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## **Preface**

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## **Genetics of type 1 diabetes**

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Alberto Pugliese

Type 1 diabetes (T1D) is a chronic condition of insulin deficiency resulting from the autoimmune destruction of pancreatic  $\beta$  cells. Genetic factors influence both susceptibility to and resistance from T1D. These factors include inherited polymorphisms, epigenetic mechanisms regulating the expression of inherited alleles, and post-transcriptional regulatory mechanisms. This article reviews the current knowledge about the genetics of T1D and the plausible mechanisms of susceptibility and resistance.

## **Environmental causes: dietary causes**

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Outi Vaarala

It has been shown in animal models that dietary factors modify the cytokine profile of islet-infiltrating immune cells, which have an effect on the development of autoimmune diabetes. Weaning to hydrolyzed formula instead of cows' milk formula decreases the incidence of autoimmune diabetes in animal models because of a shift to Th2 cytokine profile in islet-infiltrating T cells. In humans, the evidence from epidemiologic case-control studies and from the first prospective follow-up studies of children at genetic risk of type 1 diabetes is contradictory, and further prospective follow-up studies with longer follow-up times are needed. Furthermore, the available data suggest that risk ratios related to dietary risk factors are relatively low, which implies that the etiologic fraction of an individual dietary factor is small. Despite this, the elimination of an identified risk factor could result in prevention of type 1 diabetes in many children yearly.

Heikki Hyöty

During the last year, viruses have received new attention as potential triggers of type 1 diabetes mellitus (T1D). Research in the pathogenesis of T1D has increased in the area of enteroviruses, which several epidemiologic studies have shown to be associated with human T1D. Still, it is unknown whether a virus can cause T1D in humans, possibly excepting congenital rubella, which seems to be associated with diabetes in a considerable proportion of infected children. Although other viruses also deserve attention, the supporting evidence is less convincing than that for enteroviruses and congenital rubella. The commencement of large-scale multicenter studies specifically designed to confirm the possible role of enteroviruses makes it likely that any causal relationship will be uncovered in the next few years.

**Virally induced inflammation and therapeutic avenues in type 1 diabetes**

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Urs Christen, Amy Juedes, Dirk Homann, and Matthias G. von Herrath

RIP-LCMV mice mirror many aspects of human type 1 diabetes; research using this animal model has led to the development of various theories of how to abrogate disease, including by blocking local inflammation early in disease, blocking chemoattraction of lymphocytes early after infection, or by inducing regulatory lymphocytes. In the early stage of immunopathogenesis, chemokines and inflammatory cytokines actively kick-start the autodestructive process, propagating disease development. Deleting aggressive lymphocytes (removing the drivers of the  $\beta$ -cell destructive process) shows promise as a therapeutic intervention. Introduction of a secondary viral infection during the prediabetic phase causes inflammation that also can stop the diabetogenic response.

**Disease prevention with islet autoantigens**

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George S. Eisenbarth and Jean M. Jasinski

Type 1A (immune-mediated) diabetes mellitus is now a predictable disorder, and its onset can be prevented or delayed in animal models with therapies that include the administration of islet autoantigens. To date, therapies that can delay but not prevent anti-islet autoimmunity in animal models have not delayed the development of the disease in humans. Basic and physician scientists are addressing a number of barriers to the development of effective preventive therapy, with important recent progress in monitoring immune responses to  $\beta$ -cell-specific autoantigens. It is likely that optimal prevention of type 1A diabetes mellitus will depend on the ability to abrogate pre-existing autoimmunity directed at  $\beta$ -cell-specific peptides.

Recent introduction of well-characterized and -standardized antibodies tests has improved the feasibility of immunologic screening for type 1 diabetes mellitus (T1D). Prediction based on HLA genetic screening followed by cytoplasmic-islet-antibodies testing of individuals at increased genetic risk is efficient, but misses those with a low-risk genotype who develop T1D. Several prospective studies are following individuals at increased risk for T1D. Prevention strategies include eliminating exposure to triggering factors (*primary prevention*) or arresting autoimmune phenomena before the clinical disease (*secondary prevention*). Scant available data on triggering mechanisms of the autoimmune process limit the feasibility of primary prevention strategies. Major studies of secondary prevention include the administration of insulin, nicotinamide, or vitamin D, none of which have been successful.

### **Treatment of type 1 diabetes mellitus to preserve insulin secretion**

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Kevan C. Herold

Understanding of the pathogenesis and treatment of type 1 diabetes mellitus has been evolving since the disease was recognized as a chronic autoimmune process. Clinically significant insulin secretion is present in most patients, and retention of insulin secretion seems to be the most reliable and clinically significant endpoint for interventional studies. Initial trials involving broad-spectrum immunosuppressive agents to preserve insulin secretion showed clinical benefit, but recent approaches focus on inducing tolerance to avoid toxicities and the need for continuous immunosuppression. Strategies include administering islet antigens or other agents that enhance protective regulatory responses or specifically inactivate or eliminate pathogenic cells. Ultimately, correction of the disease will require cellular and immunologic approaches to restore  $\beta$ -cell mass and prevent recurrent autoimmunity.

### **Autoreactive T cells in human type 1 diabetes**

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Timothy I.M. Tree and Mark Peakman

Studies on T-cell targets reveal the potential for disease-related and human leukocyte antigen (HLA) allele-related peptide epitopes to be identified, using current technology. Studies using these epitopes, coupled with T-cell clone analyses, provide strong evidence that circulating autoreactive T cells are available for analysis in the peripheral blood of patients with type 1 diabetes (T1D). Functional examination of T-cell clones and T cells in the blood indicate that many responder cells have a Th1-like, pro-inflammatory phenotype. T-cell assay technology is becoming more refined and sensitive, but there is unlikely to be a "quick fix" solution to the direct and reliable enumeration of autoreactive T cells in peripheral blood. This article reviews literature that suggests that there can

be no substitute for the quality of information to be gained from the systematic analysis of T-cell clones and their epitopes. It is likely, therefore, that the ability to combine HLA-restricted epitope discovery with assays using functional read-outs, such as cytokine production, in carefully defined populations of patients with T1D, will be ultimately rewarding.

### **β-Cell replacement therapy (pancreas and islet transplantation) for treatment of diabetes mellitus: an integrated approach**

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David E.R. Sutherland, Angelika Gruessner, and  
Bernhard J. Hering

Type 1 diabetes (T1D) continues to represent a therapeutic challenge. Complications from secondary diabetes, observed in 30% to 50% of patients affected by T1D, result in poor quality of life, premature death, and considerable health care costs. The principal determinant of the risk of devastating diabetes complications is the total lifetime exposure to elevated blood glucose levels. Therefore, establishing safe and effective methods of achieving and maintaining normoglycemia will have substantial implications for the health and the quality of life of individuals with diabetes. Currently, the only way to restore sustained normoglycemia without the associated risk of hypoglycemia is to replace the patient's glucose-sensing and insulin-secreting pancreatic islet β-cell islets, either by the transplantation of a vascularized pancreas or by the infusion of isolated pancreatic islets.

### **Engineering islets: lessons from stem cells and embryonic development**

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Michelle J. Doyle and Lori Susse

The attempts to understand pancreatic cell-type specification and apply this information to direct the differentiation of insulin-producing cells from various sources have produced significant advances in the past few years. The steady progress of embryonic stem and stem/progenitor cell isolation, growth, and manipulation, combined with new technologies for genetic manipulations and lineage tracing and a greater understanding of the endogenous factors required for β-cell differentiation and expansion, has made the identification of alternative sources of insulin-producing cells a possibility. These fields are still young but continued collaborative efforts between researchers of many different scientific disciplines will allow clinicians to achieve the common goal of generating alternative sources of β cells for therapeutic purposes.

### **The role of continuous glucose sensors in diabetes care**

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Satish K. Garg, Halsley K. Hoff, and H. Peter Chase

Continuous glucose monitoring enables convenient and automatic monitoring of glucose levels with minimal fingersticks, leading to improved glycemic control. Numerous studies concluded that the

Medtronic MiniMed Continuous Glucose Monitoring System, which consists of a subcutaneous sensor and an external monitor, reduced wide glucose excursions, improved diabetes control, and lowered hemoglobin A1C values. The GlucoWatch2 Biographer is the first frequent monitoring device to report real-time glucose values to patients. The noninvasive, watch-like device provides painless glucose measurement that also enables better glycemic control. There are many other technologies that are under various stages of development. However three of these technologies not yet approved in the United States include a long-term implanted sensor with external pager-sized receiver, a short-term (3-day) implantable sensor, and a noninvasive device that uses near-infrared spectroscopy.

### **Glucose sensors: toward closed loop insulin delivery**

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Chee W. Chia and Christopher D. Saudek

Continuous glucose monitoring is important for managing glycemic control in patients with diabetes. There have been significant breakthroughs in glucose sensing over the past few years with the introduction of several continuous glucose monitors for clinical use. The long-term goal of a fully automated, closed-loop insulin delivery system, however, depends on further sensor development and reliable linking to a delivery system.

### **Celiac disease associated with type 1 diabetes mellitus**

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Marian Rewers, Edwin Liu, Jill Simmons, Maria J. Redondo, and Edward J. Hoffenberg

Celiac disease is a chronic systemic autoimmune disorder associated with type 1 diabetes mellitus and induced by gliadin (gluten) proteins found in several grains. Genetically susceptible individuals can develop various forms of the disorder, ranging from asymptomatic to full-blown disease. The health consequences of this disorder can influence growth and development in the young, as well have other long-term problems for individuals as they age. This article discusses diagnosis and treatment strategies for this disorder.

### **Microvascular complications of diabetes**

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Zhiheng He and George L. King

Several theories of the pathogenesis of microvascular complications of diabetes (diabetic retinopathy, nephropathy, and neuropathy) have been proposed: (1) generation of reactive oxygen species and oxidative stress, (2) activation of polyol pathway, (3) formation of advanced glycation end products, (4) induction of flux through the hexosamine pathway, (5) altered expression and action of growth factors, and (6) activation of protein kinase C. Based on these theories, specific interventions are feasible to prevent the

development of diabetic complications even if satisfactory euglycemic control is not achieved.

**Emerging therapies: controlling glucose homeostasis, immunotherapy, islet transplantation, gene therapy, and islet cell neogenesis and regeneration**

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James A. Ruggles, Donald Kelemen, and Alain Baron

This article examines potential emerging therapies for type 1 diabetes by controlling glucose homeostasis, immunotherapy, islet transplantation and gene therapy, and islet cell neogenesis and regeneration. For glucose homeostasis, correction of insulin deficiency has been the classic focus; however, more recent data indicate that deficiency of another glucoregulatory  $\beta$ -cell hormone, amylin, and exaggerated glucagon secretion together lead to excessive postprandial glucose excursions. Prevention of immune-mediated  $\beta$ -cell destruction involves either preventing or halting the autoreactive T-cell attack directed against  $\beta$  cells or making  $\beta$  cells better able to withstand immune attack. The recent identification of  $\beta$ -cell growth factors and development of stem cell technologies provide a potential route for the reversal of diabetes by means of  $\beta$ -cell regeneration. Finally, there is  $\beta$ -cell replacement or substitution, which covers a wide range of intervention strategies, including human whole pancreas transplantation, xenotransplantation, cell-based therapies, gene therapy, stem cells, and drug therapy, to promote  $\beta$ -cell proliferation and neogenesis.

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