Preface

A unique feature of the normal immune system is that, while being able to mount responses to virtually all antigens of the environment, it also exhibits tolerance to its own components, a property that prevents attack of the body's own tissues. At times, however, self-tolerance breaks down, and the immune system fails to recognize self-antigens and mounts a misguided immune attack against its own tissues, which culminates in autoimmune disease. Currently, a growing number of disorders affecting virtually all organs or tissues of the human body have a proven or a strongly suspected autoimmune etiology. Their prevalence is worldwide and their etiology remains under investigation. In the past few years, our understanding of autoimmunity has witnessed important advances. This volume commemorates the 100th anniversary of the discovery of the first human autoimmune disease by Julius Donath and Karl Landsteiner in 1904 in Vienna. It comprises a collection of papers that show some of the ways in which insight into autoimmunity is opening new avenues for understanding their etiology and for designing novel immunointervention strategies.

The first part of the book is concerned with innate immunity, a branch of the immune system mainly directed to recognition of invariant molecules of infectious agents. Most of them are essential for pathogen survival and are conserved and shared by groups of pathogens. The innate immune system is essential for the activation of the adaptive immune response, capable of coping with a high mutation rate and antigen heterogeneity of infectious agents, and generating a long-lasting immune memory. Addressing its role in induction, progression, and protection of myocarditis, a disease linked to adenovirus or coxsackievirus that accounts for approximately 25% of all heart failure in North America, Noel Rose *et al*. tackle brilliantly the daunting task of bringing together the many facets of innate immunity in autoimmunity. They discuss in detail four of the major components of the innate response found to contribute to disease susceptibility: the complement system, natural killer cells, macrophages/dendritic cells, and early-acting proinflammatory cytokines. Also important in the innate immunity branch are toll-like receptors (TLRs) present on a variety of cell types. Paul N. Moynagh reviews the crucial involvement of TLR9 in mediating the immunostimulatory effects of bacterial DNA, potentially leading to activation of B cells and production of autoantibodies independently of T cells. Another example of the interplay between innate immunity and autoimmunity is discussed in the paper from the Terry Du Clos laboratory. Here, members of the pentraxin family, a phylogenetically ancient, highly conserved component of the innate immune system, are shown to bind microbial determinants and autoantigens, and to have the potential

to interact with the adaptive immune system through the complement system and Fcγ receptors. In studies of autoimmune type 1 diabetes, an autoimmune disease caused by T cell–mediated destruction of insulin-producing β cells in the pancreatic islets of Langerhans, Terry L. Delovitch and coworkers show how a subset of T cells act as regulators of both innate and adaptive immune responses. Since this cell population seems to be important in maintaining immune homeostasis, a further understanding of its role offers promise for the development of novel therapies for the prevention of diabetes.

The second part of this book focuses on genetic susceptibility. While early studies revealed that human autoimmune diseases require an inherited contribution, their genetics remains the focus of much investigation. Marta E. Alarcón-Riquelme discusses how the availability of the human genome sequence is playing an essential role in unraveling complex disease genetics, and how human genome scans are providing new discoveries. Most interesting is the observation that some of the genes identified are shared among various autoimmune diseases. In a search for factors that promote autoimmunity, Bruce Richardson's laboratory is exploring DNA methylation, an important determinant of chromatin structure that modifies gene expression through localized effects on the nucleosome polymers. Their article elegantly describes how the results can be used to predict functional, biochemical, and genetic alterations in T cells from patients with idiopathic lupus, and how failure to maintain T cell DNA methylation and chromatin structure contributes to human lupus. In myasthenia gravis, an organ-specific antibody-mediated autoimmune disease characterized by an immune response against the nicotinic acetylcholine receptor on the neuromuscular junction, the data described by Ann Kari Lefvert support the notion that the disease is polygenic, with subgroups of patients having different genetic backgrounds. Also polygenic is human lupus. C. Yung Yu and coworkers describe the strong association of complete C4A and C4B deficiencies with human lupus, providing support for the interpretation that C4A deficiency is a genetic risk factor for this disease.

Discussed in the third part of this volume are some potential triggers of autoimmunity that affect different organs. In rheumatic fever, a disease occurring as a delayed sequel of throat infection by *Streptococcus pyogenes* in 3–4 % of untreated children, Jorge Kalil and coworkers clearly show how molecular mimicry between streptococcal antigens and human heart tissue leads to rheumatic heart lesions. In this process, $CD4^+$ T lymphocytes are the major effectors of heart lesions, and several histocompatibility leucocyte antigen (HLA) class II molecules are associated with the disease worldwide, leading to multiple valvular lesions and/or mitral valve regurgitation. By contrast, in other disorders, no infectious agent has been identified. For example, celiac disease is an intestinal disorder caused by an inflammatory T cell response to gluten peptides bound to HLA-DQ2 or -DQ8, molecules with a preference for peptides that contain negatively charged amino acids. As described in the article from Frits Koning's laboratory, posttranslational modification of gluten is critical for the generation of a repertoire of T cell stimulatory peptides, an observation that may be relevant for other HLA-associated disease. The paper from Michael Hertl's laboratory dis-

cusses the pathogenic role of autoantibodies and the potential role of autoreactive T cells to desmogleins in pemphigus vulgaris. Aiming to develop antigen-specific immunotherapies, the authors put the emphasis on autoaggressive T cell epitopes and on a subset of T cells that may be critical in the maintenance/restoration of tolerance against desmogleins. Also unclear is the trigger involved in myasthenia gravis pathogenesis. Here, circumstantial evidence suggests a primary role of the thymus. Having established a model of intrathymic inflammation localized to the thymic medulla, Arnold I. Levinson *et al*. attempt to determine how intrathymic expression of the neuromuscular muscle type of acetylcholine receptors is involved in immunopathogenesis.

The fourth part of this volume is devoted to targets of autoimmunity. Paola Migliorini *et al*. focus on development of autoantibody-mediated nephritis. They review data indicating that distinct damage mechanisms probably coexist and play a role in the different phases of poststreptococcal nephritis, Goodpasture's syndrome, and systemic lupus nephritis. The contribution from Ansar Ahmed's laboratory lucidly addresses the role of hormonal factors in autoimmunity. Their effects have been demonstrated in many experimental settings. In humans, exposure to estrogens occurs through various sources, including physiological estrogens that vary during the lifetimes of women, pharmacological estrogens given for medical reasons and environmental estrogens, or endocrine-disrupting chemicals, (pesticides, plastic products, detergents, industrial by-products, municipal sewage–contaminated water that contains metabolites of estrogen-based contraceptive drugs). Nevertheless, their effects are complex and remain incompletely understood. Also important in deciphering autoimmunity are studies of the role of $CD4^+CD25^+$ regulatory T cells, discussed by Yi-chi M. Kong *et al*. in experimental murine autoimmune thyroiditis. Yet, our lack of understanding autoimmunity is perhaps best illustrated by the complexity of immune phenomena described in multiple sclerosis. This chronic inflammatory disease of the central nervous system represents one of the most common neurological diseases of young adults in developed countries. Its hallmarks include focal plaques of white matter demyelination, presence of autoreactive T cells in the blood of most patients, and autoreactive T cells and antibodies in the lesions. Arguing that the autoimmune responses in the affected patients are not invariably detrimental, but may even be beneficial, the provocative article from Hans Lassmann's laboratory challenges the "autoimmune hypothesis" of multiple sclerosis. Future work is required to provide a better understanding of the pathogenesis of this disease.

What could underlie the loss of tolerance in autoimmunity? As discussed in the fourth part of this volume, the reason may well relate to crippling of signaling pathways that govern the discriminatory potential of lymphocytes. Our immune system functions properly only because lymphocytes communicate with one another constantly. Recognizing molecules that are part of our body as self-antigens and distinguishing them from those that come from the external environment, lymphocytes instruct their relatives to attack invaders or produce growth factors or antibodies. This high-fidelity recognition is achieved through a network of intracellular communications wherein lymphocyte receptors are able to sense the nature of encountered molecules and to generate signals that are appropriately

delivered to the internal machinery, allowing specific functional responses. As in other cells, the amount of signals generated is fine-tuned for optimal transmission, and kinases and phosphatases control most activities. The chapter on B cells sheds light on the biochemical and molecular aberrations that are responsible for the aberrant lupus B cell biology. Inactivation of genes encoding B cell signaling molecules leads to autoimmune phenomena, and crippled signaling pathways are detectable in the B lymphocytes from patients with systemic autoimmunity. Focusing on rheumatoid arthritis, Ana M. Blasini and Martín A. Rodríguez summarize how abnormalities in T cell responses seen in patients with systemic autoimmunity can be related to identifiable signaling abnormalities. In lupus too, T cells display diverse cellular and cytokine abnormalities. The paper form George C. Tsokos's laboratory elegantly describes biochemical abnormalities that underwrite the diverse T cell abnormalities in lupus. Here, the decreased T cell receptor–associated ζ chain in effector T cells is due mostly to increased degradation, rather than to decreased transcription. Lupus T cells also express increased amounts of the transcriptional repressor CREM that binds IL-2 promoter, thereby limiting its expression. Of further importance is the increased spontaneous aggregation of lipid rafts on the surface membrane of lupus T cells, an abnormality that may contribute to the well-established overexcitable T cell phenotype. Altered signaling in both B and T cells also might account for the aberrant rates of apoptosis in lupus. Koji Yasutomo argues that the resulting increased levels of free-circulating chromatin represent a potential source of antigen trigger in systemic autoimmunity.

Finally, the recent advances in the field of autoimmunity have given clinicians exciting new tools for diagnosing and treating autoimmune disorders. The final section of the book discusses state-of-the-art therapeutic intervention strategies. The rationale for B lymphocyte depletion therapy in autoimmune disorders stems from the paramount role of B cells in autoimmunity. Jonathan Edwards *et al*. discuss in detail its potential for clinical applications, the logistics employed, and the clinical results obtained with anti-CD20 antibody. While the precise mechanisms of action remain to be elucidated, an alternative to this therapy is based on study of B lymphocyte longevity. Following migration to the periphery, the selection and survival of B cells are controlled by a variety of signals. Longevity factors, such as B lymphocyte stimulator (BLyS), also called BAFF, TALL-1, THANK, or zTNF4, that support differentiation of selected B cells into mature long-lived B cells are critical in determining the capacity to mount protective immune responses and to generate deleterious autoimmune responses. Their vital role in survival and maturation of B cells is discussed by William Stohl. In experimental animals, treatment with BLyS/BAFF antagonists ameliorates disease progression and enhances survival. Since patients with lupus, rheumatoid arthritis, or systemic sclerosis overexpress this longevity factor, and because a phase I clinical trial in lupus patients with a neutralizing anti-BLyS monoclonal antibody has documented the safety and biological activity of this BLyS antagonist, additional phase I and phase II clinical trials with a variety of BLyS antagonists are currently under way. Another unifying theme in autoimmune diseases is the involvement of cytokines that play key roles throughout the whole

course of the disease, from induction to effector functions. Hence, the control of autoimmunity by cytokine and anti-cytokine treatments represents a potential immunointervention strategy. The simplest approach, already in practice, is the specific inhibition of their action. As discussed in detail by Pierre Miossec, the use of TNFα inhibitors has provided clear evidence of the direct role of cytokines in complex inflammatory diseases. Another more physiological approach consists in stimulating endogenous regulatory mechanisms to restore an adequate balance. However, as Alan Tyndall and Paul Hasler point out, just as there is no consensual unifying mechanism in autoimmune diseases, there is no single successful treatment strategy. Most patients with severe autoimmune diseases are treated with a combination of glucocorticosteroids and immunosuppressive agents, but some either do not respond or require more toxic drugs to achieve or maintain clinical remission, and this subgroup poses a serious treatment dilemma. Rather than total eradication of clonal autoimmunity, hematopoietic stem cell transplantation techniques aim at resetting an imbalance in the complex immune network. The authors posit that this emerging alternative could be a viable option for selected autoimmune diseases patients. Currently, through an international collaboration, around 700 patients have received such treatment. The experience gained from the phase I and II clinical studies is sufficiently encouraging to be exploited in designing phase III randomized comparative trials in the major diseases.

Other potential immunointervention strategies have not reached the stage of clinical trials. In autoimmune uveitis, a disease that affects the inner eye of about 2% of the Western population, $CD4^+$ T $helper_1$ cells recruit inflammatory cells that can irreversibly destroy photoreceptors and neuronal tissue within the eye, leading to decreased vision or even blindness. Gerhild Wildner *et al*. describe several peptides mimicking a retinal autoantigen. Even though some of them are pathogenic in a rat model of experimental uveitis, they do not induce oral tolerance, thus indicating that pathogenic antigens are not obligatory oral tolerogens. The paper by Marc Monestier and coworker reviews the pathogenesis of atherosclerosis, with a particular emphasis on the role of the immune system. They also discuss studies that have addressed the importance of autoantibodies in this disease. Although their exact function is still not understood, manipulating humoral autoimmunity may represent a novel therapeutic or prophylactic approach in atherosclerosis. In their chapter, Silvia S. Pierangeli *et al*. review the molecular and intracellular pathways mediated by anti-phospholipid antibodies in platelets and endothelial cells that lead to thrombotic events. A better definition of the nature of the antiphospholipid antibody–target tissue interaction and the mechanism(s) by which these antibodies cause thrombosis may lead to devising new targeted treatment modalities. Finally, antigen-specific therapy represents a promising avenue for treating autoimmune diseases. It involves vaccination with autoantigens in a tolerogenic fashion, i.e., by nasal administration, oral feeding, and DNA vaccination, thought to induce regulatory T cells that produce anti-inflammatory cytokines. In the closing chapter, Matthias G. von Herrath and coworker focus on factors that influence the induction of autoantigen-specific regulatory T cells. In animal models, vaccination with autoantigens was successful in the prevention of

autoimmune diseases, such as type 1 autoimmune diabetes and experimental allergic encephalomyelitis. In contrast, it has been more difficult to see an immediate benefit in human clinical trials.

Thus, the study of autoimmunity has penetrated several fields of medicine, such as neurology, cardiology, nephrology, endocrinology, gastroenterology, dermatology, and rheumatology. Integrating autoimmunity concepts with a variety of disorders, this book aims to provide both researchers and clinicians with a basic understanding of discoveries tangential to their own areas. As these advances push back the frontiers of our understanding of autoimmunity, it is likely that further studies of these and related pathways will provide means to tease apart some of the molecular strands involved in the complex interactions that culminate in autoaggressive immune reactions. Future insight into elucidating autoimmunity will have an impact on the pursuit of new and better designs of improved diagnosis and treatments.

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