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Complexity and heterogeneity – the defining features of autoimmune disease

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Dr Sanz received his MD degree from the University of Santander Medical School in Spain and trained in molecular immunology with Don Capra at the University of Texas Southwestern Medical School. He was Chief of the Division of Allergy, Immunology and Rheumatology at the University of Rochester from 1996 to 2012 as well as the director of the Rochester Autoimmunity Center of Excellence; the Center for Biodefense of Immunocompromised Populations; the Center for Translational Immunology. Since 2012, he has been the Emory University Mason Lowance Professor of Medicine and Pediatrics and Georgia Research Alliance Distinguished Scholar in Human Immunology; Chief of Rheumatology and Director of the Lowance Center for Human Immunology. He is the Scientific Co-Leader of the NIH Autoimmunity Centers of Excellence Network, a member of the Steering Committee of the Immune Tolerance Network (ITN) and of ITN Autoimmunity Assessment Group. His research focuses on the regulation of human B cells and plasma cells, the mechanisms of B cell autoimmunity and the therapeutic targeting of B cells in autoimmune diseases. Dr Sanz is an elected member of the Association of American Physicians. He received the 2019 Lupus Insight Prize from the Lupus Research Alliance.

Autoimmune conditions encompass tissue-specific diseases, like type 1 diabetes (T1D), skin blistering diseases, multiple sclerosis (MS) or myasthenia gravis, and systemic diseases, like Systemic Lupus Erythematosus (SLE), vasculitides, rheumatoid arthritis (RA), and systemic sclerosis (Figure 1). While the ultimate cause(s) of clinical autoimmunity remain unknown, it is accepted that it results from accumulation of pathogenic autoreactive immune effector cells. In turn, the generation of pathogenic precursors is enabled by defective immunological tolerance promoted by genetic susceptibility, licensed by epigenetic modification and triggered by environmental factors, including the endogenous microbiome (Figure 1). Finally, clinical disease ensues through the induction of effector cells directed against target antigens that may or may not be the same as the triggering antigens responsible for the initial breakdown of tolerance. A high degree of heterogeneity, both between diseases and within a single disease, is a major feature of, and a challenge for, our understanding and treatment of human autoimmunity. Nevertheless, there is strong evidence that clinical autoimmunity can be preceded by a prolonged pre-clinical phase. The study of pre-clinical and early autoimmunity, defined as the very early stages of clinical diseases before full-blown disease develops, offers a unique opportunity to understand the triggering events and the central inducing mechanisms that underpin disease development before multiple downstream pathways and amplifying loops are recruited. It stands to reason that at this late immunological stage, which may correspond to a relatively early clinical time point, it will be much harder to separate cause from consequence; to assign mechanistic priority to specific pathways; and to induce disease remission — a goal that for full-blown disease might, at that point, require pleotropic agents or combination therapy. In contrast, analysis of pre-clinical or early disease as well as the study of autoimmune diseases after disease remission induced by biological agents offers a unique opportunity to dissect the primordial cause and triggering pathogenic events of human autoimmunity.

In this issue, the authors delve into the triggers, mechanisms, pathways that contribute to autoimmune disease development. They discuss the latest studies to identify personalized, more effective treatments for disease and review how big data 'omics approaches are revolutionizing the study of these highly heterogeneous diseases. Slight-Webb *et al.*, review current knowledge of specific immune pathways that are engaged in the initial stages of preclinical autoimmunity with special emphasis on SLE, RA, T1D. In addition, she discusses subsequent events and mediators that associate more closely with clinical disease onset. This very productive area of research could be central to our ability to understand disease pathogenesis, to develop predictive biomarkers in high-risk patients and to design treatments capable of preventing the development of clinical disease.

Frances Lund

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Frances Lund, PhD is a Professor and Chair in the Department of Microbiology at the University of Alabama at Birmingham. Dr. Lund's lab studies the immune cells that suppress or exacerbate mucosal inflammation with the long-term goal of developing therapeutics to treat immunopathology associated with chronic infectious, allergic and autoimmune disease. She is particularly interested in characterizing the roles that cytokine-producing 'effector' B cells play in modulating inflammation and T cell-mediated immunity to pathogens, autoantigens and allergens.

Nündel and Marshak-Rothstein's review addresses the role of innate immunity as an early initiator of autoimmune disease. They focus on a unique subset of patients that exhibit defective clearance of cytosolic nucleic acids or increased signaling through the nucleic acid sensor STING, which results in enhanced type I interferon production. They also present newer animal data pointing to the participation of type II and type III interferons in auto-inflammation. Notably, they review the roles of STING in B and T cells and how altered nucleic acid sensing may dysregulate these adaptive immune cells and promote a critical role for CD4 T cells in auto-inflammation.

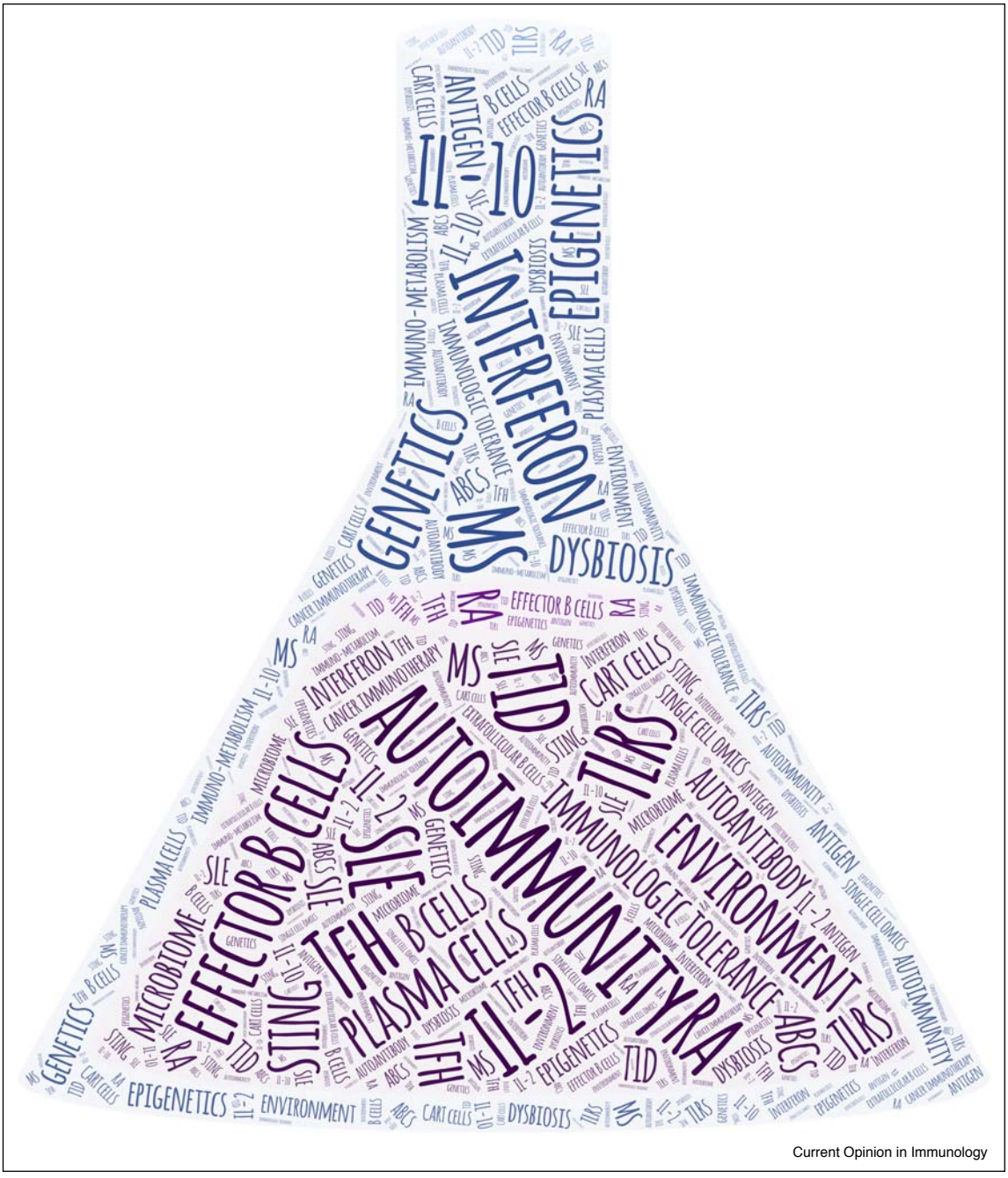
A very vibrant area of research in human autoimmunity has been triggered by the success of immune checkpoint inhibitors (CPI) in cancer immunotherapy. These drugs target natural checkpoints integral to the ability of the immune system to enforce tolerance for self-antigens. While it is not understood whether the development of autoimmunity is required or advantageous to achieve anti-tumor efficacy, it is not surprising that these agents induce autoimmune manifestations in many patients. Kavita Dhodapkar provides an in-depth review of the T and B cell immunological abnormalities associated with the development of autoimmune complications in cancer immunotherapy and discusses the potential association with the microbiome. In contrast to spontaneous autoimmunity with its long incubation period, CPI-associated autoimmunity provides a unique opportunity to understand the early events that lead to autoimmune manifestations and may facilitate development of predictive biomarkers and preventive therapies.

Silverman et al. provide a timely overview of the endogenous microbiome with special emphasis on recent work examining gut dysbiosis in SLE. They describe specific associations between the microbiome and disease activity and lupus nephritis and outline potential mechanisms of disease induction through intestinal barrier defects, antigenic cross-reactivity, autoantibody development, and Th17 expansions. Finally, the authors propose that SLE gut dysbiosis and disease-associated immune abnormalities may reinforce each other and discuss how this model may also apply to other human diseases.

One of the major ways in which the microbiome shapes immune homeostasis is by regulating metabolic processes in the host cells. Laurence Morel's group delves in the metabolic pathways that are dysregulated in autoimmune disease, focusing on mechanistic studies using SLE autoimmune mouse models. They highlight the metabolic abnormalities that are often seen in immune cells isolated from autoimmune patients and mice and discuss how drugs that specifically target these 'altered' metabolic pathways could be used in a highly selective way to attenuate the autoimmune response without general suppression of protective immunity induced by vaccination and infection.

Given the central antibody-dependent and independent roles played by B cells in autoimmune disease, it is not surprising that B cell depletion with drugs like Rituximab have dramatically changed the treatment of ANCA-vasculitis, IgG4-RD, RA and autoimmune blistering diseases, like pemphigus. Newer agents with more potent depletion activity are also changing the approach to other diseases including Relapsing Multiple Sclerosis (ocrelizumab) and in an exciting development announced during the assembly of this issue, obinutuzumab received an FDA Breakthrough Therapy Designation for Lupus Nephritis (https://www.lupusresearch.org/existing-drug-gazyva-gets-expedited- for-lupus-nephritis/). Barnas, Looney and Anolik

Figure 1



The primordial alphabet soup of autoimmune disease. This issue reviews the field's progress in identifying the myriad array of cellular, metabolic, genetic and environmental cues that can contribute to human autoimmune disease and describe new approaches to treat these complex and heterogeneous diseases.

provide an update on the status of anti-B cell therapies with an incisive discussion of the heterogeneity and functional diversity of human B cells. The authors emphasize the data showing the importance of complete B cell depletion and discuss alternative approaches, the need for plasma cell targeting and the challenges associated with that goal.

While, as discussed in the Barnas' review, evidence demonstrating the benefit of complete B cell depletion continues to accumulate, this approach also eliminates B cells that may have the ability to prevent or ameliorate autoimmune disease. Simon Fillatreau's review reminds us of the known immunosuppressive functions of B cells and describes recent findings regarding the protective

role for IL-10 producing B cells in human MS and murine EAE. In addition, he discusses the interesting correlation between drugs showing efficacy in MS and the capacity of those treatments to support the development and maintenance of IL-10 producing regulatory B cells.

Ellebrecht, Lundgren and Payne address the important issue that total B cell depletion removes B cells that are required for immune protection. Indeed, B cell depletion is associated with increased infections, defective responses to vaccination and long-term hypogammaglobulinemia. The authors discuss the clearly advantageous strategy of selectively depleting pathogenic antigen-specific B cells — an approach that can be now applied with new technologies in diseases that that are driven by a limited number of antigens. They describe the use of genetically engineered T cells (CART cells) to eliminate antigen-specific B cells or antigen-specific CD8 and CD4 T cells; and to suppress antigen-specific autoreactive B and T cells with CAR T-regulatory cells.

Mike Cancro and Ann Rothstein *et al.* pick up on the theme of pathogenic B cell subsets and review the age or autoimmune associated B cells (ABCs) that are expanded in autoimmune patients and individuals who present with chronic inflammation due to infection or aging. The authors discuss the interesting observation that fate of B cells activated with TLR ligand and antigen is dictated by the nature of the TLR ligands. They outline how TLR7 and TLR9 ligands can direct whether the antigen-activated B cells will be recruited into the autoimmune ABC compartment or will be removed from the repertoire through programmed cell death.

Another pathogenic B cell subset is the pathogenic autoantibody producing plasma cell. Plasma cells and in particular, bone marrow long-lived plasma cells are not targeted by anti-B cell therapies and therefore, their therapeutic elimination represents an unmet need in human autoimmunity. In his review, Radbruch discusses the importance of plasma cells in autoimmunity; their developmental and survival requirements; the significance of their elimination as a required step towards tolerance restoration; and the challenges faced for their elimination. Finally, he discusses tantalizing work on potential strategies for the elimination of antigen-specific plasma cells.

The development of the long-lived plasma cells that reside in the bone marrow requires cognate T cell help. Abhinav Seth and Joe Craft discuss our still growing appreciation for the roles that T follicular helper (Tfh) cells play in driving autoreactive B cell and plasma cell responses. They remind us that the Tfh subset is not a monolithic population in either healthy or autoimmune individuals but is instead composed of phenotypically and functionally heterogeneous cells. They describe the varying environmental and developmental cues that program Tfh cells to acquire their functional attributes and discuss how we might probe Tfh heterogeneity to selectively target the pathogenic Tfh populations in autoimmune disease.

Andre Ballesteros-Tato and Amber Papillion also pick up the theme of Tfh cells in Lupus. They review data showing that the levels of IL-2 are decreased in SLE patients and describe how reduction in IL-2 availability can drive autoimmune disease by altering the balance between suppressive Tregs and pathogenic Tfh cells. The authors discuss promising pre-clinical and early clinical trials showing that supplementation with low dose IL-2 can reset the Treg/Tfh balance away from immunopathology and toward a more immunoregulatory environment.

The review from Lawrence Steinman *et al.* steps away from focusing on how to treat clinical autoimmunity to thinking about how to reset the immune system and re-establish self-tolerance. Although animal models demonstrate the promise of antigen-specific tolerance (AST) induction in autoimmune and allergic disease, data from early phase clinical trials to treat human autoimmunity are still emerging. Here, Steinman describes the successful use of AST therapy to tolerize patients that are undergoing protein or gene replacement therapy and discusses how similar approaches are being taken in autoimmune diseases like T1D, MS, Neuromyelitis Optica, and Celiac Disease where dominant and, in some cases, single autoantigens are responsible for driving clinical disease.

Finally, Soumya Raychaudhuri *et al.* provide us with a roadmap to the future of studying autoimmune disease by focusing our attention on immune single cells. They describe the powerful methods that can be leveraged to link T lymphocyte specificity to gene expression, phenotype and the underlying epigenetic programs that dictate the potential functional properties of these cells. While these newer 'omics approaches are revolutionizing our understanding of how functional inputs and outputs from single cells are integrated into the global (auto)immune response, the authors also point out the need to develop more sophisticated tools to analyze and amalgamate these complex data sets.

Collectively, this series of mini-reviews highlights recent progress in defining the cellular, metabolic, genetic and environmental cues that can each potentially contribute to human autoimmune disease (Figure 1). While dissecting all of the factors to identify the primordial cause and triggering pathogenic events of human autoimmunity is still daunting to contemplate, the promising new approaches that are being taken to identify the early stages of autoimmunity, to treat clinical disease, and to re-engage tolerance mechanisms gives hope that we will continue to improve diagnosis and treatment for the many individuals who suffer from autoimmune disease.