

PERSPECTIVE

Primary Immunodeficiencies: A Field in Its Infancy

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A paradigm shift is occurring in the field of primary immunodeficiencies, with revision of the definition of these conditions and a considerable expansion of their limits. Inborn errors of immunity were initially thought to be confined to a few rare, familial, monogenic, recessive traits impairing the development or function of one or several leukocyte subsets and resulting in multiple, recurrent, opportunistic, and fatal infections in infancy. A growing number of exceptions to each of these conventional qualifications have gradually accumulated. It now appears that most individuals suffer from at least one of a multitude of primary immunodeficiencies, the dissection of which is helping to improve human medicine while describing immunity *in natura*.

The field of human primary immunodeficiencies (PIDs) has witnessed considerable success (1, 2) since its emergence in the 1950s, highlighted by the discovery of X-linked agammaglobulinemia (3), congenital neutropenia (4), and severe combined immunodeficiency (SCID) (5). Its development has saved the lives of tens of thousands of patients with PIDs and other conditions worldwide and has given rise to ground-breaking concepts in immunology and beyond. The clinical description of over 200 diseases, for which more than 100 genetic etiologies have been described, has provided opportunities for diagnosis and genetic counseling. Moreover, an understanding of the pathogenesis of PIDs has paved the way for immunological interventions, with proof-of-principle demonstrated for new treatments, such as immunoglobulin G replacement, bone marrow transplantation, and gene therapy, in patients with PIDs (1). Key discoveries in fundamental biology have also emerged from the forward genetic identification of many hitherto unknown PID-causing genes, such as the ubiquitous DNA-repair regulator *ATM* in patients with ataxia telangiectasia (6) and a gene expressed in the thymus—the tolerance regulator gene *AIRE*—in patients with severe autoimmunity (7). PIDs have probably had an even greater biological impact on the definition of host gene function *in natura*—i.e., in the setting of a natural ecosystem—a unique added value of studying the human model (8). It is commonly thought that most, if not all PIDs, have been described.

On the contrary, we would argue that there has been a subtle but profound paradigm shift, revisiting the definition of PIDs and heralding a formidable expansion of this field (Table 1).

The Expanding Universe of PID-Defining Clinical Phenotypes

What is a PID? There is, quite rightly, a consensus that “primary” refers to a disease-causing genotype. However, there is a common misconception that “immunodeficiency” should be defined by an “immunological” phenotype, in the hematopoietic sense of the term, i.e., a detectable molecular or cellular anomaly in the blood. Such phenotypes are often quantitative, changing with the technological means available to measure them, and any threshold put forward to define a deficiency at the population level is necessarily arbitrary. Moreover, host defense is not restricted to the blood. Despite these inherent limitations, PIDs have historically been defined and classified according to immunological phenotypes (9). Paradoxically, epidermodysplasia verruciformis (EV)—a life-threatening inherited predisposition to warts caused by oncogenic papillomaviruses discovered in 1946 and, as such, probably the first PID to be described—was not considered to be a PID until two EV-causing genes were identified in 2002 (10), due to its lack of an overt immunological phenotype. A clinical definition of PIDs is therefore more rigorous, and the most conservative definition is death due to inborn errors of immunity, or a threat to life, if the illness can be rescued by drug treatment. A more controversial issue is the definition of impaired immunity; it is surprisingly still not universally accepted that any given life-threatening infection results, by definition, from an immunodeficiency, whether inherited or acquired (11). Life expectancy at birth did

not exceed about 20 to 25 years, mostly due to infectious diseases, until the end of the 19th century and the advent of Pasteur’s microbial theory of disease. This implies that most humans remain immunodeficient, although their immunodeficiency is masked by medical progress (11). Immunodeficiency is probably also common in other animal and plant species. In any case, given the strong epidemiological evidence documenting the importance of genetic background in predisposition to infections, any severe infectious illness may be considered a potential PID-defining phenotype (11). Many other relevant clinical phenotypes have been identified, including autoimmunity (7, 12), angioedema (13), granulomas (14), autoinflammation (15), hemophagocytosis (16), and thrombotic microangiopathy (17). A few PIDs also confer predisposition to allergy (18) or oncogenic virus-induced cancers (10, 19), and other tumors may also be associated with certain PIDs (6, 20, 21). It seems highly likely that other phenotypes defining PIDs will be discovered in the near future.

Toward a Single Phenotype per Patient

It is also commonly thought that PIDs confer predisposition to multiple phenotypes—multiple infections in particular—in individual patients, as seen in children with agammaglobulinemia (3), neutropenia (4), or SCID (5). However, following on from the example of EV (10), an increasing number of PIDs are being shown to confer predisposition to a single type of infection, or a narrower range of infections than might be expected, in otherwise healthy patients (22). Disorders of properdin and the terminal components of complement confer predisposition to *Neisseria* (23), and X-linked lymphoproliferative syndrome confers predisposition to Epstein-Barr virus disease (19). More recently, disorders of the interleukin-12–interferon- γ (IL-12–IFN- γ) circuit have been shown to confer predisposition to infections caused by mycobacteria and, to a lesser extent, *Salmonella* (24). Similarly, disorders of the Toll–IL-1 receptor–nuclear factor kappa B (TIR–NF- κ B) pathway have been shown to predispose individuals to pneumococcal and, to a lesser extent, staphylococcal infections (25). Perhaps the most striking example is that seen with disorders of the Toll-like receptor 3 (TLR3) pathway suggested by ongoing work in our lab and UNC-93B–IFN- α/β pathway (26), which confer a selective predisposition to herpes simplex virus encephalitis (HSE). The infectious phenotypes that the disorders of the IL-12–IFN- γ , TIR–NF- κ B, and TLR3–IFN- α/β pathways confer in humans are much narrower than those of the corresponding mutant mice, at odds with the T helper cell 1/T helper cell 2

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(T_H1/T_H2) and TLR paradigms (8). There is therefore much redundancy in host defense *in natura*, with nonredundant human genes ranging from the “public” genes required for protective immunity to multiple microbes to the “private” genes conferring specific immunity to one pathogen. These findings are consistent with the earlier description of mutant mice with a narrow range of vulnerability (e.g., mice deficient in Mx1, Nramp1, Ly49H, and Tlr4), although these mice were neither challenged with many pathogens nor tested in a natural ecosystem (27). In any case, other PIDs have also been found to confer predisposition to a very specific autoimmune phenotype (7, 12). Moreover, whereas patients with mutations in the *FOXP3* (28) or *AIRE* (7) immune genes governing peripheral and central tolerance display relatively broad autoimmunity, those with disorders of cell-autonomous Fas-dependent apoptosis mostly present with autoimmune cytopenia (29). Finally, several PIDs confer a selective predisposition to one of several other phenotypes (6, 7, 10, 12–20). Thus, it is now clear that PIDs may underlie the occurrence of a single phenotype, including a single infectious disease, in otherwise healthy patients. Furthermore, it is likely that a number of “idiopathic” syndromes may reflect hitherto unknown PIDs.

Toward Single Illnesses at Any Age

Infections in children with PIDs are commonly thought to persist constantly, to recur, or both. However, some PIDs occurring in infancy have been found to have a spontaneously favorable outcome, with no relapse in most cases. Examples include IL-12p40 and IL-12Rβ1 deficiency, associated with

mycobacterial disease (24); IL-1 receptor-associated kinase 4 (IRAK-4) deficiency, associated with pneumococcal disease (25); and UNC-93B (26) and TLR3 deficiency again as suggested by ongoing work in our lab, associated with HSE. Patients with these disorders typically suffer from one episode of infection in childhood, rarely two, with no relapses occurring from the patient’s teenage years onward. Immunity to the corresponding pathogen is therefore selectively compromised in childhood, but not in adulthood. In these PIDs, adaptive immunity to secondary infections may progressively compensate for poor innate immunity to primary infection. Alternatively, innate immune responses may improve with age. These observations strongly suggest that children with one or a few common life-threatening infections who respond to anti-infectious agents and later fare well may suffer from hitherto unknown PIDs. The possibility that inherited vulnerability in childhood and subsequent protection in adulthood in these patients results from the maturation of innate or adaptive immunity, or both, may have considerable implications for the development of vaccination strategies. Conversely, some PIDs remain clinically silent for a long period and first manifest in adulthood, forming a mirror image of early-onset PIDs silenced in adulthood. Adult-onset PIDs include common variable immunodeficiency (30) and dominant IFN-γR1 deficiency (24). The late onset may reflect impaired adaptive immunity to reactivation or secondary infection, or exposure to microbes not encountered in childhood, although this is less likely. In any event, PIDs can no longer be restricted to chronic diseases of early onset, and the elucidation of PIDs underlying infectious and

autoimmune diseases tightly associated with a specific age may shed light on the important and largely unknown mechanisms governing age-dependent immunity.

Toward Nonhematopoietic PIDs

Although the clinical presentation of PIDs may be much narrower than initially thought in terms of age window and range of phenotypes, the range of cells affected is broader. An absence of one or several leukocyte subsets is a hallmark of some of the most familiar PIDs, including agammaglobulinemia (3), congenital neutropenia (4), and SCID (5). A first hint at the involvement of nonhematopoietic cells came from the Di George and nude syndromes, which are immunological phenocopies of SCID caused by extrahematopoietic defects that preclude thymic development (31). Moreover, it is clear, but often overlooked, that host defense requires the activity of both hematopoietic and nonhematopoietic cells, and some PIDs actually affect both types of cells. For example, dyskeratosis congenita (21) and anhidrotic ectodermal dysplasia with immunodeficiency (32) are associated with multiple infections, making the pathogenesis of some infections unclear. Conversely, some molecules endowed with a basic metabolic function in multiple cells appear to be particularly critical for leukocytes. These molecules include mediators of granule secretion, which are of particular importance in natural killer and T cells (16). Other PIDs are associated with tissue-specific infections with a single pathogen; this is the case for EV, in which keratinocytes fail to control the development of certain papillomaviruses (10), and HSE, in which herpes simplex virus replicates in the central nervous system (26),

Table 1. Multiple paradigm shifts in primary immunodeficiencies.

Primary immunodeficiencies	Conventional	Novel
Patient and population levels		
Frequency	Rare	Common
Occurrence	Familial	Sporadic
Age at onset	Childhood	Adulthood
Prognosis	Spontaneously worsening	Spontaneously improving
Phenotype level		
Disease-defining clinical phenotypes	Opportunistic infections*	Other infections and phenotypes†
Number of phenotypes per patient‡	High	Low (even single)
Number of episodes per patient§	High	Low (even single)
Disease-causing cellular phenotypes	Hematopoietic	Nonhematopoietic
Genotype level		
Disease-causing genes per patient	One (monogenic, Mendelian)	A few (oligogenic, major genes)
Mode of Mendelian inheritance	Autosomal and X-linked recessive	Autosomal dominant
Clinical penetrance	Complete	Incomplete
Mutations	Inherited from the parental genome	Germ line de novo or somatic

*Infections occurring in patients with overt immunological abnormalities. †Autoimmunity, allergy, virus-induced cancer, angioedema, granulomas, hemophagocytosis, autoinflammation, thrombotic microangiopathy. ‡For example, infectious agents. §For example, infectious phenotypes.

suggesting a critical, if not exclusive role for nonhematopoietic cells in pathogenesis. Finally, other PIDs affect nonhematopoietic cells, with no detectable impact on leukocytes; for example, congenital malformations of the skull base confer a predisposition to pneumococcal meningitis (33), and both cystic fibrosis and primary ciliary dyskinesia impair mucociliary clearance, resulting in severe pulmonary infections (34). Other PIDs that affect nonhematopoietic cells will probably be discovered, particularly in patients with tissue-specific lesions.

Toward Common, Sporadic, and Complex PIDs

Rarity is generally considered a hallmark of PIDs, despite genetic epidemiological data strongly suggesting that most humans carry inborn errors of immunity. However, cases of Mendelian predisposition to common infections, such as tuberculosis, have been reported (35). Moreover, some individuals display autosomal recessive resistance to common pathogens, such as *Plasmodium vivax*, HIV-1, and norovirus, due to mutations in the *DARC*, *CCR5*, and *FUT2* genes, respectively. This indicates that mutant alleles conferring Mendelian resistance may be positively selected by pathogens. It also demonstrates that most (vulnerable) individuals have bona fide autosomal dominant PIDs with respect to these pathogens (22, 36). Moreover, PIDs are not necessarily familial, and a number of sporadic infectious and autoimmune illnesses may result from autosomal dominant PIDs. The underlying mechanisms may involve the inheritance of mutations with incomplete penetrance from an affected parent, as in dominant STAT-1 deficiency (24), de novo dominant lesions in the germ line, such as dominant IFN- γ R1 deficiency (24), or even somatic mutations, such as dominant Fas mutations in the hematopoietic lineage (29). Furthermore, a more complex inheritance pattern may also be involved in infectious diseases, as shown by the HbS allele conferring protection against severe *Plasmodium falciparum* malaria (37) and the two major susceptibility genes for leprosy, *PARK2/PACRG* and *LTA* (38). Similar patterns are observed for allergies, as reported for asthma and severe atopic dermatitis, for which several major susceptibility genes, including *ADAM33* (39) and *FLG*, encoding filaggrin (40), respectively, have been reported. A similar pattern has also been found for autoimmunity, with the human leukocyte antigen class II region having a major effect and other genes a more modest effect on type 1 diabetes (41), and for granulomatous diseases, with inflammatory bowel disease, in which the *CARD15/NOD2* (42) and *IL23R* (43) genes have been implicated. A common hypomorphic variant of *RNASEL* has also been

shown to confer a predisposition to prostate cancer associated with the xenotropic murine leukemia-related retrovirus (44). Thus, PIDs should not be considered to be restricted to the conservative notion of rare, familial, recessive, Mendelian traits, if only because there is no such thing as a strict Mendelian trait in multigenic organisms.

Concluding Remarks

It is now clear that most, if not all individuals, suffer from at least one PID, the clinical expression of which depends on exposure to ad hoc environmental factors, infectious or otherwise. Future research will focus on the clinical description, genetic characterization, and immunological investigation of these novel PIDs. This field was ostensibly born in the 1950s, after two decades of gestation (2), but remains in its infancy, with considerable potential for growth. What clinical implications might we predict in this rapidly expanding field, beyond the improvement of established means of diagnosis and treatment? Novel PIDs will probably guide the development of immunostimulatory drugs, such as granulocyte colony-stimulating factor, in patients with neutropenia (4), IFN- γ in patients with mycobacterial diseases (24), and IFN- α in patients with HSE (26). The development of potent and safe immunosuppressive drugs, such as antibodies and chemical inhibitors, may also benefit from the description of novel PIDs. One can even predict that most specialties in human medicine will benefit considerably from the expansion of PIDs, as immunity at large is central to physiology and pathology, because most tissues are subject to environmental assaults and contain myeloid and lymphoid cells. The field of PIDs is also important for immunologists, because it provides an opportunity for the genetic dissection of protective immunity and tolerance to self in the setting of a natural ecosystem. This unique feature of the human model is important in light of the natural selection of species, because it makes it possible to define the ecologically relevant function of host defense genes most likely to be subject to evolutionary selection (11, 22). The emerging connection between clinical genetics, epidemiological genetics, and evolutionary genetics, with the definition of PIDs in this context, constitutes a new frontier in immunology. Together, these disciplines make possible the genetic dissection of past and present human immunity *in natura*, thereby shedding new light on the function and evolution of the immune system.

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