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Genetics of Pediatric Immune-Mediated Diseases and Human Immunity

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Abstract

Primary immunodeficiency diseases (PIDs) are a rapidly growing, heterogeneous group of genetically determined diseases characterized by defects in the immune system. While individually rare, collectively PIDs affect between 1/1,000 and 1/5,000 people worldwide. The clinical manifestations of PIDs vary from susceptibility to infections to autoimmunity and bone marrow failure. Our understanding of the human immune response has advanced by investigation and discovery of genetic mechanisms of PIDs. Studying patients with isolated genetic variants in proteins that participate in complex signaling pathways has led to an enhanced understanding of host response to infection, and mechanisms of autoimmunity and autoinflammation. Identifying genetic mechanisms of PIDs not only furthers immunological knowledge but also benefits patients by dictating targeted therapies or hematopoietic stem cell transplantation. Here, we highlight several of these areas in the field of primary immunodeficiency, with a focus on the most recent advances.

OVERVIEW OF MONOGENIC PRIMARY IMMUNODEFICIENCIES

There are over 450 disorders/gene defects leading to inborn errors of immunity, and this list continues to grow annually (1) (**Figure 1**). The advent of the primary immunodeficiency field is often credited to a 1952 publication from Colonel Ogden Bruton (2) describing a young male patient with recurrent severe infections, absent gamma globulins, and normal total protein. As a proof of concept, the patient was given monthly injections of gamma globulin. He demonstrated marked improvement, with no further episodes of sepsis in the observed period. This disease was later recognized as X-linked agammaglobulinemia (XLA) due to deficiency of Bruton tyrosine kinase (BTK). Genetic discovery of the *BTK* gene was not achieved until 1993, by using positional cloning (3) and by investigating B cell–specific tyrosine kinases (4). Prior to this, patients with features of primary immunodeficiency had been reported, including patients with ataxia-telangiectasia in 1926 (5) and Wiskott-Aldrich syndrome in 1937 (6). By the 1950s, in addition to XLA, other recognized disorders of the immune system included congenital neutropenia (7), familial hemophagocytosis syndrome (8), X-linked chronic granulomatous disease (CGD) (9), and severe combined immunodeficiency (SCID) (10, 11). However, genetic determinants for many of these conditions were not identified until decades later. For example, cells from patients with CGD were initially noted to have a functional defect in the intracellular killing of organisms and a defective NADPH oxidase system. The genetic defect in *CYBB* was defined years later, by using positional chromosomal mapping and by identifying a unique RNA transcript that was elicited by subtracting patient RNA from normal RNA (12, 13). The first finding of a genetic determinant of one form of SCID, which comprises disorders characterized by severe T cell defects, was a serendipitous discovery of adenosine deaminase deficiency in two patients with immunodeficiency (14). About 20 years later, linkage mapping identified variants in the common gamma chain cytokine receptor as genetic determinants of X-linked SCID (15, 16).

Classically, autosomal recessive (AR) and X-linked recessive inheritance patterns have been observed in PIDs. Over time, additional disorders with dominant inheritance patterns and even somatic or mosaic patterns have been identified. The International Union of Immunological

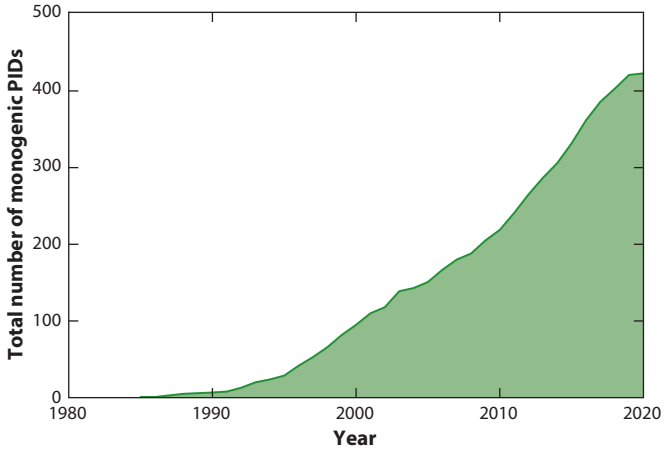

Figure 1

Total number of known monogenic primary immunodeficiency diseases (PIDs) with an underlying monogenic cause tabulated by year of first publication. The list of monogenic PIDs was extracted from the most recent update (December 2019) to the 2019 International Union of Immunological Societies Inborn Errors of Immunity Committee report (1; updated from **https://iuis.org/committees/iei/**).

Societies (IUIS) Inborn Errors of Immunity Committee publishes a report biannually to depict advances in the field, dividing diseases based on the predominant phenotype (1, 17). In the most recent classification, there are nine groups identified, with the tenth table representing phenocopies of PIDs. The broad clinical heterogeneity of these classifications reflects the diverse functions of the immune response and the consequences of perturbations, from severe infections associated with complete T cell deficiencies to autoinflammation seen with alterations of the type I interferon system to bone marrow failure syndromes.

Importantly, fundamental principles in immunology have been advanced by studying patients. A now classic example of this are deleterious variants in the *FOXP3* gene leading to immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome. This rare hemizygous disorder typically presents in early infancy and is characterized by enteropathy, dermatitis, type 1 diabetes mellitus, hypoparathyroidism, and cytopenias. IPEX syndrome was first described clinically in 1982 in a large kindred of males with diarrhea, endocrinopathies, autoimmune hemolytic anemia, dermatitis, and infection as well as autoimmunity (18). About 20 years prior to the initial description of IPEX syndrome, the mutant mouse strain referred to as scurfy was identified (19). Mice develop scaly skin, splenomegaly, and lymphadenopathy and die prematurely at about three weeks of age. Linkage analysis localized the genetic defect to Xp11.23-Xq13.3 (20, 21). It was not long thereafter that positional cloning identified *Foxp3* as the gene responsible for the scurfy syndrome in mice (22), with subsequent recognition of *FOXP3* as the gene responsible for IPEX syndrome (23–25). Shortly after that, Foxp3 was determined to be the master transcription factor defining $CD4^+CD25^+$ regulatory T cells (Tregs) (26–28). Studying pathogenic variants of *FOXP3* found in patients has been informative in discerning the importance of the structural domains of the protein.

The discovery of patients with a genetic deficiency of the autoimmune regulator (AIRE) protein also illustrates how studying patients can help advance immunological knowledge. Autoimmune polyglandular syndrome type 1 (APS-1/APECED) is an autosomal recessive disorder caused by biallelic loss-of-function (LOF) and, more recently discovered, heterozygous dominant-negative (DN) variants in *AIRE*. The classical phenotypic triad is hypoparathyroidism, adrenal insufficiency, and chronic mucocutaneous candidiasis; additionally, a wide range of organ-specific autoimmunity to both endocrine and nonendocrine organs is observed (29). The disorder was initially described in a small series of reports in 1929 and 1943 by astute clinicians who recognized the clinical patterns in large families (30). The genetic determinant was discovered in 1997, when positional cloning narrowed the location of the causative gene to the region encoding the protein now known as AIRE (31, 32). The discovery of this genetic defect in patients, and the subsequent engineering of a mouse strain with an *Aire* gene mutation, led to enhanced understanding of the role of central tolerance and expression of peripheral tissue-specific transcripts in the thymus to prevent autoimmunity (30, 33). Benoist, Mathis, and colleagues (34) demonstrated that the AIRE protein is predominantly expressed in medullary thymic epithelial cells, underpinning the critical link between AIRE and ectopic expression of peripheral antigens during thymic education of T lymphocytes.

Interestingly, for both IPEX syndrome and APECED, the spectrum of disease present in individual patients can vary considerably, even in patients with identical genetic variants (30, 35, 36). Diversity in the genotype-phenotype continuum is not uncommon in PIDs, and in some instances it underpins the extent of immune deficiency or autoimmunity present.

Here, we focus on advances in our understanding of genetic mechanisms of PIDs and highlight recent studies of immunologic lessons from investigating molecular mechanisms of PIDs. We concentrate on groups of disorders that have rapidly grown based on genetic discoveries, including the unique human immune responses to viral infection, type I interferonopathies,

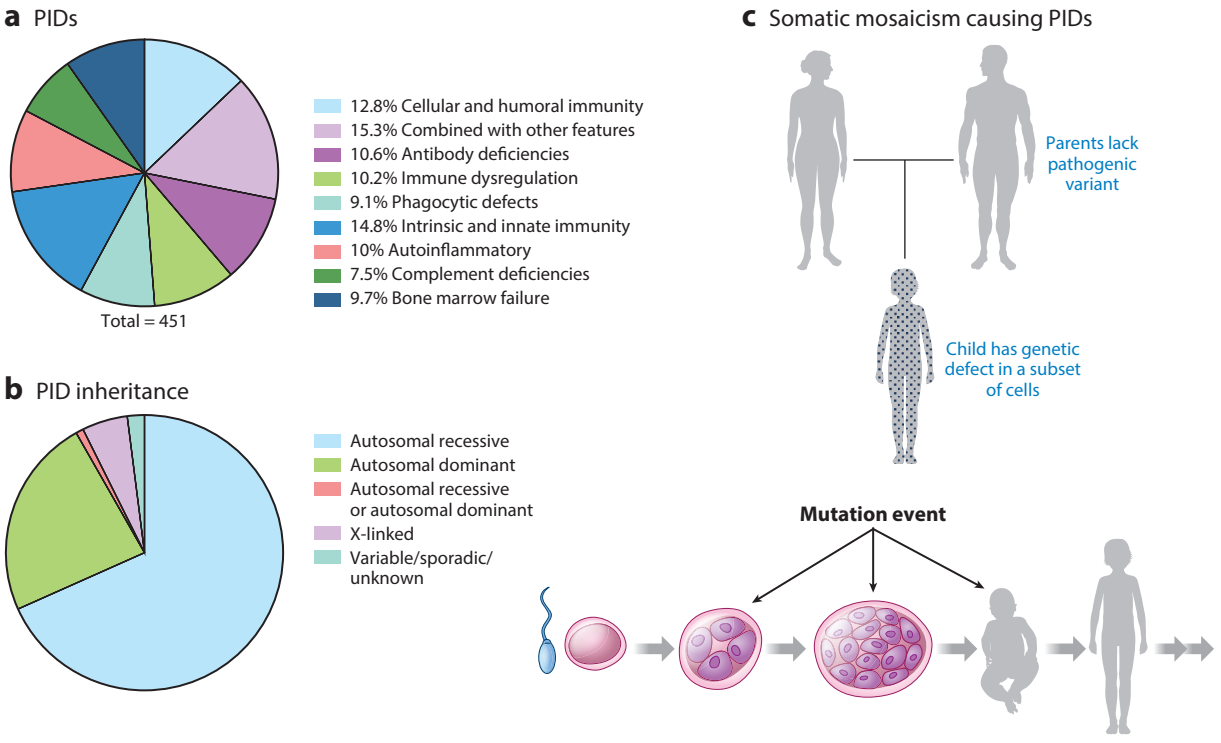

Figure 2

Genetic inheritance of primary immunodeficiency diseases (PIDs). (*a*) PIDs affect a wide range of immune cell functions and can be classified into nine categories. (*b*) Multiple mechanisms of inheritance account for disease (1; updated from **https://iuis.org/committees/iei/**). (*c*) Other genetic mechanisms of PIDs include somatic mutations not present in the germ line of the patients' parents, which can occur in gametes, during embryogenesis, and beyond. Images on the right adapted from Servier Medical Art (**https://smart.servier.com**), provided by Les Laboratoires Servier. They are available for reuse under the CC-BY 3.0 Unported license (**https://creativecommons.org/licenses/by/3.0/legalcode**).

autoinflammatory disorders, and primary immune regulatory disorders (PIRDs). Finally, understanding the genetic mechanisms of PIDs not only provides us with a better understanding of the human immune response but also is essential for advancing both the clinical care of these patients and the development of new functional diagnostics.

GENETIC MECHANISMS OF PRIMARY IMMUNODEFICIENCY DISEASES

PIDs are a diverse group of genetic disorders of the immune system (1; updated list at **https://iuis.org/committees/iei/**) (**Figure 2**). Most PIDs are inherited in an AR manner. Autosomal dominant (AD) disorders are the next-largest category, followed by X-linked disorders and sporadic disorders, or those with unknown genetic inheritance. While most AR PIDs are due to LOF, AD diseases result from several interesting and immunologically complex mechanisms including gain-of-function (GOF), haploinsufficiency, or dominant-negative effects on the encoded protein. Interestingly, for a few PIDs either one or two affected alleles (AD or AR) can cause similar disease, for example APECED (*AIRE*) and *TREX1*-associated autoinflammatory syndrome. There are also several examples of diseases caused by pathogenic variants in the same gene; for

example, at least three clinical phenotypes have been described with CARD11, including SCID-like disease (AR LOF), antibody deficiency and lymphoproliferation (AD GOF), and atopy with infections (AD LOF, including dominant-negative) (37).

Genetic changes causing PIDs include single-nucleotide variants and structural variants such as nucleotide insertions or deletions of varying sizes and copy number variants, the vast majority of which are rare in the population databases (<0.01% allele frequency). There is also emerging evidence that some cases of PIDs thought to be sporadic may be due to interactions between more common susceptibility variants and rare variants, as demonstrated in a recent study of >1,000 patients, most of whom had adult-onset and/or sporadic disease (38). PIDs can also result from somatic mutations that arise either in the patient or potentially in the gamete of the parent (**Figure 2**). For example, somatic FAS variants cause autoimmune lymphoproliferative syndrome (ALPS) phenotypically similar to germ line disease (39). Mosaic variants in the *NRLP3* gene cause neonatal-onset multisystem inflammatory disorder (NOMID) in children with clinical symptoms similar to germ line disease (40, 41). The overall number of patients with PIDs due to postzygotic somatic mosaicism is thought to be relatively low based on rare case reports in the literature. However, a recent study evaluated PID genes in 128 families suspected to have mosaicism (either somatic or gonadal/inherited), looking for AD or X-linked disease (42). Approximately 25% of families had mosaic disease, with 60% of those patients having somatic mosaicism. Disease-causing mosaic variants of *NLRP3*, *FAS*, and *NOD2* were identified (42). These data suggest that somatic mosaicism may be an overlooked cause of PIDs. This diversity in genetic mechanisms of PIDs highlights the complexity of the human immune response and the ways in which diseases arise and disrupt the normal immune response.

IMMUNOLOGIC LESSONS FROM NATURE

Complementary studies of patients with genetically defined PIDs and animal models have provided insight into the complexity and function of the human immune system. The field of primary immunodeficiency is a natural wedded effort between medicine and science and effortlessly flows from bedside to bench and back. Here, we focus on four major insights into the human immune response, including discussion of areas where animal models have both aided and potentially hindered our understanding of immunological processes.

Host Response to Viral Infection

The specificity of infectious susceptibility in PIDs can serve to educate on the differences between human and animal immunity. For example, there are differences in immunologic requirements for control of viral infection. Adequate control of viral infections initially relies on innate immune responses to limit viral replication and spread. Host cells possess pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), responsible for the recognition of certain viral RNA or DNA features. The activation of PRRs leads to downstream signaling cascades and the production of type I/III interferons critical for antiviral responses (**Figure 3**). Type I interferons bind to IFN-α/β receptors 1 and 2 (IFNAR1, IFNAR2). Receptor-associated Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2) are then activated and phosphorylate the transcription factors signal transducer and activator of transcription 1 (STAT1) and STAT2, leading to the association with interferon regulatory factor 9 (IRF9) to form the interferon-stimulated gene factor 3 (ISGF3) complex. This complex binds interferon-stimulated regulatory elements (ISREs) in the promoters of both interferons and interferon-stimulated genes (ISGs) (43). IRF7 is induced by type I

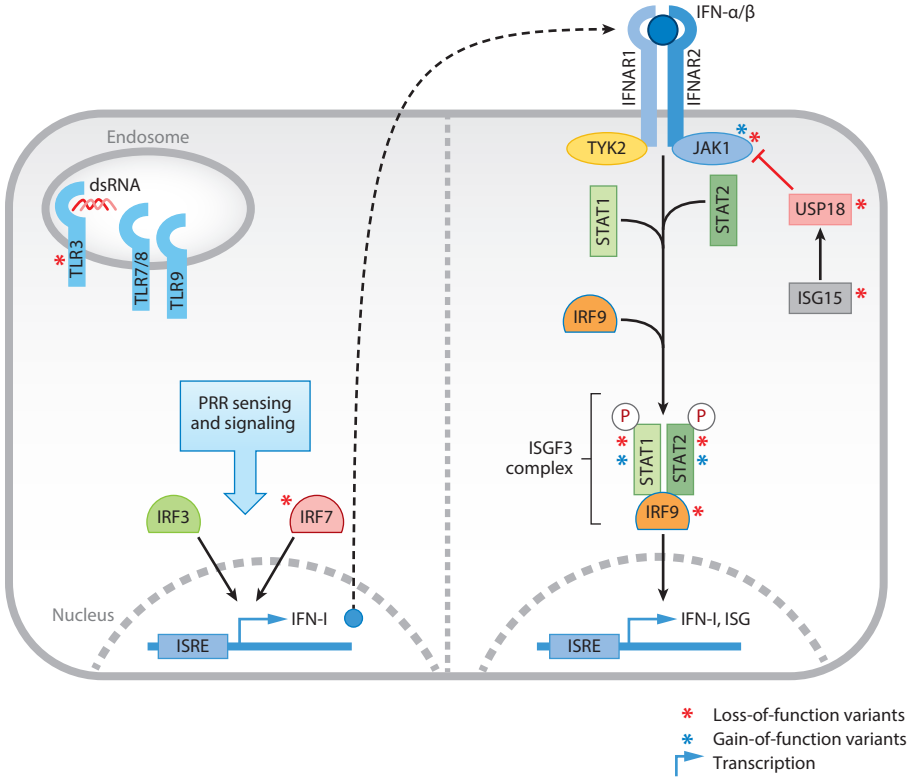

Figure 3

Simplified schematic of IFN-I signaling. PRRs on host cells sense stimuli; for example, the endosome-associated TLR3 recognizes dsRNA. Ultimately, signaling cascades converge on the activation of IRF3 and/or IRF7, which translocate to the nucleus, bind ISREs, and induce transcription of IFN-I. IFN-α/β bind to IFNARs, leading to IFNAR1 and IFNAR2 dimerization. Next, receptor-associated JAK1 and TYK2 are activated and lead to the phosphorylation and activation of STAT2 and STAT1. The activated STAT1 and STAT2 form a complex with IRF9 known as the ISGF3 complex, which translocates to the nucleus to bind ISREs and dictate transcription of ISGs. USP18 assists in downregulation of IFN-I signaling and is stabilized by ISG15. Selected variants leading to disrupted IFN-I signaling are discussed in the text. Abbreviations: dsRNA, double-stranded RNA; IFNAR, interferon receptor; IFN-I, type I interferon; IRF, interferon regulatory factor; ISG, IFN-stimulated gene; ISGF3, interferon-stimulated gene factor 3; ISRE, interferon-stimulated regulatory element; JAK1, Janus kinase 1; PRR, pattern recognition receptor; STAT, signal transducer and activator of transcription; TLR, Toll-like receptor; TYK2, tyrosine kinase 2; USP18, ubiquitin-specific peptidase 18.

interferons and participates in a positive-feedback loop and the amplification of type I/III interferon responses in mice and humans (44).

Patients with genetic defects that impair IFN-α/β signaling have difficulties controlling viral infections. Although these variants occur in a common pathway, the patterns of disease susceptibility observed in affected patients with monogenic PIDs vary. Severe influenza pneumonitis has been observed in patients with AD GATA2 deficiency, AR IRF7 deficiency, and AR IRF9 deficiency (45–47). GATA2-deficient patients are susceptible to severe pulmonary influenza, yet several other infections are commonly reported, including infections of nontuberculous mycobacteria, viruses such as Epstein-Barr virus and human papillomavirus, and fungi. GATA2-deficient patients have deficiencies in natural killer cells, monocytes, B cells, and dendritic cells, and in

particular, plasmacytoid dendritic cells, which may contribute to the enhanced susceptibility to multiple infections, including severe influenza infection (44). In contrast, patients with IRF7 deficiency have a very narrow spectrum of disease susceptibility seemingly limited to severe influenza. The patient in the initial description of IRF7 deficiency was seropositive for several viruses, including human cytomegalovirus; varicella zoster virus; adenovirus; and other respiratory viruses such as respiratory syncytial virus (RSV) and parainfluenza viruses 1, 2, and 3, indicating exposure without severe illness. This suggests that in humans, IRF7 may be redundant in host defense against many other viruses (46). Conversely, in mice, IRF7 may serve a more extensive role in antiviral immunity, as *Irf7*-deficient mice are susceptible to multiple RNA and DNA viruses (48).

Patients deficient in IRF9 are unable to form functional ISGF3 complexes. This results in impaired responses to type I interferons and restricted induction of ISGs following interferon stimulation. In the initial report of this PID, a patient with severe pulmonary influenza had a homozygous variant in *IRF9* located in an essential splice site, resulting in LOF due to a mutant transcript and truncated IRF9 protein lacking exon 7 (47). The mutation had a negative impact on the interaction of IRF9 with STAT proteins via the IRF association domain. This patient suffered from other infectious complications requiring a separate hospitalization for RSV, recurrent fevers, recurrent uneventful bronchiolitis, and biliary perforation following measles, mumps, and rubella (MMR) vaccination. In vitro, cells from this IRF9-deficient patient were more susceptible to several viruses, including influenza A virus, vesicular stomatitis virus, RSV, and parainfluenza virus (47). However, the most striking clinical finding was severe influenza infection. In a subsequent report, a family with IRF9 deficiency had difficulty controlling several different viral infections, with multiple prolonged and severe illnesses. This second variant led to a complete loss of protein expression and absent ISG expression, which may account for differences in the observed phenotypes (49). Again, the level of residual IRF9 activity and the subsequent ability to induce an appropriate complement of ISG expression may vary based on the genetic variant identified. Certainly, there are some caveats in this comparison, as different experimental cells were studied, and studies with larger cohorts are needed. Data in mice also support the notion that IRF9 is an important mediator of the antiviral interferon response to a wide range of viral infections. Mice deficient in IRF9 have impaired control of viral replication after infection with lymphocytic choriomeningitis virus, and instead of resolving an acute infection, they develop a chronic infection characterized by $CD8^+$ T cell exhaustion (50). Patients harboring deleterious variants of other genes in this pathway, such as *STAT1*, *STAT2*, *JAK1*, *TYK2*, and *IFNAR2*, despite having an increased susceptibility to severe viral infections, have not been reported to suffer from severe pulmonary influenza (51–55). In addition, many other PIDs are characterized by recurrent or severe viral infections, but an increased susceptibility to severe influenza infections has not been documented in the majority of these disorders. Overall, identifying monogenic variants in patients with severe influenza has helped establish the importance of the IRF9- and ISGF3-dependent type I/III interferon responses in the control of influenza in humans. Even with these observations, care must be taken in the interpretation of the infectious susceptibility, as only a handful of patients have been reported thus far.

TLRs represent another area of innate immune responses where data from patients have provided insight into unique or altered responses in human immunology. TLRs are germ line–encoded receptors designed to recognize a diverse array of microbial structures. PIDs have thus far been identified in one TLR gene (*TLR3*) and several signaling molecules. TLR3 recognizes dsRNA and activates IRF3 and NF-κB to elicit antiviral type I and type III interferon responses. Intriguingly, pathogenic variants of *TLR3* and the TLR3 signaling pathway predispose patients to herpes simplex virus 1 (HSV-1) encephalitis, an infection that is typically associated with gingivostomatitis (56). Variants of genes encoding other proteins in this pathway, including UNC93B1,

TRIF, TRAF3, TBK1, and IRF3, also result in disease (57–59). More recently, two heterozygous missense LOF variants of *TLR3* were identified. The variants were associated with AD TLR3 deficiency, characterized by a defect in pulmonary epithelial cell–intrinsic immunity to influenza virus (60). These observations are distinct with regards to infectious outcomes compared to observations in TLR3-deficient mice, which have varying responses to viruses ranging from reduced survival to impaired virus control to improved survival with influenza despite increased viral titers in the lung (57). Indeed, there is likely redundancy in the TLR3 pathway for human immunity, with relatively exclusive reliance on TLR3 for host defense to HSV-1 in the central nervous system and pulmonary influenza.

Together, investigations of the genetic etiology of susceptibility to viral infection in patients have led to the discovery of significant redundancy that could not have been predicted from studies in model organisms.

Autoinflammatory Disorders

Autoinflammatory disorders are monogenic disorders caused primarily by a dysregulated innate immune response and are differentiated from autoimmune disease by the relative lack of autoantibodies or antigen-specific T cells. These disorders have been clustered based on common underlying mechanisms; such clusters include inflammasomopathies with dysregulated IL-1β activation, interferonopathies, and disorders with abnormalities in protein folding. Classically, autoinflammatory disorders were a group of disorders defined by the monogenic periodic fever syndromes, including familial Mediterranean fever, but they have expanded to encompass a larger group with underlying innate immune system pathology (61).

Unchecked interferon responses: interferonopathies. Although type I interferons serve a critical role in antiviral immunity, left dysregulated, type I interferons can lead to autoimmunity and immunopathology. PRR-mediated activation of ubiquitin E3 ligases and kinases leads to the activation of latent transcription factors and ultimately induction of expression of type I interferon genes and other proinflammatory cytokines, which modulate the innate and adaptive immune responses. Type I interferonopathies are a group of autoinflammatory disorders characterized by upregulation of type I interferon signaling, including upregulation of ISGs (62). Aicardi-Goutières syndrome (AGS) is an autoinflammatory disorder exemplified by inflammation of the brain and skin, and patients have increased levels of IFN-α in the cerebrospinal fluid and serum. The recognized clinical spectrum of the syndrome has expanded and includes chilblains, glaucoma, hypothyroidism, cardiomyopathy, intracerebral vasculitis, peripheral neuropathy, bowel inflammation, and systemic lupus erythematosus (63). Infectious complications are not commonly noted in AGS patients and are not a prominent feature in patients with type I interferonopathies. Genetic variants leading to AGS are heterogeneous, including variants of *TREX1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, *ADAR1*, *IFIH1*, and *DNASE2*. The disorder is caused by aberrant activation of nucleic acid receptors, from either a GOF in a signaling molecule that activates the type I interferon response or a LOF in key negative regulators of the system (64). It is noteworthy that variants in individual genes lead to a spectrum of clinical phenotypes and disease severity, and such variability is also observed among family members harboring the same variant. Mice deficient in *Trex1* develop lethal autoimmunity, and the fundamental role of type I interferons in pathogenesis was corroborated by the observation that $Trex1^{-/-}Ifnar1^{-/-}$ mice were protected. An interferon-independent component may coexist in these patients, as $Trex1^{-/-}$ mice do not develop neuroinflammation, a key feature of AGS (65). Furthermore, mice with *Adar1* mutations were not rescued by crossing the mice onto the $Ifnar1^{-/-}$ background (66). Treatment with

baricitinib, a Jak1/2 inhibitor, improved clinical manifestations, reduced the need for glucocorticoids, and suppressed the interferon signature in patients with interferonopathies (67). Patients with autoimmune conditions such as systemic lupus erythematosus also have elevated ISGs (68), suggesting immunopathogenic overlap between these syndromes. Analysis of type I interferon–response genes and concurrent measurement of proinflammatory cytokines in patients with undifferentiated systemic autoinflammatory diseases may aid in the diagnosis, classification, and treatment of these patients by differentiating canonical interferonopathies from conditions with chronic versus transient ISG elevation (69).

Additional evidence for the pathogenicity of type I interferons in humans came with the description of siblings with a homozygous missense variant of *STAT2* leading to GOF (70). In this case, the siblings suffered from episodes of marked neuroinflammation and systemic inflammation, with elevated ISGs. This variant was silent in the heterozygous state (unaffected parents), which contrasts with the AD pattern recognized in STAT1 and STAT3 GOF disease. In the homozygous state, there is increased IFNAR signaling, demonstrated by prolonged JAK/STAT signaling and transcriptional activation, secondary to loss of STAT2 regulatory activity. The variant hinders the interaction of STAT2 with ubiquitin-specific peptidase 18 (USP18), an important STAT2-dependent negative regulator of IFN-α/β signaling. USP18 regulates desensitization through displacement of JAK1 from the IFNAR2 receptor subunit, supported by STAT2, which functions as an adaptor protein (**Figure 3**). The interaction of STAT2 with USP18 was localized to the coiled-coil domain of STAT2. Similarly, in one report, patients with USP18 deficiency had a comparable phenotype, thought to be due to a loss of negative feedback on IFNAR (71). Another defect noted in this spectrum is in ISG15, a protein that promotes USP18 stability. Patients with ISG15 deficiency fall on the milder end of the spectrum, demonstrating intracranial calcification and increased expression of ISGs, but they lack severe viral infections and have enhanced susceptibility to mycobacterial disease (72, 73). By contract, mice with ISG15 deficiency have a broad susceptibility to viral infections (74). LOF variants of STAT2 are associated with increased susceptibility to viral infections due to the loss of the transcription factor complex ISGF3 (52) (**Figure 4**). Therefore, in humans, STAT2 participates in the regulation, both positively and negatively, of its own signaling pathway. In summary, excessive activation of the type I interferon response pathway or inadequate downregulation of these responses underlies the etiopathogenesis of the interferonopathies. With regard to type I interferon responses, balance is essential, as PIDs have been identified that are characterized by both defective and excessive innate immune signaling.

Other autoinflammatory disorders. Autoinflammatory disorders have expanded due to rapid advances in genetic sequencing and now include diseases with several unique mechanisms underlying the clinically apparent autoinflammation. Here, we discuss the characteristics of four of these disorders.

Adenosine deaminase type 2 (ADA2) deficiency is an autoinflammatory disorder known as deficiency of ADA2 (DADA2) and is caused by AR variants of *ADA2* (*CECR1*). Initial publications documented pathogenic variants of this gene leading to early-onset systemic vasculitis and stroke (75, 76). Recently the clinical spectrum of disease phenotypes has rapidly grown, and additional hematologic and immunologic manifestations have been described. Hematologic manifestations include cytopenias such as pure red cell aplasia (PRCA) that mimics Diamond-Blackfan anemia, bone marrow failure (BMF), and lymphoproliferation. Immunodeficiency and autoimmune features are also variably present, including mild hypogammaglobulinemia, recurrent infection, autoimmune cytopenias, and systemic lupus. Recurrent and severe infection tend to be seen in the patients with BMF. Time of disease onset varies but is typically in childhood, with most patients presenting before ten years of age and the patients with PRCA presenting in infancy (77).

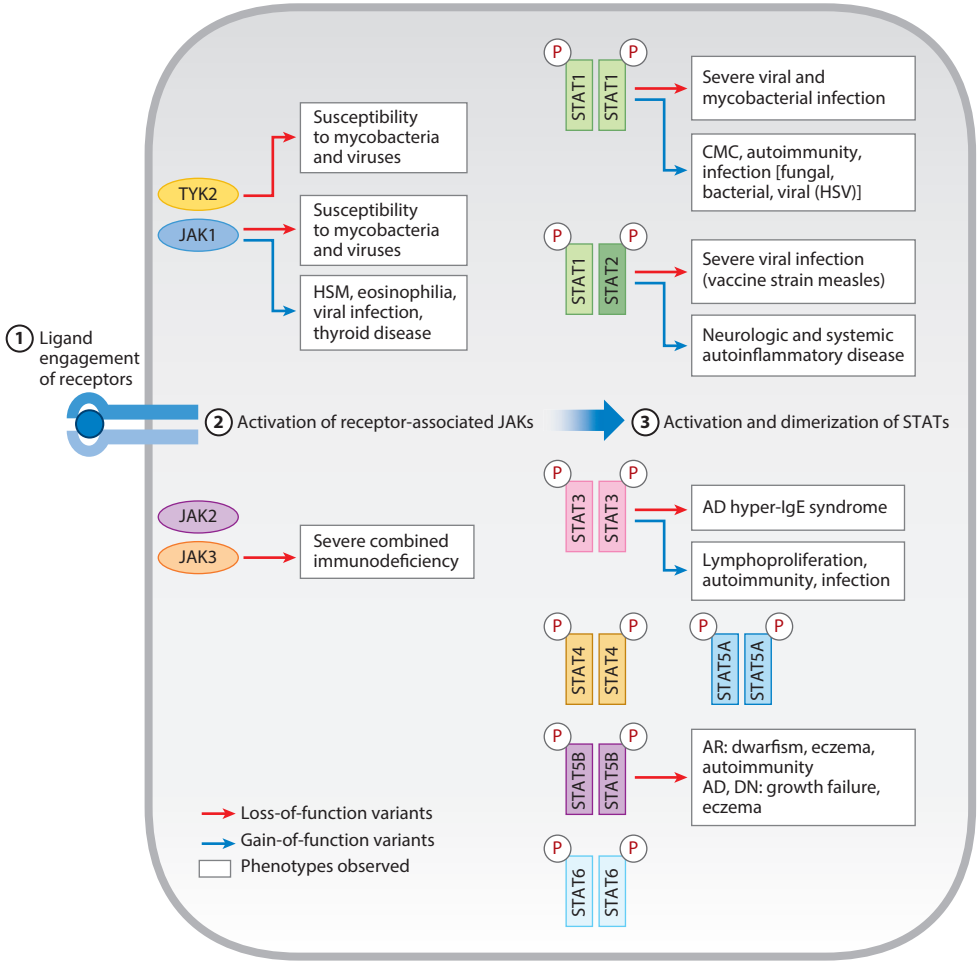

Figure 4

Monogenic primary immunodeficiencies of the JAK/STAT pathway. (①) Ligands, such as cytokines, hormones, and colony-stimulating factors, engage receptors, leading to (②) activation and phosphorylation of the JAK family of nonreceptor tyrosine kinases and phosphorylation of the intracellular tail of the receptor. The four JAKs (JAK1, JAK2, JAK3, TYK2) selectively bind to specific receptor chains. (③) STATs then bind to the cytoplasmic domain of the receptor and are subsequently phosphorylated and activated, allowing for dimerization and translocation to the nucleus to regulate gene expression. LOF variants (*red arrows*) and GOF variants (*blue arrows*) leading to primary immunodeficiency diseases are depicted in the illustration. White boxes denote the phenotypes observed in patients harboring the assorted variants. Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CMC, chronic mucocutaneous candidiasis; DN, dominant negative; GOF, gain of function; HSM, hepatosplenomegaly; HSV, herpes simplex virus; JAK, Janus kinase; LOF, loss of function; STAT, signal transducer and activator of transcription; TYK, tyrosine kinase.

ADA2 is highly expressed in myeloid cells and serves a nonredundant function in humans, as its deaminase activity does not compensate for a loss of ADA1 function in patients that develop SCID. Mice lack an ortholog to ADA2, and the in vivo function of ADA2 in humans remains yet to be fully elucidated, though studies have hinted at a role in immune response regulation and differentiation, particularly at sites of inflammation (78). A genotype-phenotype association in DADA2 was recently defined based on the level of residual ADA2 enzymatic activity and may have

implications for treatment responsiveness and clinical management (79). In addition, a type I interferon signature has been variably observed in some patients, but larger cohorts are needed to establish a correlation with disease activity (80, 81).

Deficiency of the interleukin-1 receptor antagonist (DIRA) is an autoinflammatory disorder characterized by sterile inflammation of the skin and bones and is due to recessive variants of *IL1RN*, which encodes IL-1 receptor antagonist (IL-1Ra). Under normal circumstances, IL-1Ra binds with high affinity to IL-1R1. However, binding of IL-1Ra does not result in the receptor conformational change seen with agonists and fails to recruit the intracellular IL-1 receptor accessory protein, which is required for signal transduction. In patients lacking IL-1Ra, the binding of IL-1α and IL-1β to the IL-1 receptor continues unconstrained. As a result, patients present at birth, or shortly thereafter, with severe systemic inflammation and skeletal abnormalities including multifocal osteomyelitis, periostitis, arthritis, and pustular skin lesions (82, 83). High levels of inflammatory cytokines including IL-1β, IL-6, IL-8, and TNF-α are produced by patient peripheral blood mononuclear cells, and production is further accentuated when cells are stimulated with lipopolysaccharide (LPS). Patients have a prompt and dramatic response to treatment with recombinant IL-1Ra. Interestingly, the phenotype of the *Il1rn*-deficient mouse lacking IL-1Ra protein is distinct from that of patients. The original mouse model created on the mixed background (C57BL/6J × 129/Sv) had a modest phenotype with lower body weights and reduced survival after LPS administration, but it had improved survival after *Listeria monocytogenes* challenge (84). Breeding the mice onto a different background (BALB/cA) led to the development of a chronic inflammatory arthritis resembling rheumatoid arthritis (85). However, mice first demonstrated signs of arthritis at five weeks of age, and >80% had arthritis by eight weeks of age. This is in contrast to patients with DIRA, who have symptoms around the time of birth. Arterial inflammation and psoriasis-like skin inflammation have been noted on different genetic backgrounds as well, reinforcing the notion that disease susceptibility in the animal model likely depends on underlying genetic loci that modify the phenotype (86, 87). In humans, the disease has been documented in patients from multiple continents and of different genetic backgrounds, but the disease severity and phenotype are preserved. In addition, the disease is sometimes present at the time of birth, and there is also evidence of in utero inflammation (88), suggesting that baseline IL-1R signaling requires exquisite control in humans. Thus, in this case, genetic investigation of disease in children led to targeted life-saving therapy and pointed to different immunologic mechanisms of regulation of the inflammasome and IL-1 signaling in mice and humans.

IL-36 is another IL-1 family member that when dysregulated leads to autoinflammation. Deficiency of the IL-36 receptor antagonist (DITRA), caused by AR variants of *IL36RN*, leads to recurrent episodes of pustular psoriasis with associated systemic inflammation and fever (89). IL-36 cytokines are induced by inflammatory cytokines such as TNF-α, IL-17A, and IL-22, and published data imply a link between Th17 cytokines and the IL-36 cytokines (90). Loss of the IL-36 receptor antagonist (IL-36Ra) results in dysregulated IL-36α, IL-36β, and IL-36γ signaling, and as a consequence, IL-36, IL-8, IL-6, and TNF-α production by keratinocytes increases. Mice that overexpress IL-1F6, the mouse ortholog to IL-36α, develop cutaneous inflammation with many features of psoriasis, and if they are bred to have a concurrent IL-F5 (mouse IL-36Ra ortholog) deficiency, skin abnormalities are enhanced (91). In mice, IL-36 cytokines regulate the IL-23/IL-17/IL-22 pathway (92). The interplay between the Th17 and IL-36 cytokines and resultant proinflammatory milieu has provided some guidance for therapies for DITRA patients. Biologic therapies, including TNF-α inhibitors, IL-12/IL-23 inhibitors, and IL-17 inhibitors, have demonstrated benefit; however, biological inhibition with anti-IL-1 therapies has been less successful (93).

While autoinflammatory disorders generally do not have positive autoantibodies, there are several diseases with overlapping features. One such disease with a unique underlying etiopathogenesis is caused by variants of the *COPA* gene, which encodes coatomer subunit α of the coat protein complex I (COPI). This complex is important for membrane trafficking between the endoplasmic reticulum (ER) and the Golgi apparatus. COPA deficiency is characterized by autoimmune interstitial lung disease, inflammatory arthritis, and immune complex–mediated renal disease (94). The majority of the patients present in childhood (age <5 years), and many present with pulmonary hemorrhage. Many patients also have high-titer autoantibodies. The variants were mapped to the highly conserved WD40 functional domain of the COPA protein. Although COPA protein expression and localization are normal, the mutant COPA proteins have impaired binding to dilysine motifs of proteins destined for retrograde transport from Golgi apparatus to ER. Primary cells from patients demonstrate increased ER stress markers, increased autophagosome and endolysosome size, and impaired autophagy catabolism. Consequently, patients with COPA variants have an increase in Th17-priming cytokines and $CD4^+$ T cells produce increased IL-17 after ex vivo stimulation with phorbol 12-myristate 13-acetate and ionomycin. These studies nicely demonstrate how defects in an essential trafficking pathway can lead to inflammation and autoimmunity.

A knock-in mouse model expressing a patient-derived missense variant of *Copa* developed lung disease similar to that observed in patients but did not develop inflammatory arthritis or significant autoantibodies (95). Cytokine-producing, activated T cells were increased, and through a series of bone marrow chimeras and thymic transplantations the authors of this study demonstrated that mutant Copa in the thymic epithelium results in a defect in thymic negative selection, thus allowing for the escape of autoreactive T cells. They also detected a reduced frequency of suppressive $Foxp3^+$ Tregs, and $CD4^+$ T cells were sufficient to cause disease upon transfer into Rag2-deficient mice. The mechanisms leading to the impaired thymic negative selection remain to be elucidated, but the authors postulated that since macroautophagy is important to thymocyte selection and tolerance, a mutant Copa and disrupted macroautophagy may underlie this defect. Together with data from patients demonstrating autoantibodies and increased Th17 cells, this mouse model suggests that the immunopathology observed in COPA patients is multifactorial and is likely due to both autoinflammation and autoimmunity.

PRIMARY IMMUNE REGULATORY DISORDERS

In contrast to the PIDs that cause susceptibility to infection or autoinflammation, diseases of immune dysregulation, or PIRDs, lead to a spectrum of clinical symptoms due to defects in the regulation of the immune response (96, 97). Patients with PIRDs often present with lymphoproliferation, inflammation, and organ-specific autoimmunity and frequently have susceptibility to infection and increased risk of malignancy. Management of patients with PIRDs presents a unique challenge, as careful titration of immunosuppressant medications is often necessary. The wide spectrum of diseases is evident by the different classification within the immune dysregulation category from the IUIS, ranging from disorders including familial hemophagocytic lymphohistiocytosis syndromes to very early onset colitis (1). The common feature of these diseases is a failure to control the immune response, and many of these disorders are due to defects in T cell tolerance, with classic examples being IPEX and APECED syndromes, as previously discussed.

As with other PIDs, PIRDs caused by heterozygous-dominant genetic variants tend to exhibit the most phenotypic variability. STAT3 GOF syndrome is caused by germ line single-nucleotide variants of *STAT3*, leading to GOF in the encoded protein (98–100) (**Figure 4**). Common features include lymphoproliferation, autoimmune cytopenias, poly-autoimmunity, susceptibility to infection, and growth failure, but the clinical manifestations are broad and variable. Some of the

major organ systems affected include the gastrointestinal tract, with enteropathy and hepatitis; the pulmonary system, with interstitial lung disease; and the endocrine system, with early-onset diabetes. A recent systematic review summarized the clinical features and treatments of patients with this disease, many of whom required significant immunosuppressive therapy (101). Heterozygous germ line variants in all domains of the STAT3 protein have been documented, though most are found within the DNA-binding domain, and all lead to increased transcriptional activity. Alterations in baseline and stimulated STAT3 phosphorylation as well as in the kinetics of dephosphorylation have been observed with different STAT3 variants (100, 102, 103). It is uncertain whether there is a clear genotype-phenotype correlation in this disease, although one study has suggested a correlation between molecular studies of the STAT3 signaling cascade and the clinical manifestations of autoimmunity and lymphoproliferation (103). However, variants with the highest STAT3 activity based on in vitro modeling do not necessarily correlate with a more severe phenotype, and penetrance of this AD disorder is incomplete. In instances where Tregs were examined, the majority of patients had reduced Treg levels and multiorgan autoimmunity (101). Indeed, the relative balance of STAT3 and STAT5 activity and skewing of the Treg/Th17 polarization axis, along with the increased SOCS3 expression and resultant impaired Foxp3$^+$ Treg responses, may contribute to this phenotype (104–106). However, STAT3 is broadly expressed and certainly other cell types or signaling pathways may play a role. In addition to functioning downstream of the gp130 family of cytokine receptors, STAT3 is activated downstream of several additional cytokine receptor families as well as downstream from receptor tyrosine kinases such as epidermal growth factor receptor (107).

In classical STAT signaling, after a cytokine engages its receptor, one of the four JAK family members is activated (**Figure 4**). Subsequently, the JAK phosphorylates the receptor, and STAT molecules are recruited, phosphorylated, and dimerized prior to translocating to the nucleus to instruct alterations in gene expression. Despite there being only four JAK family members and seven STAT family members, cytokines signaling through the JAK/STAT pathway exert a wide array of cellular effects (108). It is conceivable that human disease impacting an isolated component of this pathway can be instructive in these situations. JAK1 is activated downstream of several cytokines that also ultimately engage and activate STAT3. JAK1 GOF has several overlapping and unique features when compared with STAT3 GOF (109). Overlapping features include hepatosplenomegaly, thyroid disease, and failure to thrive. By contrast, JAK1 GOF patients had more severe atopic dermatitis, as well as marked eosinophilia with eosinophilic organ infiltration and liver cysts. Several experimental models demonstrated increased STAT1 signaling with JAK1 GOF. Experimental models demonstrated increased basal STAT1 activation and upregulation of STAT3 following stimulation. Treatment with ruxolitinib (a JAK1/2 inhibitor) improved the clinical manifestations, and in vitro it limited JAK-STAT pathway activation (109).

Both STAT3 and JAK1 have corresponding disorders with LOF, with AD STAT3 LOF causing susceptibility to infection, elevated IgE, and multiple nonimmunologic manifestations such as scoliosis and aneurysms (107) (**Figure 4**). JAK1 LOF is AR and associated with susceptibility to mycobacterial disease and viral infection (53). Patients with both GOF and LOF variants of these and other JAK/STAT proteins may help advance understanding of the factors contributing to signal integration in this signaling system.

Immune dysregulation can also be the presenting sign of other PIDs not strictly classified as PIRDs. Genetic sequencing of such patients has revealed an expanded spectrum of diseases associated with variants of genes that were previously considered responsible for a single disorder. For example, combined immunodeficiency with associated granulomas and/or autoimmunity (CID-G/AI) has been described in patients with hypomorphic variants of recombinase-activating genes 1 and 2 (*RAG1*, *RAG2*). Null variants of *RAG* cause SCID, with absent T and B cells. However, a

diverse array of clinical and immunological phenotypes has been described in patients with partial RAG activity, due to T and B cell dysregulation (110, 111). Hypomorphic variants of *RAG* can result in variable residual recombinase activity, leading to Omenn syndrome, atypical SCID, and CID-G/AI. In general, the CID-G/AI group has the highest level of residual recombinase activity, followed by atypical SCID, with Omenn syndrome and SCID patients having very low levels or null activity. Omenn syndrome generally presents in early childhood with expanded oligoclonal autologous T cells that infiltrate organs and cause manifestations including erythroderma, hepatosplenomegaly, lymphadenopathy, eosinophilia, and high IgE levels. Atypical SCID patients have low but detectable levels of autologous T cells with reduced function and tend to have more autoimmunity, in particular autoimmune cytopenias. Patients with both Omenn syndrome and atypical SCID lack adequate T and B cell responses to pathogens and are highly susceptible to severe infections requiring stem cell transplantation (112). By contrast, patients with CID-G/AI less commonly have severe infection but exhibit organ-specific autoimmunity and inflammatory manifestations and can present later in life. Patients with atypical SCID or CID-G/AI have variable B cell numbers and often have normal IgG, IgA, and IgM levels. The location of the variant in the protein structure and the type of variant (nonsense, frameshift, splice site, or missense) are somewhat predictive of phenotypes; however, variability remains. T and B cell repertoire analysis of patients with hypomorphic RAG variants has demonstrated decreased diversity of T cells, including Tregs, and B cells from these patients, which sets the stage for autoimmunity and immune dysregulation (111, 113).

CLINICAL ASPECTS OF IDENTIFICATION OF MOLECULAR MECHANISMS OF PRIMARY IMMUNODEFICIENCIES

The ability to uncover genetic determinants of PIDs can have profound implications for patients. For example, it may lead to a change in diagnosis or targeted therapy, definitive therapy such as hematopoietic stem cell transplantation (HSCT) or possibly gene therapy, as well as the ability to provide genetic counseling and data on prognosis for patients and family members. Genetic testing once relied upon in-depth phenotyping to test for a handful of single gene variants. However, current clinical testing standards rely on next-generation sequencing (NGS) and include large panels (>200) of genes, exome sequencing, and in some cases whole-genome sequencing. Single-gene testing or chromosomal microarray is reserved for cases with a strong family history, with a very clear clinical phenotype, or where there is difficulty sequencing the particular gene by NGS (e.g., the most common 2-bp deletion in *NCF1* causing chronic granulomatous disease is not detected by NGS) (114). While relatively straightforward for known disorders, the discovery of novel genetic causes of disease or the substantial expansion of a clinical phenotype depends upon proving pathogenicity of identified genetic variants by demonstrating altered function of the encoded protein in a relevant model system (115, 116). The methods used for variant annotation, filtering, and prioritization are diverse, and many annotation sources can be applied. Manual inspection of the curated prioritized variant list is time-consuming, and it is necessary to have some understanding of the patient's clinical phenotype. Uncovering genetic mechanisms of disease and the specific inflammatory pathways involved in disease pathogenesis has been instrumental in guiding therapy for numerous PIDs.

The importance of identifying an underlying genetic cause of disease and functional studies of the immune response of such patients is underscored by the ability to now successfully manage a number of PIDs with off-label use of targeted therapies. For example, abatacept [cytotoxic T lymphocyte antigen 4 (CTLA-4) IgG fusion protein] has been used to treat patients with CTLA-4 haploinsufficiency and LPS-responsive beige-like anchor (LRBA) deficiency, a disorder leading

to altered transport of CTLA-4 to the cell surface. Patients with CTLA-4 haploinsufficiency and LRBA deficiency exhibit humoral defects and autoimmunity, in particular interstitial lung disease and enteropathy (117–120). Treatment of both disorders with abatacept has been reported successful (118, 121, 122). Other examples include canakinumab (antihuman IL-1 IgG monoclonal antibody) for DIRA and jakinibs for STAT3 and STAT1 GOF and interferonopathies (123). HSCT has the potential to provide long-term treatment for many PIDs, and as genetic discovery of PIDs continues, the range of PIDs treated with HSCT continues to expand (124). Additional studies in model organisms will also likely be important to delineate whether replacement of the hematopoietic compartment has the potential to treat disorders in which the altered gene is more ubiquitously expressed (for example, JAK/STAT disorders).

In some cases, a genetic diagnosis can lead to the use of HSCT for diseases not previously thought to be amenable to such treatment. Very early-onset inflammatory bowel disease (VEOIBD), defined as inflammatory bowel disease (IBD) diagnosed before six years of age, accounts for ~15% of pediatric patients with IBD. Most cases of IBD are likely polygenic, with patients having a genetic susceptibility and the right combination of environmental and host factors. Nevertheless, at least 50 genetic disorders have been noted to cause IBD-like pathology, many of which are classified as PIDs (125, 126). AR LOF variants of *IL10* and *IL10RA* or *IL10RB* cause VEOIBD that occurs within the first few months of life and is characterized by severe enterocolitis with perianal and penetrating fistulas and abscesses (127, 128). Patients may also suffer from chronic folliculitis, arthritis, and infections. Conventional therapies are largely unsuccessful. HSCT has been used as treatment and can successfully induce sustained remission (129). Other PIDs with IBD appearing as a hallmark feature at a young age, and that may be amenable to HSCT, include IPEX syndrome, X-linked lymphoproliferative disease type 2, CGD, and Wiskott-Aldrich syndrome. Early genetic diagnosis in patients with VEOIBD has the potential to change management and outcomes in these patients.

THE FUTURE OF GENETICS IN PEDIATRIC IMMUNE DISEASE

Investigation and discovery of the genetic causes of PIDs over the last four decades have yielded invaluable insights into human immunity. Because patients with immune-mediated disease were studied, we now understand how developing T cells in the thymus are exposed to tissue-specific antigens, the role of the interferon response in human infection, and the importance of tight regulation of the immune response for preventing autoinflammation and immune dysregulation, to name just a few points. Moving forward, there are several important issues concerning genetic identification of pediatric immune disease that will be essential to address for disease discovery.

First, new approaches to genetic discovery beyond current strategies for exome and genome sequencing are required. A large study from Stray-Pedersen et al. (130) evaluated 278 families with suspected PID. Using a combination of exome and targeted microarray, they achieved a genetic diagnosis in ~40% of unrelated probands. These genetic findings changed diagnoses and treatments in many cases. However, ~60% of patients were well-phenotyped and thought likely to have monogenic disease but still could not be diagnosed. The finding of a genetic cause of disease in ~40% of patients is consistent with exome sequencing of other cohorts of nonconsanguineous patients such as children with intellectual disability (131), suggesting that this challenge is not limited to PID patients. This study also highlighted the importance of structural variants, which were identified in ~10% of patients, largely by targeted microarray and not exome sequencing. Enhanced approaches to identify such structural variation will be important for the discovery of novel genes. Somatic genetic variation and mosaicism are also likely more relevant to PIDs than previously recognized (42), and sequence coverage with exome and genome sequencing is likely

to miss many of these disease-causing variants if a minority of cells harbor the variant. For example, patients with somatic ALPS harbor pathogenic FAS variants in most double-negative T cells (DNTs), but due to mutation events in hematopoietic precursors that confer a survival advantage to DNTs, the variant is present in a relatively small proportion of other immune cells (39). In the case of somatic ALPS, DNTs are purified prior to sequencing. However, this presents a challenge for genetic testing if the target population harboring the mutation is unknown, and for disease caused by low-frequency alleles in multiple cell types. It is also possible that what looks like a monogenic disease is actually the result of multiple interacting genetic factors, including the combination of common susceptibility variants and deleterious monogenic variants, as recently demonstrated with genome sequencing in a cohort of 1,318 patients with sporadic PID (38). Finally, variants in noncoding regulatory regions and other mechanisms of genetic variation such as epigenetic changes may also account for the 60% of patients who remain undiagnosed.

Next, as we identify potentially disease-causing genetic variants, methods to rapidly perform functional screens will greatly aid in determining whether an identified variant alters the function of the encoded protein. Even for variants of genes known to cause disease, it can be difficult to know whether a new variant is disease causing, particularly if only a handful of patients have been described or there is phenotypic heterogeneity. This has become especially challenging for the physician receiving clinical genetic sequencing reports with variants of uncertain significance (114). This also brings up the challenge of demonstrating the pathogenicity of a variant discovered in a single patient. These findings should not be overlooked, however, as many fundamental discoveries have been made starting with a single patient, adhering to Casanova et al.'s (116) guidelines for demonstration of pathogenicity in such settings.

Finally, we should look beyond mice as model organisms for investigation of new genetic variants in patients. While useful for disease modeling and treatment studies, such models can be time-consuming and may not be the most efficient means to determine whether an identified genetic variant is disease causing. Alternative model systems may have the potential to demonstrate pathogenicity of genetic variants. For example, studies in zebrafish were used to demonstrate pathogenicity of *CECR1* variants in DADA2 (76) and interrogate defects in neutrophil trafficking due to defects in *RAC2* found in patients (132). In vitro systems such as organoids also hold the potential to more rapidly validate a genetic variant in a relevant system. Additionally, a 3D culture system for T cell differentiation was recently demonstrated to be useful for differentiating T cell intrinsic versus extrinsic defects in patients with severe T cell deficiency (133).

This summary of the future of genetics of pediatric immune disease is not all-encompassing, but it demonstrates the exciting opportunities in the field. We have an unprecedented capacity for genomic testing of patients, and we still have a great deal to learn from children with rare immune diseases. Moving forward, continued collaborations between clinicians and immunologists will be essential to advance this field, make new discoveries about the human immune response, and offer our patients enhanced diagnostics and treatment.

SUMMARY POINTS

1. Primary immunodeficiency diseases (PIDs) present with a wide range of clinical and immunologic phenotypes.
2. Genetic causes of PIDs include Mendelian inheritance of genetic variants as well as somatic mosaicism.

3. Identification of monogenic genetic defects of the human immune system has revealed unexpected roles for the encoded proteins that could not always be predicted from model organisms.

FUTURE ISSUES

1. Following identification of a disease-causing genetic variant, questions remain regarding the best approach to treating patients, with options including targeted biologic therapies, hematopoietic stem cell transplantation, gene therapy, and personalized small molecules.
2. Many patients with apparent monogenic immune diseases remain undiagnosed, and additional methods to identify genetic mechanisms of disease are needed.
3. The rapid evolution of genetic testing of patients with immune system disorders has left a gap in the ability to functionally validate genetic variants.
4. Model systems are needed to quickly and efficiently test the immunologic consequences of novel genetic variants, in order to advance our understanding of the human immune response.

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