

Everything is Autoimmune Until Proven Otherwise

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Abstract It is astounding to consider that virtually, every textbook of physiology in every medical school in the world does not include a chapter on immunology. On the other hand, virtually, in every textbook in internal medicine, immunology and immune response overlaps with every tissue and every organ. Indeed, historically, the concept of the immune response was recognized primarily in the setting of allergy and/or anaphylaxis. Indeed, the very concepts of infection, microbiology and host protection are relatively new sciences. In fact, it was little more than 100 years ago when washing hands became what is now coined “standard of care.” How different it is in 2013, where one finds Handi Wipes for shoppers to use at grocery stores to protect themselves from the flora on shopping cart handles. Autoimmunity is even a newer concept without going into the well-known history of Paul Ehrlich and hemolytic anemias, the LE cell, and the beginning field of serology (and rheumatoid factor discovery). It is apparent that our understanding of autoimmunity has become linked hand-in-glove with new tools and investigational probes into serology and, more recently, the cellular immune response. With such discoveries, a number of key observations stand out. Firstly, there are a great deal more autoantibodies than there are autoimmune diseases. Second, there are a great deal more of autoimmune diseases than was believed in 1963 on the occasion of the publication of the first textbook of autoimmune diseases. Third, autoimmune diseases are, for the most part, orphan diseases, with many entities afflicting too few patients to excite the financial limb

of pharmaceutical companies. In this special issue, we have grouped a number of papers, many of which were presented at the recent Congress of Autoimmunity that focus on issues that are not commonly discussed in autoimmunity. It reminds us that due to the ubiquitous nature of the innate and adaptive response, that there are a large number of diseases that have either an inflammatory and/or specific autoimmune response, we have to keep an open eye because everything is potentially autoimmune until proven otherwise.

Keywords Autoimmunity · Environmental factors · Tolerance · Sex and gender

The number of autoimmune diseases was once limited to the obvious entities of hemolytic anemia, systemic lupus, and rheumatoid arthritis. It now includes at least 100 such entities. Interestingly, our definition and classification of these diseases, which include virtually every organ and tissue in the human body, are very much dependent on defining a unique signature, i.e., either an autoantibody or a cellular response that reacts with self. It is not surprising therefore that the growth of autoimmune diseases has been dependent on a corresponding increase in database of serology and cell-mediated immunity. On the other hand, it is equally apparent that there are innate immune responses, some of which may have memory that can be extraordinarily important in not only the regulation of the immune response and the potential breach of tolerance but also in the natural history of tissue destruction. Indeed, cellular immunology has become a virtual smorgasbord of cells, subpopulations, and lineages. Much of these data are dependent on studies in the mouse and of course the use of knock-in and knock-out strains; much of these data hopefully have the ability to be extrapolated to humans but, in some cases, that may well be a leap of faith.

The International Congresses of Autoimmunity, which are held every 2 years, attempt to bring young scientists in one venue to discuss technological advances, new diagnostic techniques,

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and especially to create an open dialogue that may lead to new therapeutic ventures. In the most recent Congress of Autoimmunity held in Granada, Spain, in 2011, there was particular emphasis placed on gender, sex hormones, pregnancy, and autoimmunity and this led to a unique publication which focused entirely on these issues [1–15]. The next Congress of Autoimmunity to be held in Nice, France in 2014 will focus on diagnostic criteria and classification of autoimmune diseases. The volume herein focused on unique topics that are not often put together in one umbrella. They include, for example, discussions of the hygiene hypothesis and helminths, serpins, tolerance in primary immune deficiency syndromes, and multicentric reticulohistiocytosis. These are not common areas for discussion and it is hoped that this volume will attract attention by its focus on these less common themes. The literature on autoimmunity grows in an exponential fashion, and we note, for example, that so much of it is linked to new “toys” and technologies that allow further molecular dissection of the immune response. We note that studies of nucleotide polymorphisms gave way to genome-wide association studies, which gave way to deep sequencing, and which now must go together with proteomics and epigenetics. Yet, how much closer are we to understanding the etiology of autoimmunity? For one thing, study of the genetic basis has, for the most part, been disappointing, with the increased recognition that the genetic components are far more complex than once believed. We know that autoimmune disease requires a genetic and an environmental basis [6, 7, 16–19], but even more, we recognize that to understand autoimmunity, we need to go into the concepts of autoinflammation and the innate immune response. The damage in many clinical situations, such as, for example, myocardial infarction, is significantly influenced by the inflammatory response. Furthermore, inflammatory response likely has a genetic component and individual variation. The use of vaccines should be applauded but also with the recognition that there will be aberrant individual responses to both the antigens and potentially the adjuvant. The use of biologics comes with its own set of disease risks and side effects and, for the most part, still does not achieve the concept of a magic bullet, i.e., therapy entirely specific for a selective immunopathology. We conclude by noting a number of recent reviews and literatures [18–33] that highlight these concepts and reminding our readers that the immune response is everywhere.

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