

CONTENTS

Foreword: Immunodeficiency—Improving the Deficiency of Knowledge	xiii
Rafeul Alam	

Preface	xv
Jordan S. Orange	

From Infectious Diseases to Primary Immunodeficiencies	235
Jacinta Bustamante, Shen-Ying Zhang, Horst von Bernuth, Laurent Abel, and Jean-Laurent Casanova	

The field of primary immunodeficiencies has expanded, thanks to the exploration of novel clinical phenotypes and their connection with morbid genotypes, and the subsequent exploration of new patients who have known primary immunodeficiency-defining clinical phenotypes and their connection with novel morbid genotypes. This two-way process is becoming increasingly active, particularly for patients who have infectious diseases in whom the underlying immunologic and genetic causes remain mostly unexplained. The authors review how the exploration of children who have clinical infectious diseases caused by mycobacteria, pneumococcus, and herpes simplex virus recently led to the description of three new groups of primary immunodeficiencies. These three examples justify the continuation of the genetic exploration of novel infectious phenotypes and novel patients who have infections. This challenging process will eventually reap its rewards, to the benefit of patients and their families.

Congenital Neutropenia Syndromes	259
Kaan Boztug, Karl Welte, Cornelia Zeidler, and Christoph Klein	

Congenital neutropenia syndromes comprise a heterogeneous group of inherited disorders. Hereditary conditions associated

with low neutrophil counts are persistent and need to be differentiated from neutropenia secondary to autoimmune processes or other pathologic conditions, such as myelodysplasia or leukemia. Clinically, congenital neutropenia is characterized by recurrent bacterial infections. Recently, several novel genetic defects were described in patients with congenital neutropenia, shedding light on the pathophysiology of these rare diseases.

The Hyper-IgE Syndromes

277

Alexandra F. Freeman and Steven M. Holland

The hyper IgE syndromes (HIES) are rare primary immune deficiencies characterized by elevated serum IgE, rash, and recurrent bacterial infections of the skin and lung. Autosomal dominant HIES, the most common disease in this group, results from *STAT3* mutations and has a variety of connective tissue and skeletal abnormalities. The genetic etiologies of the more rare autosomal recessive forms still need delineation. Treatment of these syndromes has relied on prophylactic and therapeutic antimicrobial agents and aggressive skin care. The new and evolving genetic and immunologic understandings of this previously elusive set of diseases should lead to more effective disease-specific therapies.

Hemophagocytic Lymphohistiocytosis and Other Hemophagocytic Disorders

293

Alexandra H. Filipovich

Hemophagocytic disorders result when critical regulatory pathways responsible for the natural termination of immune/inflammatory responses are disrupted or overwhelmed. Hemophagocytic disorders reflect pathologic defects that alter the normal crosstalk between innate and adaptive immune responses, and compromise homeostatic removal of cells that are superfluous or dangerous to the organism. Although hemophagocytic disorders are considered rare, increased awareness of these conditions has led to more frequent diagnoses, more rapid initiation of life-saving treatments, and new insights into the molecules and pathways involved in natural immune down-regulation. Furthermore, improved understanding of the immunologic abnormalities revealed by hemophagocytic disorders informs potential new treatments for life-threatening multisystem organ dysfunction related to sepsis in the intensive care unit setting and severe cases.

Immune Dysregulation in Primary Immunodeficiency Disorders

315

Troy R. Torgerson

The past several years have brought an increased awareness of the prevalence of autoimmunity and immune dysregulation among patients who have primary immunodeficiency disorders (PID). The recent clinical and molecular definition of PID, in which the

primary defect is in the immunoregulatory compartment of the immune system, has offered insight into the basic mechanisms of immune tolerance, which has provided new targets and new techniques to study immune tolerance in PIDD. Many of these studies have focused on the presence and function of regulatory T (T_{REG}) cells in PIDD, particularly since the discovery of murine and human syndromes associated with T_{REG} deficiency. This article focuses on the current state of knowledge regarding the role of T_{REG} in various PIDD that have clinical features indicative of dysregulated immunity.

Genetic Defects of Apoptosis and Primary Immunodeficiency 329
Helen C. Su and Michael J. Lenardo

Programmed cell death is important for maintaining lymphocyte homeostasis. Several human-inherited diseases with impaired apoptosis have been identified at the genetic level: autoimmune lymphoproliferative syndrome, caspase-8 deficiency state, and X-linked lymphoproliferative syndrome. These diseases feature excess lymphocyte accumulation, autoimmunity, or immunodeficiency. Elucidating their molecular pathogenesis has also provided new insights into the signaling mechanisms regulating apoptosis and lymphocyte activation.

Chromosome 22q11.2 Deletion Syndrome: DiGeorge Syndrome/Velocardiofacial Syndrome 353
Kathleen E. Sullivan

DiGeorge syndrome, or chromosome 22q11.2 deletion syndrome, is a disorder affecting multiple organ systems. The immunologist may be called on to coordinate complex medical care tailored to the specific needs and unique clinical features of each patient. This article focuses on the immune system, but patients require a holistic approach. Attention to cardiac, nutritional, and developmental needs in early infancy is important, and it is critical to identify the rare infants who require either a lymphocyte or thymus transplant. Later, speech and school issues dominate the picture. Allergies and autoimmune disorders also may be troubling for some school-age children.

Common Variable Immunodeficiency: An Update on Etiology and Management 367
Patrick F.K. Yong, Michael Tarzi, Ignatius Chua, Bodo Grimbacher, and Ronnie Chee

Common variable immunodeficiency (CVID) represents a heterogeneous group of primary antibody deficiency disorders characterized by recurrent infection and by inflammatory, granulomatous, and autoimmune complications. Recently, there have been significant advances in understanding the pathogenesis of the disease, with five genetic mutations identified in patients who have a CVID

phenotype. Clinical care also has progressed with refinements in treatment and the development of classification schemes for prognostic and research purposes. Significant delays in diagnosis remain, however. It is likely that more genetic defects will be identified in the future, further shrinking the pool of patients who have CVID of unknown cause.

Genetic Diagnosis of Primary Immune Deficiencies

387

Massimo Morra, Ute Geigenmuller, John Curran,
Irene R. Rainville, Tim Brennan, Judd Curtis, Vienna Reichert,
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Gene testing in primary immune deficiencies (PIDs) once was limited to expert academic laboratories, but now is easily available to physicians with a broad range of clinical expertise. Such testing can establish or confirm a suspected diagnosis and also may predict future disease risk in advance of clinical signs and symptoms, inform reproductive decision making, and guide clinicians in selecting the most appropriate therapeutic options. This article, based on the authors' experience and a review of the published literature, discusses some of the advances and challenges currently encountered in the clinical molecular genetic diagnosis of PIDs.

Principles of and Advances in Immunoglobulin Replacement Therapy for Primary Immunodeficiency

413

Melvin Berger

During the last 2 decades, the continued development and the large-scale production of polyclonal immune serum globulin (ISG) preparations with improved safety and tolerability profiles have allowed treatment to focus on quality of life and long-term freedom from the complications of primary immune deficiency disease, rather than just on freedom from severe acute infections and survival. Available ISG preparations allow routine therapy by a variety of routes and regimens that can be tailored to suit individual patients. Continued vigilance is required, however, because problems with emerging diseases, and the costs and availability of ISG are likely to present continuing challenges.

Advances in Hematopoietic Stem Cell Transplantation for Primary Immunodeficiency

439

Andrew R. Gennery and Andrew J. Cant

The molecular bases of most primary immunodeficiencies (PID) have been discovered. Long-term follow-up of patient cohorts treated with antimicrobial prophylaxis has demonstrated good short-term prognosis but with increasing morbidity and mortality over time. The results of hematopoietic stem cell transplantation

(HSCT) for PID have improved incrementally over time, with survival and cure of 90% for some defined diseases. This article examines the advances in HSCT for PID and argues that HSCT should be considered earlier for most patients.

Gene Therapy for Primary Immunodeficiencies

457

Adrian J. Thrasher

Primary immunodeficiencies are a group of disorders that are highly amenable to gene therapy because of their defined pathophysiology and the accessibility of the hematopoietic system to molecular intervention. The development of this new therapeutic modality has been driven by the established morbidity and mortality associated with conventional allogeneic stem cell transplantation, particularly in the human leukocyte antigen-mismatched setting. Recently, several clinical studies have shown that gamma retroviral gene transfer technology can produce major beneficial therapeutic effects, but, as for all cellular and pharmacologic treatment approaches, with a finite potential for toxicity. Newer developments in vector design showing promise in overcoming these issues are likely to establish gene therapy as an efficacious strategy for many forms of primary immunodeficiencies.

Index

473