Molecular Pathology of Type 1 Diabetes mellitus
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Molecular Pathology of Type 1 Diabetes mellitus

Volume Editor  Matthias G. von Herrath, La Jolla, Calif.

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Preface

I am very pleased to present the 4th volume in the series *Current Directions in Autoimmunity* with a focus on insulin-dependent diabetes. Type 1 diabetes (T1D) as well as multiple sclerosis (MS) are thought to be T-cell-mediated autoimmune diseases, where autoaggressive lymphocytes lead to destruction of β cells or oligodendrocytes, respectively. Despite more than two decades of research, there are still many issues in autoimmune diabetes that are unclear and we do not understand. For example, although genetic factors clearly predispose to T1D, there have to be other environmental factors that tie into disease pathogenesis to explain the limited concordance of diabetes in monozygotic twins (30–40%). Further, it is not well understood how β cells die in vivo. Inflammatory cytokines, perforin-mediated lysis by cytotoxic T lymphocytes and FAS-dependent apoptosis have all been implemented through various experimental systems. Most importantly, the crucial autoantigens targeted by the autoaggressive response are still not well defined. This makes induction of antigen-specific tolerance as a strategy to prevent autoimmune diabetes difficult. However, other interventions relying on the induction of regulatory circuits have been used in animal models with good success. In the following I will give a brief overview over the chapters in this book and how they relate to these pertinent issues.

Genetic factors involving MHC susceptibility alleles are known to predispose to T1D from studies in humans (Bach, Garchon and van Endert) as well as the nonobese diabetic (NOD) mouse model (Serreze and Leiter). Initial enthusiasm has been somewhat dampened by the realization that the genetic etiology of autoimmune diabetes is complex and multifactorial involving the interaction of many susceptibility and protective loci. However, it will likely be possible to gradually determine the function of each gene in relation to disease in conjunction with the other susceptibility or protective alleles. It is an important realization that a significant proportion of the genes that correlate with disease
incidence and severity have no clearly defined immunological function at this point. Additionally, some of them might be directly protective for β cells or enhance their regenerative capacity. The links between genes and autoreactive T-cell responses are explored by Ridgeway and Fathman, who present some intriguing novel findings in their chapter. With modern technology we will be able to further unravel this complex network and establish the links between genetically determined functions, the environment and the immune system.

Environmental factors such as viral infections, nutrition and the gut as the major interface between our surroundings and the immune system are thought to have an important influence on disease development from studies in animal models (Solly, Honeyman and Harrison) and based on the fact that concordance of diabetes in monozygotic twins at risk is around 30–40%. Indeed, interesting novel results indicate that certain viral infections of the gut, for example rotaviruses, can have a statistically significant association with diabetes development in young children. The underlying mechanisms are not clear at this point. It is possible that similarity between viral and self-determinants (‘molecular mimicry’) leads to enhancement of autoaggressive responses. However, there is no direct in vivo proof for mimicry in T1D to date. Additionally, viral infections are excellent inducers of inflammation and antigen-presenting cell activation. This could lead to enhanced attraction of lymphocytes to an immune-privileged site such as the islets and increased presentation of self-antigens. Although these considerations make viruses excellent candidates for inducing or enhancing diabetes development, direct proof has remained scarce. One explanation for this failure to establish a direct link to date is that a viral infection can largely differ in terms of its effect on T1D depending on dose, strain and timing of infection (von Herrath, Oldstone, Homann and Christen). These findings underline the need for precise and in-depth immunological analyses that will have to accompany ongoing clinical trials or prospective studies. It is well possible that different infection patterns prevailing in regions of the world can explain the geographic divergence that has been noted for T1D. Another issue worth mentioning is that incidence of T1D is on the increase in industrialized countries. Environmental factors such as nutrition, use of antibiotics and hygiene standards might be partly responsible, but better understanding of T1D immune pathogenesis will be required to evaluate this hypothesis.

Autoreactive lymphocytes with the ability to attack β cells can escape thymic selection and are found in lymphoid organs and the blood. How is tolerance to autoantigens maintained? Important findings relevant to this theme are presented by Kreuwel and Sherman, who have investigated this issue in an antigen-specific model for T1D. An issue linked to the breaking of self-tolerance is, which effector pathways are utilized by autoaggressive lymphocytes once they have been activated, to destroy β cells. Studies from Thomas and Kay
have provided us with more insight into the importance of perforin produced by activated cytotoxic T cells and interferon-γ as well as TNF-α in killing the β cell. The current knowledge supports the notion that multiple detrimental immunological influences can act on the β cell simultaneously and that it will be a challenging task to build a death-resistant islet cell as an interventive approach. A crucial step could be the identification of essential ‘bottlenecks’ in death pathways and their targeted inhibition.

Not all components of an ongoing autoreactive process are necessarily damaging to the targeted organ. Indeed, autoaggressive and autoreactive regulatory responses have been described in many experimental models for autoimmune diseases. These coexist in a relatively fragile equilibrium, which is usually shifted in favor of the aggressive response before clinically manifested autoimmunity (in diabetes associated with destruction of more than 90% of all β cells) develops. Several differential ‘regulatory circuits probably exist (Quinn, Kumar, Jensen and Sercarz) and not all of them are antigen-specific. Enhancing the regulatory component by external immunization with the ‘regulatory’ autoantigens via the oral, nasal or intramuscular (DNA vaccines) routes has been successful in preventing diabetes in several animal models (Arreaza, Sharif, Cameron, Chen and Delovitch/von Herrath et al.). In these experiments the curative effect extended over the life of the animal without requiring continuous immunizations and interleukin-4 was an important mediator of protection. Induction of autoreactive regulatory cells is therefore an attractive strategy to prevent T1D, because it allows for antigen-specific regulation. However, in order to bring this intervention closer to a potential application in humans, we still have to overcome several obstacles. For example, it is not precisely known how to optimize efficacy, which effector mechanisms are used by autoreactive regulatory cells and how to safely choose the appropriate autoantigen suited for immune intervention.

Cytokines are a crucial regulator of autoimmunity at several levels. Timing of their induction, expression levels and precise localization appear to be very important in addition to the class of cytokine (Green and Flavell). Cytokines can act directly on the β cell, influence systemic activation and death of autoaggressive T cells and can help to induce or maintain regulatory T cells. Cytokine networks contain a certain redundancy and are therefore difficult to dissect using transgenic and knockout approaches. Novel regulatory promoters such as those employed successfully in Green’s models are of help to overcome some of this complexity.

It is important to constantly compare the features of animal diabetes models with the facts we really know about the human disease in order to establish their validity. Autoantibodies to islet cell antigens are commonly found in prediabetic individuals and can serve as a marker to assess the risk to develop
T1D in humans (Pietropaolo and Eisenbarth). Autoreactive T cells are more difficult to assess and Sønderstrup and Durinovitch-Bello offer us insight into this theme. It is known that antibodies do not contribute to diabetes pathogenesis, a finding that holds true in both humans and various animal models. Further, autoreactive T cells are found in humans as well as mouse models. Evidence suggests that the autoreactive process spreads from targeting certain initial self-antigens to a more diverse antigenic repertoire that involves aggressive as well as regulatory components. To date, it is not clear which antigen (insulin, GAD, heat-shock protein or IA-2) is the crucial primary diabetes antigen.

Therapeutically, since the primary antigens are still unknown and individuals at risk are frequently identified late during pathogenesis, when the autoreactive process has already spread to secondary islet antigens, induction of tolerance specific to one or a few autoantigens is not easily feasible. Therefore, current promising interventions to inhibit recurrent autoimmunity or rejection of islet grafts involve either more generalized inhibition of lymphocyte activation for example by the use of costimulatory blockers or induction of regulatory cells. The chapters of Gaglia and Harlan, Chatenoud and Delovitch/von Herrath discuss the most important aspects of such interventions. For example, blockade of CD40/CD40L interactions has been giving preliminary successful results in transplantation tolerance. Induction of CD25-positive regulatory T cells is a current important area of investigation and finally, autoantigen-specific (i.e. insulin) regulatory T cells are promising possibilities that are discussed in this book.

I would like to express my sincere thanks to all of the contributors for their excellent efforts, and to the Series Editor, A.N. Theofilopoulos, for commissioning me to edit this fourth volume. Due to their input, the book presents a state-of-the-art overview on the pathogenesis and current interventions of T1D and will be of value for investigators interested in understanding autoimmunity.

Matthias G. von Herrath, MD