WHAT IS HOT IN AUTOIMMUNITY

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Abstract

Late 2008 and 2009 have been rich of new developments in our knowledge in the pathogenesis, susceptibility, and putative treatments of autoimmune diseases. In general terms, it is now clear that the discovery pace in immunology in general and autoimmunity in particular is exponential and warrants a timely discussion. We herein review the major issues that have been addressed in the basic, clinical and translational fields of autoimmunity in the leading journals over the past 18 months. Of note, major scientific issues are being addressed with a tremendous effort, as in the case of the T helper 17 paradigm or the role of T regulatory cells or the long overlooked innate arm of the immune system, while an increasing number of translational works are being performed with promising data for a bedside impact. The ultimate implication from the recent literature is that autoimmunity is rapidly becoming a uniform scenario in which similarities significantly outnumber differences in terms of pathogenesis and mechanisms. For this reason a comprehensive yet brief review of the published reports encompassing all aspects of autoimmunity will prove helpful to basic scientist and clinicians alike to prompt new research directions.

Keywords: Immune tolerance; T helper 17; T Regulatory; Autoimmune Disease.

Hot topics and common themes in autoimmunity

The most recent International Congress of Autoimmunity held in Porto was the ideal setting to determine the major ongoing developments in the world of autoimmune diseases. As we recently discussed, the spectrum of autoimmunity phenotypes is rapidly becoming more uniform thus suggesting that healthcare providers should also change their professional profiles accordingly.[1] The most recent epidemiology estimates that up to 5% of the world population is affected by one of the several diseases of putatively autoimmune pathogenesis. While new paradigms have been recently proposed (as in the case of the Th17 response or T regulatory cells), several hot topics have been addressed in the recent literature. Our discussion will be arbitrarily subdivided in terms of either effector/regulatory mechanisms (as in the case of Th17 or innate immunity), susceptibility factors, or clinical conditions.

Search methods

A MEDLINE database search was performed with the terms 'autoimmunity' limited to the major peer-reviewed journal publications (particularly *Science, Nature, Nature Medicine, Nature Immunology, Journal of Immunology, Journal of Autoimmunity, Autoimmunity Reviews*) and the January 2008 - October 2009 time frame to provide a tentative illustration of the current research efforts in the field.

Th17 takes it all

T cell tolerance and the related issue of the new interleukin 17 and interleukin 22-producing T helper population (Th17) have been the major stars in the autoimmunity literature over the past months. Ultimately, several of these observations could potentially lead to new therapeutic approaches in the wide range of autoimmune conditions. The recent report of the crucial role of IL-23 in the development of an effective Th17 response represents an ideal example of these potential[2] while new signaling mechanisms are being determined.[3] Further, direct therapeutic implications can be gathered from data recently obtained on halofunginone[4] or

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the IL-22 role in the mucosal defense against infectious diseases.[5] Multiple additional lines of evidence contribute to our understanding of this important mechanism in the regulation of the immune response[6-24] and may ultimately prove helpful in our understanding of autoimmune diseases.[25]

Coming up for AIRE

The autoimmune regulator gene (AIRE) is crucial in the destruction of self-reactive T cells during the development and maturation process[26] and T cells escaping central deletion could be ultimately inactivated in the periphery by new mechanisms that remain to be fully elucidated. More experimental data on AIRE-related issues can be found elsewhere.[27-45]

Regulatory T cells at the autoimmunity crossroad

T cell tolerance may also be induced through other mechanisms,[46] as well illustrated by data on the intraclonal competition,[47] differential induction of transcription factors,[48] and direct clinical impact[49] of T regulatory cells. Further, accurate flow cytometry analyses determined that the subgroup of CD4 CD8 double positive FoxP3 positive cells is in fact composed of different subtypes[50] with obvious implications in data interpretation for other studies. Several other studies in the leading journals have addressed the importance of T regulatory cells in the determination of autoimmunity.[51-63]

B cells in autoimmunity

The issue of B cell-mediated tolerance or autoimmunity induction was addressed by multiple studies.[64-70] Of particular interest, it has been demonstrated that B cells may contribute to tolerance maintainance through natural autoantibodies[67,71] while the enzyme IDO may induce B cells to trigger autoimmunity in rheumatoid arthritis.[68]

An innate taste for autoimmunity

There is increasing awareness that the innate immune arm is crucial to determine tolerane or autoimmunity. This was reflected by numerous studies over the past months addressing the role of dendritic cells[72-82] or other components of the innate immune response.[83-96] A representative example comes from the observation that vitamin A and the toll-like receptor (TLR) 2 contribute to the maintainance of tolerance acting on dendritic cells.[52] Similarly, exciting experimental data provide a link between the innate response and apoptosis with the Th17 response.[10] To this regard, the role of apoptosis and autophagy in the autoimmune scenario has also been widely investigated in the past months[97-101] as well illustrated by comprehensive articles.[39,40,102]

Usual and unusual suspects in the individual susceptibility to autoimmunity

The assumption that genes and environmental factors interact in determining the onset of autoimmune diseases is now established. Accordingly, several articles have been dedicated to the genetic[103-111] and environmental bases of disease. Among the latter, the role of infectious agents, both viral and bacterial[6,112-119] has been investigated. Nevertheless, new factors have been strengthened in their potential involvement and include epigenetic[107,120-124] and sex chromosome[125-130] changes. Among the latter, the recently suggested role of Y chromosome changes[125,130] is complementary to the sex-related theory for sex-unbalanced autoimmune diseases[127] that is strengthened by the clinical observations in Turner syndrome.[128] New candidates for the modulation of gene transcription affecting the immune response are being continuously suggested by experimental data. Indeed, the amount of data supporting the importance of small RNA (microRNA) in the modulation of the immune response has been exponentially increasing over the past months[131-133] and we expect that *in vivo* applications will follow in the next months.

Clinical and translational developments

As expected the number of basic scientific findings was paralleled over the past months by translational and clinical implications in several autoimmune conditions. From a more general standpoint, new developments have been proposed in terms of imaging techniques[134] and serum analyses.[135]

The involved diseases included in particular systemic lupus erythematosus[38,136-144], Sjögren syndrome,[145-147] multiple sclerosis,[148-157] type 1 diabetes,[91,158-169] autoimmune thyroid disease,[170-172] and the sequelae of organ transplantation.[49, 173-178] As an example, the prevention of acute and chronic allograft rejection through the manipulation of T regulatory cells[49] appears to be a translational development while proteomics can provide some of the missing pieces in the autoimmunity puzzle.[179] Intriguing data are being obtained also in more rare conditions,[37,180-185] in less strictly autoimmune settings,[45,186,187] or in new therapeutic approaches[43,188-193] with new putative complications.[194]

What to look for in the next 12 months

As briefly discussed in this article, the research efforts in autoimmunity have provided several exciting developments over the past months and prepared us to further discoveries that are expected to follow shortly. As an example, we believe that the time and the status of knowledge are ready for direct therapeutic uses of our findings in the field of T regulatory cells. Similarly, we expect that the findings on microRNA or epigenetic changes will soon provide applications in animal models of autoimmune diseases.

All new developments ultimately lead to more new questions but technology progress allows to maintain an exponentially growing pace towards unraveling the numerous misteries of autoimmunity. As a result, the mosaic of autoimmunity[195,196] appears today to be closer to its completion.

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