Targeted strategies directed at the molecular defect: Toward precision medicine for select primary immunodeficiency disorders

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Activity Objectives:

1. To recognize the increasing spectrum of syndromes with immune dysregulation and immunodeficiency.
2. To understand how the molecular pathology underlying these syndromes can be targeted by novel personalized treatments.

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Primary immunodeficiency disorders (PIDs) represent a range of genetically determined diseases that typically have increased susceptibility to infections and in many cases also have evidence of immune dysregulation that often presents as autoimmunity. Most recently, the concept of gain-of-function mutations associated with PIDs has become well recognized and adds a new dimension to the understanding of this group of disorders, moving beyond the more commonly seen loss-of-function mutations. The rapidly expanding genetic defects that have been identified in patients with previously uncharacterized PIDs has opened up the potential for targeted therapy directed at the specific disease-causing abnormality. This has been driven by linking PID-specific genetic defects to the associated unique abnormalities in cellular signaling pathways amenable to directed therapies. These include agents that either block overactive or enhance underresponsive cellular pathways. Selected primary immunodeficiencies were chosen, the genetic defects of which have been recently characterized and are amenable to targeted therapy, as a reflection of the power of precision medicine. (J Allergy Clin Immunol 2017;139:715-23.)

Key words: *Personalized medicine, primary immunodeficiency disorders, immune dysregulation, autoimmunity, therapy, mutation*

The number of genetically defined primary immunodeficiency disorders (PIDs) has increased significantly over the past 10 to 15 years[1] related to the availability of positional cloning and, more recently, massively parallel (next-generation) sequencing. Investigations of previously uncharacterized patients using the latter technology is dramatically increasing our understanding

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Abbreviations used
APDS: Activated phosphoinositide 3-kinase syndrome
CMC: Chronic mucocutaneous candidiasis
CTLA4: Cytotoxic lymphocyte antigen 4
GOF: Gain of function
HSCT: Hematopoietic stem cell transplantation
JAK: Janus-associated kinase
LOF: Loss of function
LRBA: LPS-responsive and beige-like anchor
mTOR: Mammalian target of rapamycin
PASLI: p110δ-Activating mutation causing accumulation of senescent T cells, lymphadenopathy, and immunodeficiency
PID: Primary immunodeficiency disorder
PI3K: Phosphoinositide 3-kinase
STAT: Signal transducer and activator of transcription
T_{FH}: Follicular helper T
WHIM: Warts, hypogammaglobulinemia, infections, and myelokathexis

of the genetic basis of PIDs well beyond purely developmental abnormalities to include a range of defects affecting specific aspects of immune signaling and also moving from exclusively loss-of-function (LOF) mutations to include gain-of-function (GOF) mutations. Associated with this expanding understanding of immunologic disorders is the recognition that many of the more recently characterized PIDs include significant immune dysregulation often manifesting as autoimmunity in addition to increased susceptibility to infection.

The capacity to precisely identify the molecular basis of an immunologic disorder has also opened the door to targeted therapies focused on either enhancing or inhibiting the consequences of an individual defect. This approach represents one of the central components of precision medicine (ie, therapy directed at the specific causative defect of a particular disorder rather than applying a nonspecific therapeutic approach). It is highly likely that the identification of new genetic defects associated with immune dysfunction will lead to additional examples of targeted therapeutic approaches for optimal clinical management of the patients affected by immune disorders. In this article we present the clinical phenotype of a number of more recently characterized PIDs and introduce specific therapeutic approaches that have emerged based on the current understanding of the molecular defect linked to each disorder.

Because of space limitations, this focused discussion does not address the obvious importance of identifying the PID genotype when considering possible gene therapy or the potential contribution of the severe combined immunodeficiency genotype in the optimal approach for immune reconstitution associated with hematopoietic stem cell transplantation (HSCT).

ACTIVATED PHOSPHOINOSITIDE-3 KINASE δ SYNDROME

PIK3CD GOF mutations result in an immunologic disorder that causes accumulation of senescent T cells, lymphadenopathy, immunodeficiency, and autoimmunity. This disease is referred to either as activated phosphoinositide 3-kinase syndrome (APDS) or p110δ-activating mutation causing accumulation of senescent T cells, lymphadenopathy, and immunodeficiency (PASLI).[2-4] To

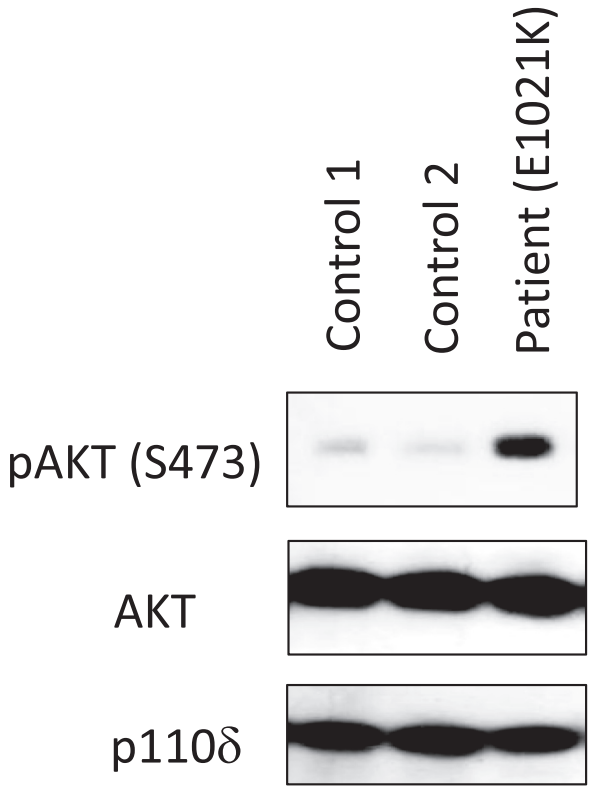

FIG 1. Immunoblot of phospho-AKT (serine 473), AKT, and PI3Kδ (p110δ) from 2 control subjects and 1 patient with APDS/PASLI (E1021K).

date, there have been 4 different heterozygous mutations defined producing GOF mutations that are associated with the following amino acid changes: E1021K, N334K, E525K, and C416R, with E1021K being by far the most common. Constitutive activation of phosphoinositide 3-kinase (PI3K) δ can also result from heterozygous splice site mutations of the *PIK3R1* gene, encoding for the p85α subunit of the molecule.[5,6] By removing the p110δ-binding site, these splice site mutations release p110δ from the inhibitory control mediated by the p85α subunit. This condition is also referred to as APDS2.

The clinical presentation of APDS/PASLI and APDS2 typically begins with recurrent sinopulmonary infections in virtually all patients.[7,8] The onset of infections is typically in childhood, ranging from infancy until the early school years. The pulmonary infections are associated with a variety of bacterial pathogens but most commonly involve *Streptococcus pneumoniae* and *Haemophilus influenzae*. In studies to date, bronchiectasis has been found to be caused commonly by the frequency and chronicity of pulmonary infections.[4,7,8] Recurrent or persistent Herpesviridae family virus infections are also seen in about half of these patients, including EBV, cytomegalovirus, herpes simplex virus, and varicella zoster virus.[7] Noninfectious complications include nonneoplastic lymphadenopathy, splenomegaly, and/or hepatomegaly in the majority of patients, as well as autoimmune disease (approximately 40%), nodular mucosal lymphoid hyperplasia (approximately 30%), and enteropathy (approximately 25%).[7,8] The most serious complication of this disorder is the markedly increased frequency of lymphoma (particularly B-cell lymphoma), a development that represents one of the major causes of mortality.[7,8] As noted, one unique