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Autoimmunity

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The identification of two distinct subsets of CD4⁺T helper (Th) cells by Coffman and Mossman [1] provided clear insight into immune diseases pathogenesis. This seminal study led to the suggestion that the interferon (IFN) γ -producing Th1 T cell subset was the major pathogenic T cell mediating diseases as diverse as Multiple Sclerosis (MS), Type 1 Diabetes, Systemic Lupus Erythematosus and Psoriasis. These conclusions were based on multiple animal models of disease and strong clinical evidence. However, in the past decade, the field has been turned upside down with multiple revelations. First, it became clear that multiple additional T cell subsets exist, including Th17, Th9, Th22 and follicular T helper cells [2–4], all of which have been implicated in autoimmunity. There was also the striking observation that one of the most potent drugs to be developed for the treatment of Crohn's disease and Rheumatoid Arthritis, TNF antagonists, exacerbates MS [5]. Next, B cells made a big comeback as therapies such as anti-CD20 and anti-Blys were shown to block human autoimmune diseases, including multiple sclerosis and T1D, autoimmune disease that had not been thought to be autoantibody-mediated [6]. Anti-CD20 mAb therapy is efficacious even in diseases like ANCA⁺vasculitis where autoantibodies are thought to be pathogenic suggesting that CD20⁺long-lived plasma cells may not be producing the pathogenic antibodies in these settings [7]. In addition, the innate immune response has been found to play a major role in many disease settings including mast cells, NK cells, macrophage (both conventional and "alternatively activated"), and even basophils and eosinophils. These cells types, influenced by toll-like receptor engagement, can regulate the initiation and severity of multiple autoimmune diseases. In this context, we have learned that self-reactivity does not develop in isolation but rather in a fine balance with the environment where the microbiota, including both commensal bacteria and pathogens, shape the immune system [8,9] and alter the immune homeostasis, in many cases, towards disease pathogenesis. Finally, there is increasing evidence that peripheral regulation of immunity, through cytokines such as IL-10 and TGF β and specialized regulatory T cells, B cells and other leukocytes regulate self-reactivity. Thus, the field of autoimmunity cannot be defined by the simple Th1/Th2 paradigm of the 1980's. Not all autoimmunity is simply a T cell-mediated disease and the approaches to therapy now span a spectrum of cytokine antagonists, modifiers of the microbial milieu and cell blocking agents across the immune spectrum.

In this compendium, leaders in the field have summarized the state of the basic and clinical research in these various new areas. Links between infections and autoimmunity; T cells and B cells; balance of pathogenic and regulatory cells guide the new clinical treatments. The issue starts with an article by Gardner et al. reviewing thymic medullary epithelial cells. The thymus

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has been at the center of immune tolerance for decades and the notion that self/non-self discrimination begins in this organ has been a central paradigm in immunology. The majority of T cells with high affinity for self-antigens are deleted in the thymus. However, how all tissue specific antigens (TSA) are expressed in the thymus to censor autoreactive T cells repertoire was an enigma in immunology for the longest period of time. The discovery of the Autoimmune Regulator (AIRE) gene revealed that AIRE promotes ectopic expression of TSA in the thymic medullary epithelial cells and mediate deletion of high affinity self-reactive T cells [10,11]. These seminal discoveries have “closed the loop” in understanding basic principles of tolerance in the thymus. However, as Gardner and colleagues describe, emerging data suggests that AIRE is also expressed in the peripheral immune compartment in the lymph node stromal cells, where it promotes TSA expression and further inhibit autoreactive T cells that have escaped thymic deletion [12]. The mechanism by which AIRE induces expression of TSAs is still not clear, but the expression of AIRE inducing TSA expression in both thymus and peripheral lymphoid tissue must play an important role in maintenance of self-tolerance and mediate central and peripheral tolerance. Another key element in the molecular understanding of early events in shaping the autoimmune repertoire has been the unexpected observation that the structure of the T cell receptor (TCR) complex on autoreactive T cells is distinct from those of conventional pathogen-specific TCRs. The review by Wucherpfennig, Mariuzza and colleagues highlights the new insights gained by solving the crystal structures of multiple autoimmune TCR–peptide–MHC complexes. These studies have revealed substantial differences in the topology of peptide–MHC interactions by these autoimmune TCRs when compared with microbe-specific TCRs. The review provides a provocative model to help explain how T cells with these receptors with a suboptimal TCR-peptide–MHC interface might escape negative selection yet still be able to mount an autoimmune pathology in tissues. Finally, in this first section, Baranzini et al. discuss current insights into the genetics of MS. Specifically, they address an important question in the field of inflammatory diseases, namely, to what extent is the genetic architecture amongst inflammatory diseases shared. This is a rapidly evolving field of investigation focused on a comprehensive assessment of the human genome for shared susceptibility loci. The authors not only summarize the wealth of information of the nature of the shared genetics among various inflammatory diseases but also try to synthesize the genetics as a road map towards phenotypes.

The compendium moves next into the periphery, where a series of reviews focus on the peripheral mechanisms of disease pathogenesis and regulation. As mentioned above, the Th1/Th2 paradigm, based on the cytokines they produce, led to an explosion of studies showed that the IFN γ producing Th1 and not Th2 cells mediate organ specific autoimmune diseases. However, it soon became clear that the loss of IFN γ did not make mice resistant to autoimmunity but in a number of experimental settings, IFN γ -deficient mice were more susceptible to autoimmune diseases [13]. This raised the issue of whether effector T cells other than Th1 cells are required for tissue inflammation. This led to the identification of an IL-17 producing T cell subset (called Th17), which has been shown to be very potent in inducing tissue inflammation and protect against extracellular pathogens like fungal infections [14].

In fact, during the last 5 years, a series of new subsets of T cells, distinct from Th1 and Th2 cells have been identified including Th17, Th9 and Th22 [4]. The growth/differentiation factors and transcription factors that are required for their generation are distinct suggesting that these T cell may be distinct from Th1 and Th2 cells and may have different properties and effector functions. However, whether these subsets are stable and retain their phenotype has also been questioned and it is becoming increasingly clear that Th17 and Th9 cells begin produce IFN γ and other cytokines when transferred in vivo. Therefore, the same T cell subset may attain the ability to produce other cytokines in the target tissue and contribute to overall function of these effector T cell subsets and this may also resolve the controversy of relative role of IL-17 vs. IFN γ in inducing tissue inflammation. Veldhoen contributes a cogent and thoughtful review

of the T cell subsets involved in autoimmunity. One goal of the review is to highlight a recent conceptual in the field, namely the notion of T cell subset plasticity. He points out that T helper cell subsets can no longer be thought of as terminally committed effector cells but can be reprogrammed depending on the local milieu at the site of inflammation. In this regard, the important linkage between environmental factors and Th subsets at the site of immune reactivity is key to the outcome of an inflammatory response. This leads to the suggestion of a central role for Th17 in orchestrating adaptive immune responses and with other subsets key in final effector functions such as regulation and B cell immunity. One of the cells that appear to “dance” with the Th17 subsets is the CD4+CD25+ Fox-P3+ regulatory T cell (Treg) subset, which is critical for suppressing out of control immune responses. Bettini summarizes the current data on Treg function and, as importantly, the nature of the Treg instability (or plasticity as noted above) in diseases such as type 1 diabetes (T1D) and multiple sclerosis (MS) suggesting that local sites of inflammation plays a key role in determining the nature of the T cell subset balance. Finally, in this section, the Yu et al. review extends this concept to a discussion of T follicular helper (Tfh) cells as the key regulators of antibody production and class switch. These cells have the ability to home to the B cells follicles by virtue of CXCR5 expression and express cell surface costimulatory receptor, ICOS, and cytokines like IL-21, which help B cell growth and antibody production. These cells, which express transcription factors (Bcl6 and Blimp1), may be a distinct T cell lineage. However, as noted above the cells may derive from other T cell subset, including Tregs or other Th cells that may express additional transcription factors and microRNAs that downregulate CCR7, upregulate CXCR5, which allow a subset of T cells to traffic to the B cell follicles where they provide help to B cells and induce class switching. Finally, in this section, Schlomchik contributes a provocative article highlighting the current central role of B cells in autoimmunity based on new insights into the biology of B cells and the efficacy of B cell targeted therapy. This leads to the presentation of a novel model that B cell Ag presentation to T cells is likely to be central to T cell activation by providing a positive feedback loop that amplifies and sustains autoimmunity. He goes on to hypothesize that activated autoreactive B cells are responsible for the initial breakdown of self-tolerance leading to a cascade of events that lead to destructive autoimmune disease.

The final section of this issue focuses on the “other” non-adaptive cells involved in autoimmunity. Flodström-Tullberg et al. summarizes the current research suggesting a role for Natural killer (NK) cells as important regulatory cells involved in exacerbating or limiting immune responses to autoantigens. This review dovetails with one by Chevonsky that highlights the critical role of the environment and commensal bacteria in the control of autoimmune diabetes. This review highlights the findings that non-pathogenic commensal microbiota present in the gut shape the effector T cell subset development and thus regulate induction of autoimmunity. Thus, together with the a number of susceptibility genes highlighted in the genetics review, we see a picture emerging that provides a holistic view of autoimmunity that links the adaptive and innate immune system in regulating immune homeostasis. Thus, it is not surprising that there is developing a new and broader armamentarium of drugs that are being tested in the autoimmune arena. In the last review of this issue, St. Clair summarizes current clinical approaches to reverse the autoimmune process in humans. The review highlights new, more targeted, therapies that are improving the treatment of autoimmune disease. The drugs span the gamut from those designed to deplete specific T and B cell subsets to those targeting aspects of innate immunity. The review ends with a discussion of the holy grail of immunology, approaches that focus on antigen-specific therapies that alone or in combination with other drugs may be effective in achieving long term disease quiescence and immune tolerance.

Biographies

Dr. Bluestone is the Clausen Distinguished Professor of Metabolism and Endocrinology, and Director of the Diabetes Center at the University of California, San Francisco. He directs the JDRF Collaborative Cell Therapy Center, and founded and directs the Immune Tolerance Network, a consortium translating potentially tolerogenic immunotherapies into the clinic. He has authored over 300 publications on diabetes and immunity while studying the regulation of T-cells in response to autoantigens and transplantation antigens, supporting a new generation of selective immunomodulatory drugs that promote immune tolerance.

Dr. Kuchroo is the Samuel L. Wasserstrom Professor of Neurology at Harvard Medical School, Senior Scientist and Co-Director of the Brigham Research Institutes, Center for Infection and Immunity, Brigham and Women's Hospital, Boston. Dr. Kuchroo works in the field of autoimmunity and has a strong interest in T cell differentiation and mechanisms by which T cells induce and regulate autoimmune tissue inflammation. Dr. Kuchroo has published over 225 original papers on autoimmune disease models, the TIM family of genes, T cell differentiation, costimulation and genetics of autoimmunity. Dr. Kuchroo lives in Newton, Massachusetts with his wife and two children.

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