The primary immunodeficiency disorders

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Abstract

The primary immunodeficiency disorders are clinically heterogeneous diseases, the majority of which arise from inborn errors in immunologically relevant genes. A high index of suspicion is required to reach a diagnosis of primary immunodeficiency, and a timely diagnosis significantly improves patient outcomes. This contribution reviews the relationships between the underlying genetic defects and the associated immunological and clinical phenotypes seen in clinical practice. Diagnostic and therapeutic approaches to primary immunodeficiencies are also discussed.

Keywords Autoimmunity; clinical immunology; genomics; infectious disease; MRCP; primary immunodeficiency

Key points

- Primary immune deficiencies present in a heterogeneous manner, and a high index of suspicion is required to diagnose primary immune deficiencies. Any patient with a suspected or proven primary immunodeficiency disorder (PID) should be referred to the care of a clinical immunologist
- Depending on the specific disease, treatments for PIDs include prophylactic antimicrobials, replacement immunoglobulin, immunosuppressive drugs, bone marrow transplantation and gene therapy
- Genomics approaches have revolutionized the diagnosis of poorly defined PID, offering patients the advantages of precise molecular diagnoses, genetic counselling and targeted immunotherapeutics

Introduction

The immune system is a complex network of cells and molecules responsible for preserving tissue homeostasis by providing defence against pathogens, performing tumour immunosurveillance and maintaining immunological tolerance. The primary immunodeficiency disorders (PIDs) are clinically heterogeneous disorders, the majority of which arise from genetic defects in immunologically relevant genes.

PIDs were once thought to be exclusively associated with recurrent infections. However, as our understanding of the complexity of cellular and signalling networks has grown, it has become increasingly apparent that the clinical consequences of mutations in PID genes extend well beyond susceptibility to infection with bacteria, viruses and opportunistic organisms. *Immune dysregulation* phenotypes of PID are commonplace and include multiorgan autoimmunity, malignancy (particularly haematological) and autoinflammatory pathology such as periodic fever syndromes. These pathologies are not mutually exclusive and are often seen in combination. Furthermore, different mutations in the same gene can lead to different PID presentations, depending on whether the net effect is gain of function or loss of function at the protein level.

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Most PIDs cause symptoms in early life. However, the heterogeneous constellation of symptoms often results in delayed diagnosis, to the patient's detriment. Adult presentations of PID tend to reflect polygenic diseases, such as common variable immunodeficiency disorder (CVID), or diseases in which environmental factors expose the underlying immunological phenotype (e.g. exposure to endemic mycobacteria can lead to the MonoMAC phenotype of GATA binding protein 2 (GATA-2) deficiency, characterized by monocytopenia and non-tuberculous mycobacterial infection).

The advent of next-generation sequencing (NGS) has revolutionized clinical immunology by allowing detailed characterization of the genetic architecture of the immune system in healthy individuals and patients with significant immunological defects (Figure 1).[1] To date, >300 distinct, monogenic primary immunodeficiencies have been described, which are classified in detail in the 2015 International Union of Immunological Societies consensus document.[2]

Below we contextualize how archetypal PIDs arise from genetic defects affecting the three stages of the immune response: (1) recognition of immunological danger, (2) immunological response to that danger, and (3) regulation of that response to restore tissue homeostasis (Figure 2). For the general physician, specific knowledge of individual PIDs is not required, but guidance on when to suspect PID and which simple investigations help in diagnosis is provided. Examples are used to highlight features specific to the perturbed stage of the immune response.

Genetic defects in pathogen recognition

All immunological responses begin with the recognition of a threat to tissue homeostasis. Discrimination between immunological 'self' and 'non-self' occurs via the identification of highly conserved motifs called pathogen-associated molecular patterns (PAMPs), which are recognized by genomically encoded pattern recognition receptors (PRRs). A variety of PRRs contribute to the recognition of viral, bacterial and fungal PAMPs, the largest family being the Toll-like receptor (TLRs). Ligation of PRRs by

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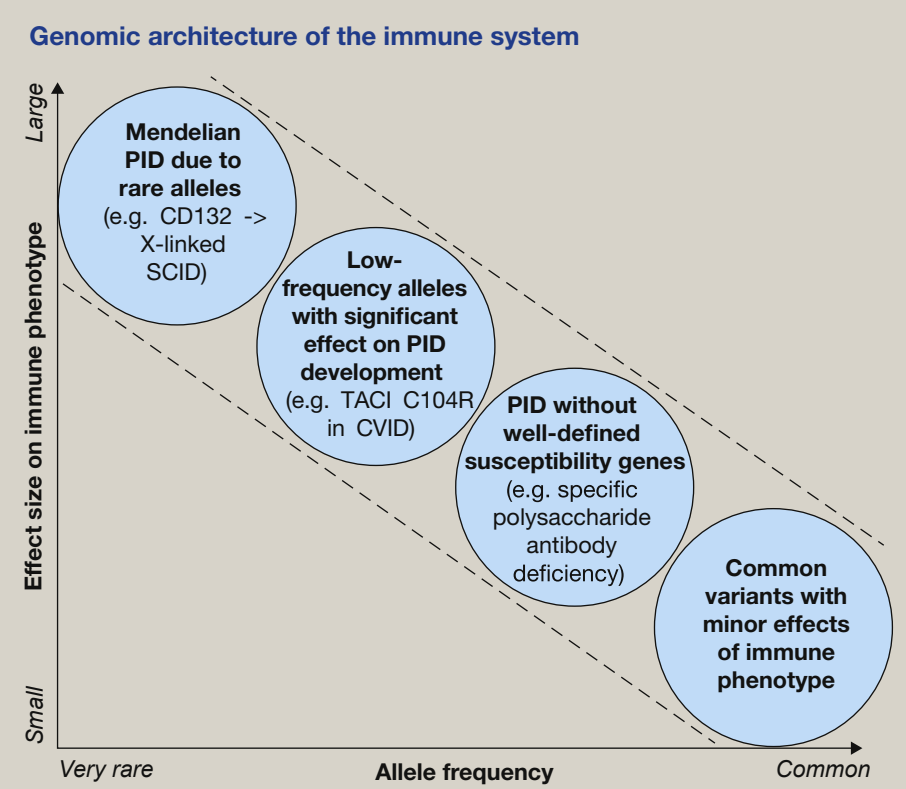

Thousands of common coding and non-coding genomic variants exist that have minor effects on an individual's immune phenotype. At the opposite end of the spectrum, there are a handful of truly monogenic primary immunodeficiency disorders (PIDs) with 100% penetrance (e.g. *CD132* mutations causing severe combined immunodeficiency disorder (SCID)). Between these extremes exist rare variants with significant effects on PID development (e.g. TACI C104R in CVID), variants that appear to lead to monogenic PID without 100% penetrance (e.g. *CTLA4* mutations) and PID without well-defined susceptibility genes (e.g. Specific IgA deficiency).

Figure 1

cognate PAMPs initiates signalling cascades that shape specific immunological responses against specific pathogens.

Immunodeficiency can occur when a PRR, its subcellular localization or its downstream signalling is disrupted. For example, Mendelian susceptibility to herpes simplex virus (HSV) encephalitis can arise from genetic defects in TLR-3, a PRR that recognizes double-stranded RNA, a by-product of HSV viral replication. Individuals with TLR-3 defects suffer from recurrent, severe HSV encephalitis from an early age. The endosomal localization of TLR-3 is critical to its function, and the polytopic protein UNC-93B facilitates TLR-3 subcellular localization. Genetic mutations that prevent interaction between TLR-3 and UNC-93B produce an identical clinical phenotype to TLR-3 defects, but neither confers susceptibility to other viral infections. Such selectivity in the role of individual proteins in the defence against specific infectious disease is not unusual: compound heterozygous mutations in the transcription factor IRF7, which controls type 1 interferon (IFN) responses, selectively confers susceptibility to severe influenza infection.

Other TLRs sense a variety of bacterial PAMPs including lipopolysaccharide (TLR-4), peptidoglycan (TLR-2) and flagellin (TLR-5), and signal through the Myddosome, a cytosolic, multiprotein complex that assembles following TLR ligation and initiates inflammatory gene expression. Mutations in two critical components of the Myddosome, MyD88 and IRAK-4, cause PID with identical clinical features.

MyD88 and IRAK-4 deficiencies are characterized by recurrent invasive bacterial infections including meningitis, sepsis, osteomyelitis, deep abscesses and ear, nose and throat infections. The spectrum of infection in these patients is narrow, despite the ubiquity of the Myddosome; *Streptococcus pneumoniae, Staphylococcus aureus and Pseudomonas aeruginosa* are the most commonly isolated organisms. Interestingly, patients become less susceptible with age, as adaptive immune responses develop against these organisms.

Defects in PRRs can also confer susceptibility to fungal infections. Dectin-1 senses β-1,3-linked and β-1,6-linked glucan from fungal cell walls. A severe PID involving both chronic mucocutaneous candidiasis and deep dermatophytosis can arise from mutations in the gene encoding CARD9, a downstream adapter protein employed by dectin-1 for signalling.

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