments have been achieved over the past years is represented by autoimmune diseases affecting the digestive and hepatobiliary systems and the present issue of *Clinical Reviews in Allergy and Immunology* is dedicated to major issues in this fascinating field. Of note, the present issue follows the line drawn by similar recent initiatives with authoritative guest editors dealing with general mechanisms of autoimmune diseases [1, 21] as well as with more specific conditions such as atopic dermatitis [22], lupus nephritis [23], allergy [24], scleroderma [25], and reproductive factors [26], just to name the special issues from the previous 2 years.

Besides the obvious peculiarities of each condition, the articles present two common themes that will be addressed in this introduction. The first issue includes the discussion of cutting-edge issues in celiac disease [27], primary biliary cirrhosis [28], autoimmune gastritis [29], and autoimmune hepatitis [30]. Further, there are comprehensive discussions of the open issues in seafood allergies as a paradigmatic example of widespread hypersensitivity [31] and of anti-muscarinic serum autoantibodies [32]. The clinical suspicion

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or diagnosis in these conditions largely relies on serum autoantibodies which, in some cases, are diagnostic cornerstones [33–37]. Nevertheless, these conditions are ideal examples of the lack of identity between a positive serum autoantibody and a disease phenotype while manifesting largely incomplete sensitivity and specificity profiles. As an ideal example, the workup of patients with a suspect of celiac disease includes several autoantibodies and each of these can be sought using different laboratory methods and commercially available kits [38]. For this reason, there is the need for a general agreement which should be evidence-based and rely on a large number of cases and controls while time- and money-saving solutions such as the recently developed neoepitope [38] await for definitive validation. One major advantage in the study of celiac disease-associated autoantibodies is the presence of a diagnostic gold standard, i.e., histology, which may favor this long-awaited validation effort. Unfortunately, this scenario is not common to other autoimmune diseases such as primary biliary cirrhosis (in which a positive antimitochondrial antibody is indeed a major diagnostic criteria) [39] or autoimmune hepatitis [30]. The case of primary biliary cirrhosis warrants further discussion particularly based on the original data presented herein and derived from a large series of seronegative patients that may well be representative of approximately 1,000 cases. The major concern in the diagnosis and management of suspect cases for autoimmune cholangitis is the possibility that serum antimitochondrial antibodies may be negative or undetectable in as many as 10–15 % of patients thus making a liver biopsy recommended, despite its lack of sensitivity [40–42]. In this issue, Bizzaro and colleagues report that the use of a newly available antibody test increases the frequency of serum autoantibodies in a large population of previously negative patients at routine indirect fluorescence thus chipping away at this minority of patients [39]. Another commonality among autoimmune diseases stems from what is previously discussed and is the lack of real population-based epidemiology [43]. We expect that the development of new more cost-effective laboratory methods for autoantibody detection will provide a solution to this gap of knowledge although the rare incidence of most autoimmune conditions will necessarily require the study of large number of subjects.

As a second issue, we cannot overlook that vitamin D is a common theme for a number of autoimmune diseases, including celiac disease and gastritis, as discussed in two original studies [44, 45]. A brief look at the biology of vitamin D allows to identify numerous pathogenetic crossroads to autoimmune diseases in which this molecule may act [46–48]. Cholecalciferol and ergocalciferol derive from dietary sources, particularly animal and fish liver, eggs, and fish oils, and cholecalciferol is also produced in the skin from 7-dehydrocholesterol (pre-vitamin D_3), through the nonenzymatic effect of sunlight ultraviolet B rays and this observation is of obvious importance considering the large geoepidemiology evidence that characterizes autoimmune diseases [43, 49–53]. The final metabolite is the active metabolite of vitamin D, i.e., 1,25-dihydroxycholecalciferol, although its serum concentrations do not correlate with vitamin D stores. There are numerous mechanisms by which vitamin D may mediate the immune function in autoimmune disease [47, 54]. A clearer example of an autoimmune disease that is regulated by the vitamin D hormone is type 1 diabetes mellitus [55] with vitamin D deficiency causing a marked increase in disease incidence, as suspected in numerous autoimmune conditions [46, 56, 57]. It is likely that the suppression of autoimmune diseases by vitamin D involves an interaction with CD4+ lymphocytes [58, 59].

In conclusion, the present issue dedicated to autoimmune and allergy diseases of the digestive and biliary systems illustrates several common themes that will warrant further studies in the future. Nevertheless, we may also hypothesize that additional candidate players will be of enormous importance in our understanding of these diseases. In particular, we expect that the study of the gut microbiota [60–62] and tissue-specific microRNA [63–66] will provide new insights into the pathogenesis of digestive diseases and should be pursued in future studies.

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