Review

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Revisiting human primary immunodeficiencies

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Abstract. Casanova J-L, Fieschi C, Zhang S-Y, Abel L (Institut National de la Santé et de la Recherche Médicale; University Paris Descartes, Necker Medical School; Necker Children's Hospital; Saint Louis Hospital; Paris, France, EU; and Shanghai Ruijin Hospital, Shanghai Jiaotong University, Shanghai, China). Revisiting human primary immunodeficiencies (Review). *J Intern Med* 2008; **264**: 115–127.

Human primary immunodeficiencies (PIDs) are often thought to be confined to a few rare, familial, monogenic, recessive traits impairing the development or function of one or several leucocyte subsets and resulting in multiple, recurrent, opportunistic and fatal infections in infancy. We highlight here the rapidly growing number of exceptions to each of these conventional qualifications. Indeed, *bona fide* PIDs include common and sporadic illnesses and may present as dominant, or even polygenic traits; their pathogenesis may involve non haematopoietic cells, and they may result in single episode of illness, with a single or multiple morbid phenotypes, some of which may involve infection, in otherwise healthy adults. We need to increase awareness of the multitude of clinical presentations of human PIDs considerably and rapidly in the medical community. Human PIDs should be considered in a wide range of clinical situations.

Keywords: human genetics, immunity, infectious diseases, primary immunodeficiencies.

Introduction

It seems odd that so few attempts have been made historically to define human primary immunodeficiencies (PIDs) and that no consensual definition has emerged. Nevertheless, a classification based on the detection of immunological phenotypes has progressively imposed a paradigm, according to which PIDs are defined by and classified according to the detection of an immunological abnormality — affecting circulating leucocytes or their products, such as Ig, in particular — in the blood [1, 2]. Despite this conservative context, around 200 clinical entities have been described, more than 100 of which now have a known genetic aetiology [3–10]. In the 50 years or so following the description of the first PIDs, such as Bruton's agammaglobulinaemia and Kostmann's neutropenia, the field has gradually expanded, and many of the most recently described PIDs are very different from the syndromes described by Bruton and Kostmann. In a recent editorial entitled 'PIDs: a field in its infancy' [6], we highlighted the multiple paradigm shifts witnessed by the field of PIDs in its first 50 years. PIDs were initially thought to be confined to a few rare, familial, monogenic, recessive traits impairing the development or function of one or several leucocyte subsets and resulting in multiple, recurrent, opportunistic and fatal infections in infancy. A growing number of exceptions to each of these conventional qualifications have accumulated over the years, particularly over the last decade. At least 12 epidemiological, clinical or genetic paradigm shifts have occurred in the field of PIDs (Table 1) [6]. We describe these developments here, focusing on a selection of 12 novel PIDs that have expanded the conventional view of PIDs. This selection is arbitrary and largely reflects our own research interests. Many other choices would have been legitimate, further

Table 1 Multiple paradigm shifts in human primary immunodeficiencies

Primary immunodeficiencies	Conventional	Novel	Examples
Epidemiological levels			
Frequency	Rare	Common	*FUT2* mutations and norovirus
Occurrence	Familial	Sporadic	*UNC93B1* and *TLR3* mutations and HSE
Age at onset	Childhood	Adulthood	CVID
Prognosis	Spontaneously worsening	Spontaneously improving	IRAK-4 deficiency
Phenotype level			
Disease-defining clinical phenotypes	Opportunistic infections[a]	Other life-threatening infections, other phenotypes[b]	Crohn's disease and impaired inflammation
Number of phenotypes per patient (e.g. infectious agents)	High	Low (even single)	Properdin and *MAC* mutations and Neisseria
Number of episodes per patient (e.g. infectious episodes)	High	Low (even single)	IL-12p40 and IL-12Rβ1 deficiency
Disease-causing cellular phenotypes	Haematopoietic	Nonhaematopoietic	*EVER1* and *EVER2* mutations and HPV
Genotype level			
Mode of Mendelian inheritance	Autosomal and X –recessive	Autosomal dominant	*STAT1* mutations and mycobacteria
Clinical penetrance	Complete	Incomplete	*IFNGR1* mutations and mycobacteria
Disease-causing genes per patient	One (monogenic, Mendelian)	Several (oligogenic, major genes)	*PARK* and *LTA* and Leprosy
Mutations	Inherited from the parental genome	Inherited from the parental germline *de novo*, or somatic	*Fas* mutations and auto-immunity

[a]Infections occurring in patients with overt immunological abnormalities.
[b]Autoimmunity, allergy, virus-induced cancer, angioedema, granulomas, haemophagocytosis, autoinflammation, thrombotic microangiopathy.

emphasizing the reality of these paradigm shifts. Needless to say, these paradigm shifts have led to a profound, much-needed revision of the definition and classification of PIDs.

Epidemiological level

From rare to common PIDs: predisposition to norovirus infection

Primary immunodeficiencies are commonly thought to be rare conditions. However, it is now clear that they can be very common, and may even affect the vast majority of the population. The best evidence that PIDs, in the strictly Mendelian sense of the term, are common is provided by the demonstration that rare resistance to infection with four common microbes is under strict monogenic control. Consequently, individuals carrying the common wild-type alleles are intrinsically susceptible to these particular pathogens. Infection with *Plasmodium vivax* is conditioned by an autosomal dominant allele leading to expression of the Duffy antigen receptor for chemokines (DARC), a key receptor for the parasite, on erythrocytes [6, 11–13]. HIV-1 infection requires another chemokine receptor, CCR5, which functions with CD4 as a coreceptor for HIV-1 on $CD4^+$ T cells [14]. Parvovirus B19 infection depends on the erythrocyte P antigen, which is the cellular receptor for this virus [15]. A more recent example is provided by infection with norovirus (i.e. Norwalk-like viruses), a leading cause of gastroenteritis [16–24]. Individuals carrying

loss-of-function *FUT2* alleles are resistant to infection, so susceptibility is autosomal dominant. The *FUT2* gene encodes an enzyme, α (1,2)-fucosyltransferase, regulating the expression of ABH histoblood group antigens on the surface of epithelial cells and in mucosal secretions and determining the secretor phenotype of intestinal epithelial cells. The role of *FUT2* in resistance and susceptibility to noroviruses was first demonstrated in experimental infections of human volunteers. More recently, epidemiological data confirmed the key role of *FUT2* in the course of natural infection. In conclusion, vulnerability to norovirus and at least three other common infections results from monogenic PIDs. Many other examples will probably be discovered in the coming years.

From familial to sporadic PIDs: herpes simplex encephalitis

Primary immunodeficiencies are typically thought to be familial, with recessive Mendelian inheritance, either autosomal or X-linked. However, some mitochondrial disorders, such as Pearson's syndrome, typically present as sporadic PIDs [25]. Sporadic cases mostly result from autosomal dominant *de novo* mutations, because they are lethal before reproductive age [26]. Examples include the rare Mendelian cases of Di George syndrome (TBX1) [27]. Perhaps the best example of sporadic PID is herpes simplex virus 1 (HSV-1), encephalitis (HSE), which has a lower penetrance than other classical dominant PIDs [28–32]. HSE is the most common form of viral encephalitis in Western countries. The HSV-1 is nearly ubiquitous and typically innocuous, yet HSE is a devastating illness that strikes previously healthy children. Two genetic defects — autosomal recessive UNC-93B deficiency and autosomal dominant TLR3 deficiency — were identified as the first genetic aetiologies of isolated HSE (Fig. 1). These defects result in the impaired production of type I and type III IFNs in response to dsRNA viral intermediates, enhancing viral replication and increasing cell death. These defects display complete penetrance at the cellular level, the sporadic nature of HSE resulting at least partly from the incomplete penetrance of both UNC-93B deficiency and TLR3 deficiency at the clinical level. Only two of the three UNC-93B-deficient and two of the seven TLR3-deficient and HSV-1-seropositive individuals developed HSE. There may be several reasons for the low penetrance observed, including age at infection (L. Abel, unpublished data). HSE is a good example — and probably the first such example — of a condition that appeared to be a pure infectious disease, a 'sporadic' encephalitis in the infectious sense of the term, which turned out to be a pure genetic disease, a 'sporadic' Mendelian trait, in the genetic sense of the term.

From childhood to adulthood onset: common variable immunodeficiency

Primary immunodeficiencies were long thought to be paediatric disorders, as most PIDs, like most Mendelian disorders, are observed principally in children. However, this may be due to the severe nature of these conditions and, as medical progress is making it increasingly possible for children with PIDs to survive to adulthood, adult patients with PIDs are increasingly being encountered. These patients pose a formidable clinical challenge to internal medicine specialists, who are typically not familiar with this group of disorders. Moreover, internists are increasingly having to treat patients with late-onset PIDs, as an increasing number of adult-onset PIDs are being described. The best known example is common variable immunodeficiency (CVID), one of the most common PIDs, which typically begins between the ages of 20 and 40, in patients with an overt immunological phenotype [33–35]. Paradoxically, there is no consensual definition or classification of CVID, but most patients with CVID have low serum IgG concentrations, despite the presence of detectable levels of circulating B cells. The clinical presentation of CVID varies greatly between patients, ranging from granulomas and lymphomas to autoimmunity and infections. CVID patients clearly form a highly heterogeneous group, and this clinical heterogeneity results partly from genetic heterogeneity. The few genetic aetiologies identified to date are autosomal recessive mutations of *ICOS* [36], *TACI* [37, 38] and *CD19* [39], impairing B-cell function. *TACI* mutations do not seem to confer autosomal dominant forms of CVID [40]. The genetic basis of

the typical, late-onset form of CVID remains largely unknown, and no genetic aetiology has been identified for most CVID patients worldwide. We may expect a diverse group of CVID-causing inborn errors of immunity to be deciphered in the near future.

From a spontaneously worsening to a spontaneously improving outcome: IRAK-4 deficiency

Primary immunodeficiencies typically worsen spontaneously over time, at least in most patients, as there are individual exceptions for most PIDs. Most, if not all patients with known PIDs would die prematurely in the absence of treatment. However, although antibiotics and Ig substitution have some effect in most patients, they can at best slow the disease process and by no means actually cure the PID [1, 2]. Even haematopoietic stem cell transplantation [41] and gene therapy [42] were recently found to be associated with life-threatening long-term complications in patients with severe combined immunodeficiency, indicating that these treatments unfortunately provide only long-term remission rather than a true cure for the disease. However, some early onset PIDs have recently been shown to have a spontaneously favourable outcome, provided that the first severe infections are well managed. Of course, such patients would also have died before the advent of antibiotics [5]. The first examples of PIDs with a spontaneously improving clinical course to be identified were IL-12Rβ1 and IL-12p40 deficiencies associated with clinical diseases caused by mycobacteria and *Salmonella* [43–47]. Other examples soon followed, such as UNC-93B and TLR3 deficiencies [28, 32]. Fas deficiency, associated with tumoral and autoimmune phenotypes, also seems to improve with age, although this trend is not as clear cut as for other diseases [48]. Perhaps the most striking example is IRAK-4 deficiency, with the suddenness, severity and mildly inflammatory features of infections in affected children contrasting with the silent and benign course of disease from adolescence onwards [49–52]. Patients with IRAK-4 deficiency do not respond to most IL-1R and TLR agonists, with the exception of the nonspecific TLR3 agonist poly(I:C) [53]. Patients with IRAK-4 deficiency are highly susceptible to invasive pyogenic bacteria, and to invasive pneumococcal disease in particular. However, no invasive infections or deaths from adolescence onwards were recorded in a series of 28 patients [49]. The underlying mechanisms may include compensatory effects of adaptive immunity or the maturation of IRAK-4-independent innate mechanisms.

Phenotype level

From opportunistic infections to other phenotypes: Crohn's disease

The clinical phenotype typically used to define PIDs is opportunistic infection — infectious disease seen only in patients with an immunological abnormality distinguishing them from the general population normally resistant to the pathogen concerned. In the last 50 years, multiple clinical phenotypes have been found to be associated with PIDs. Some involve infection, whereas others do not, and these phenotypes range from autoimmunity to tumours, from haemophagocytosis to angioedema, and from allergy to granuloma. Perhaps the most interesting example of a clinical phenotype eventually leading to the discovery of a new type of PID is the granulomatous reaction seen in Crohn's disease. Granulomas have long been known to be associated with certain PIDs, such as chronic granulomatous disease. Crohn's disease, a systemic, intestinal, 'inflammatory' disorder associated with well delimited granulomas, was recently shown, by Anthony Segal and colleagues, to result from a primary defect in systemic and intestinal inflammation [54–58]. A failure to produce inflammatory mediators leads to insufficient neutrophil recruitment, impairing the removal of bacteria and other debris. These authors also discovered a cellular phenotype underlying Crohn's disease. Patients with Crohn's disease, unlike healthy controls, had a slow, weak inflammatory reaction in response to intestinal biopsies and skin lesions. These discoveries paradoxically revealed that the main cause of Crohn's disease was the impairment, rather than the enhancement of inflammation. They also established the cellular basis for the PID underlying Crohn's disease. It remains unclear how this cellular phenotype relates to the Crohn-associated genotypes previously identified — the alleles of *IL23R* [59] and *CARD15/NOD2* [60]

— and to proposed models of the pathogenesis of Crohn's disease [58, 61]. However, whatever the relationship, this elegant work highlights the utility of searching for morbid cellular phenotypes as an alternative and complementary strategy to the search for morbid genotypes.

From multiple to a single phenotype per patient: defects of properdin and the terminal components of complement

Patients with PIDs commonly present with multiple clinical phenotypes, such as multiple infections (e.g. viral, bacterial, and fungal infections), or even a combination of phenotypes (e.g. infection, autoimmunity, allergy). However, several PIDs have been found to confer predisposition to a single phenotype, infectious or otherwise. One of the first documented examples of this situation is that of complement disorders, particularly those concerning properdin and the membrane attack complex (MAC), both of which selectively predispose patients to invasive disease caused by bacteria from the genus *Neisseria*, with *N. meningitidis* infections more frequently observed than *N. gonorrhoeae* infections [62]. Infections are invasive, typically manifesting as meningitis, and are often recurrent. Properdin deficiency is X-linked recessive. Autosomal recessive defects of the membrane attack complex affect C5, C6, C7, any of the C8 components, and C9. The age at invasive infection of patients with any of these complement deficiencies is generally greater than that at invasive *Neisseria* infection in patients from the general population with an apparently normal complement pathway. Only a small fraction of children with invasive *Neisseria* infection seem to carry any of these complement defects. However, complement levels should be measured in all children with invasive disease caused by *Neisseria*. Strikingly, patients with properdin and MAC deficiencies seem to be resistant to other pathogens, including other encapsulated pyogenic bacteria that may cause meningitis, such as *Pneumococcus* and *Haemophilus*. More recent examples of PIDs conferring a selective predisposition to a narrow range of infections include IRAK-4 [49–52, 63, 64] deficiency and other syndromes reviewed by Picard *et al.* [63]. Pure autoimmune syndromes, pure granulomatous syndromes and pure haemophagocytic syndromes have also been identified [6]. There are therefore many PIDs that present with a single phenotype.

From multiple episodes to a single episode: IL-12Rβ1 deficiency

Even in patients with a PID predisposing them to a single phenotype, such as a single type of infection, the clinical illness tends to persist or recur, as shown by the recurrent invasive disease due to *Neisseria* observed in MAC-deficient patients and the chronic course of haemophagocytosis and EBV infection in patients with X-linked lymphoproliferation (XLP) syndrome [65]. However, some PIDs predispose the individual to a single infectious episode. IL-12p40 and IL-12Rβ1 deficiencies [43–47, 66, 67] are good examples of this, as patients with these deficiencies typically present a single episode of BCG or environmental mycobacterial (EM) disease. In a series of more than 120 patients with IL-12Rβ1 deficiency and 20 patients with IL-12p40 deficiency, no recurrence of BCG disease was observed after antibiotic treatment, these patients displaying sustained remission. Moreover, BCG disease and, to a lesser extent, BCG vaccination without adverse effects, conferred protection against EM clinical disease. Similarly, only one of the patients with EM disease who responded to antibiotics relapsed (D. Kumararatne, personal communication). IL-12Rβ1-deficient patients are also susceptible to *M. tuberculosis*, which may be responsible for the sole infectious episode, even in patients vaccinated with BCG [68–71]. Incidentally, this observation provided the first evidence that severe tuberculosis in otherwise healthy children may result from a Mendelian trait. It thus appears that IL-12 and IL-23, both of which contain IL-12p40 and signal via IL-12Rβ1, are required for protective immunity to various primary mycobacterial infections, but are redundant for secondary immunity to any of these mycobacterial species, or immunity to latent infection with the primary pathogen. However, disease penetrance is incomplete, for both BCG disease in BCG-vaccinated individuals and for EM

disease in non-BCG-vaccinated individuals, indicating that IL-12 and IL-23 are also redundant for primary infection in at least some patients. These observations neatly illustrate the idea that a PID may present as a single infectious episode.

From haematopoietic to nonhaematopoietic PIDs: epidermodysplasia verruciformis

The immune system is often described as a branch of the haematopoietic lineage, consisting of myeloid and lymphoid cells. However, nonhaematopoietic cell types are also involved in immunity to infection. For example, the epithelial barriers of the skin and mucosa provide an efficient first line of defence against microorganisms. A number of PIDs have been found to affect both haematopoietic and nonhaematopoietic cells. These PIDs include anhidrotic ectodermal dysplasia with immunodeficiency, caused by mutations in *NEMO* impairing NF-κB activation in multiple tissues [51, 52, 72]. The most striking example of a pure nonhaematopoietic PID is probably epidermodysplasia verruciformis (EV) [73–76], which may ironically have been the first PID ever described, in the 1940s. The lack of an immunological phenotype prevented its inclusion in the classification of PIDs until the disease-causing gene was found in 2002. Patients with EV develop cutaneous warts caused by B1 oncogenic papillomaviruses and malignant transformation is common. Autosomal recessive EV results from mutations in one of two genes, *EVER1* and *EVER2* [75]. The encoded proteins, EVER1 and EVER2, form a complex and interact with the Zn transporter 1 (ZnT-1) [76], preventing the nuclear accumulation of Zn. In keratinocytes, mutations in *EVER1* and *EVER2* result in higher nuclear Zn concentration, increasing both HPV replication and keratinocyte proliferation. It has been suggested that EV is a disorder of 'intrinsic' immunity, affecting the nonhaematopoietic, first line of defence [73]. In any event, EV is clearly a PID, with a cellular and clinical phenotype affecting keratinocytes, and expression of the morbid genes in keratinocytes. More PIDs affecting nonhaematopoietic cells are likely to be identified in the future, particularly in patients with infections of a single tissue, such as the lungs in patients with primary mucociliary dyskinesia or cystic fibrosis [77].

Genotype level

From recessive to dominant PIDs: STAT1 deficiency

The vast majority of known PIDs segregate as recessive traits, most (over 150) being autosomal recessive and a few (less than 15) X-linked recessive. However, a growing number of autosomal dominant (AD) PIDs have been described in the last 10 years [26]. AD traits were initially thought to be unlikely to cause PIDs, because most affected patients would die before reaching reproductive age and multiplex kindreds would therefore be exceedingly rare. Some *bona fide* AD pedigrees of relatively mild PIDs were, however, identified. AD traits may also typically present as sporadic cases. Perhaps the most interesting known AD PID in the context of the present discussion on the mechanisms of heredity concerns the subtle *STAT1* mutants discovered by chance [29, 78–82]. Indeed, some mutations in *STAT1* are intrinsically loss-of-function for both IFN-α-dependent ISGF3 activation and IFN-γ-dependent GAF activation (e.g. in STAT1-deficient cells transfected with the corresponding alleles), whereas they impair GAF but not ISGF3 activation in heterozygous cells. This results in an AD predisposition to mycobacterial disease in simplex and multiplex kindreds [83–85]. Originally, mutations in *STAT1* would not have been thought to be associated with MSMD, because they were predicted to affect both GAF and ISGF3 activation. Other STAT1 mutations impairing both pathways have subsequently been identified and shown to result in a combined predisposition to mycobacterial and viral illnesses, owing to the dual impairment of IFN-α/β and IFN-γ cellular responses [79, 82]. The discovery of such subtle AD mutations in *STAT1* illustrates the current trend in PID research for PIDs to be seen no longer as restricted to a collection of recessive traits. Many more AD PIDs are likely to be identified, particularly in patients with sporadic phenotypes, whether or not these phenotypes involve infection.

From complete to incomplete penetrance: IFNGR1 deficiency

As most PIDs are Mendelian traits, they were assumed to be fully penetrant at the cellular and clinical levels.

However, most PIDs clearly display incomplete penetrance for some specific clinical phenotypes that depend strongly on exposure to environmental factors, such as the microbial flora. For example, not all patients lacking T cells develop BCG disease, as the degree of exposure to BCG differs between countries, according to national vaccination policy. Other, more subtle host and environmental factors may account for incomplete penetrance. They may be barely identifiable for PIDs predisposing patients to multiple infections, whereas they are likely to be much more apparent for PIDs predisposing patients to a single infectious phenotype. The best documented cases include IL-12Rβ1 [47, 66], TLR3 [31, 32], and STAT1 [78, 80] deficiencies. Here, we will focus on the autosomal dominant form of IFN-γR1 deficiency [86–88]. Patients with autosomal recessive complete IFN-γR1 deficiency invariably present symptoms of infection with BCG or EM in the first 5 years of life [86, 89, 90]. By contrast, patients with AD partial IFN-γR1 deficiency often remain asymptomatic for much longer periods of time, possibly even until late adulthood [86]. The range of pathogenic mycobacteria causing infection is also narrower in patients with the AD form, although diverse mycobacterial infections were recently reported in a Norwegian family [91]. Similarly, patients with the AR form often die in childhood, although a 19-year-old survivor was recently reported in the Netherlands [92]. The comparison of complete and partial IFN-γR1 deficiency illustrates the strict correlation between *IFNGR1* genotype (dominant versus recessive alleles), cellular phenotype (partial response to IFN-γ versus no response), and clinical phenotype (late onset, narrow range of infections and favourable outcome versus early onset, broad range of infections and poor outcome) [81]. Overall, for most clinical phenotypes considered, clinical penetrance at any age is lower in patients with partial than with complete IFN-γR1 deficiency.

From monogenic to complex PIDs: leprosy

Primary immunodeficiencies are commonly seen as Mendelian, monogenic traits. This is odd, because there is no such thing as a purely monogenic trait in multigenic organisms. The disease-causing gene is not isolated, and any morbid phenotype results, by definition, from the interaction between the morbid allele and the rest of the genome. Moreover, Di George syndrome, a classic example of PID, is probably polygenic in most cases, owing to the large size of the genomic deletion [27]. A plausible explanation for this Mendelian prejudice in the field of PIDs is that research in this field was led by scientists who were also clinicians, interested in deciphering the molecular genetic basis of disease to improve patient care. Whatever the mode of inheritance, the physician treating a patient will diagnose a PID if the mode of inheritance allows clear diagnosis, guiding genetic counselling, if it improves our understanding of pathogenesis, and if it provides a means of directing immunomodulatory treatment in a rational manner. In other words, there must be a sufficiently strong causal relationship between genotype and phenotype. In most cases of complex inheritance in human medicine, this causal link is not strong enough to be evoked at the patient's bedside. However, major genes, detected by positional cloning, have bridged the gap between monogenic and polygenic traits. This applies to all infectious diseases and PIDs, and has led to the discovery that leprosy is controlled by at least two major genes, *PARK2/PACRG* and *LTA* [93–96]. It is now clear that leprosy — particularly the early onset form — is also a PID, with a few major genes controlling the development of disease in infected individuals. Major genes controlling the development of many other infectious diseases are currently being deciphered, including those controlling HIV infection and tuberculosis. This work may have clinical implications in the near future.

From germline to somatic mutations: Fas deficiency

Primary immunodeficiencies are occasionally referred to as inborn errors of immunity, inherited immunodeficiencies, heritable immune defects, or congenital immunodeficiencies. In all cases, it is explicit or implicit that the primary lesions were present in the germline, whether due to a *de novo* mutation or due to a mutation inherited from a parent carrying the mutation. It has gradually become clear that somatic mutations in

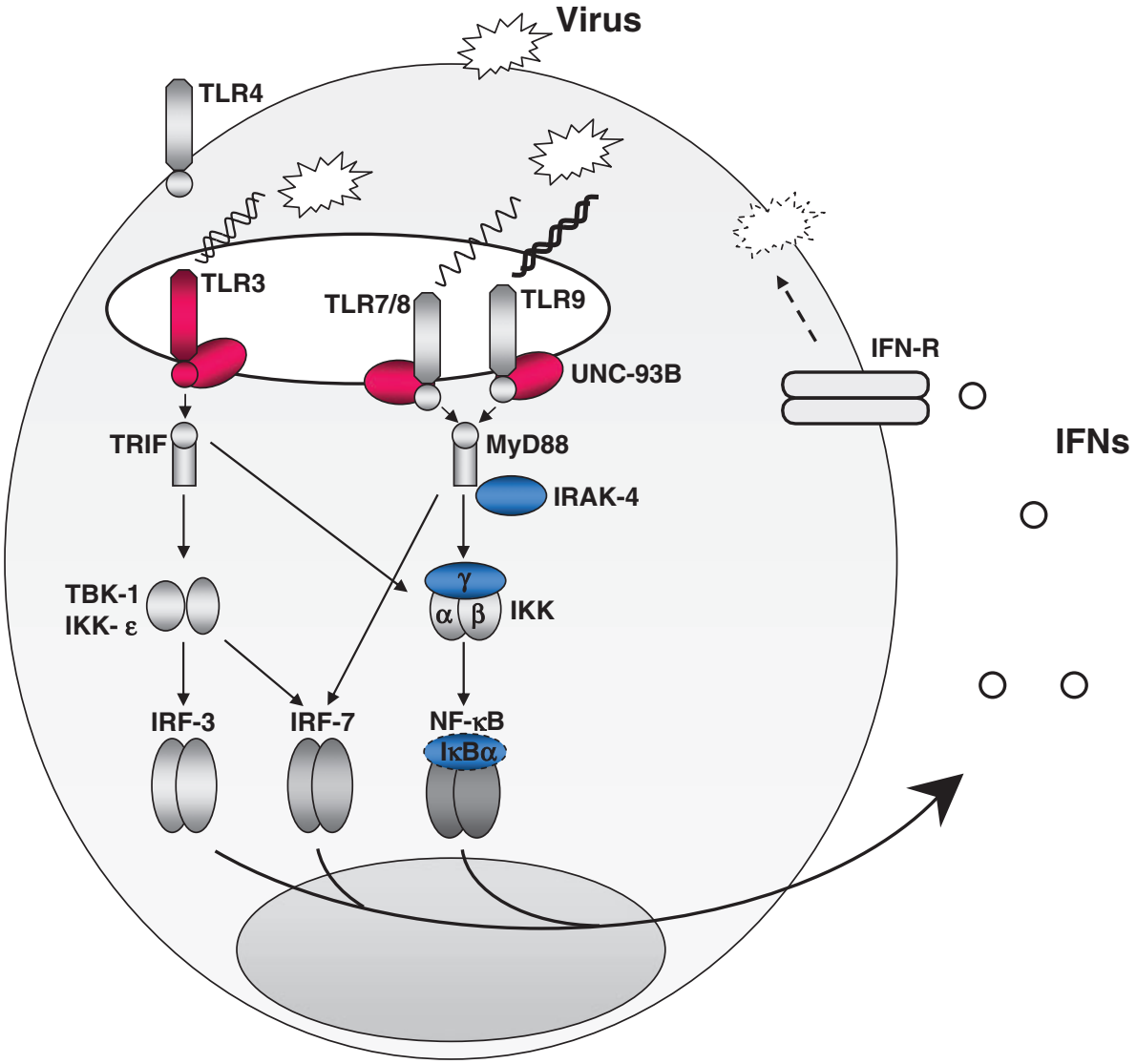


Fig. 1 Herpes simplex encephalitis is a PID. TLR3-UNC-93B-IFN signalling pathway involves in human antiviral immunity to HSV-1 in the CNS. Four (TLR3, TLR7, TLR8 and TLR9) of the five IFN-including TLRs (TLR3, TLR4, TLR7, TLR8 and TLR9) are intracellular in most cell types tested. Viral nucleic acid, including dsRNA, ssRNA and DNA, produced during virus replication are thought to be detected by TLR3, TLR7/8 and TLR9, respectively, and to induce interferon (IFN) production. The production of IFN-α, -β, and – λ in response to TLR7, TLR8 and TLR9 stimulation is impaired in IRAK-4-deficient patients, who appear to be resistant to most viruses. The induction of IFN-α, -β, -λ by TLR7, TLR8 and TLR9 is impaired in UNC-93B-deficient patients, who are prone to herpes simplex encephalitis (HSE), but appear to be resistant to most viruses. The UNC-93B-TLR3-IFN-α, -β, -λ pathway is essential for primary immunity to HSV-1 in the CNS in children, but redundant for immunity to most other viral infections. The two proteins in the TLR signalling pathways (UNC-93B and TLR3) described to be responsible for the human primary immunodeficiencies associated with isolated HSE in children are shown in red. The other three proteins in the TLR signaling pathways (IRAK-4, NEMO, IkBa) responsible for human PIDs are shown in blue.

the haematopoietic lineage may at least partly restore a normal cellular and clinical phenotype in some patients with PIDs. Following the seminal description of a reversion for ADA deficiency, examples were documented for various PIDs, including severe combined immunodeficiency, Wiskott-Aldrich syndrome, and

leucocyte adhesion deficiency [97–99]. The opposite phenomenon, in which somatic mutations in the haematopoietic lineage may result in a phenotype resembling that of the PID caused by the corresponding germline mutation, has also recently been described. The only known example to date is that of Fas/CD95, for which somatic mutations in the lymphoid lineage closely mimick the germline mutations [48, 100]. The somatic mutations in *Fas* exert a dominant-negative effect, leading to expansion of the double-positive T-cell population. No enhanced apoptosis phenotype is detected when unfractionated blood lymphocytes are tested. Enhanced apoptosis and the *Fas* mutation itself are only detected when double-positive T cells are purified. The *Fas* somatic mutation provides a selective advantage, accounting for the development of morbid cells and the subsequent progression from a silent process to clinical disease. Other somatic mutations may result in clinical syndromes typically associated with germline mutations, somatic phenocopies of inborn traits. The concept of PIDs should therefore be expanded to the sum of the somatic genomes in a patient, taking somatic variation into account.

Conclusion

We did not aim to review all known PIDs here. This would have been a daunting task, and, in any event, at least two excellent and comprehensive textbooks have already provided such a review [1, 2]. We also decided not to consider patients with autoantibodies causing autoimmune phenocopies of PIDs, such as patients with IFN-γ [101–103] and IL-6 [104] autoantibodies. Instead, we focused on a series of conditions not commonly viewed as PIDs, with the aim of convincing readers that there are many more PIDs than commonly thought. Furthermore, the multiple paradigm shifts occurring in this field in the last decade herald a formidable expansion of the field to well beyond its traditional limits. We hope this essay will convince readers that potential PIDs should be considered in diverse clinical situations. PIDs, previously thought to be rare, may soon be viewed as general, and the popular concept of immunocompetence may turn out to be an exception, consistent with all available epidemiological data. Indeed, human life expectancy at birth was once only about 20–25 years, mostly due to infectious diseases [5]. The conquests of hygiene, vaccination, and anti-infectious agents have masked the considerable vulnerability of our species to pathogens, as demonstrated by the situation still prevailing in the poorest countries of the world. The twelve examples considered here illustrate, each in its own way, how the field of PIDs has advanced in the last 50 years. They also show how the pace of progress has quickened in the last 10 years. The dissection of PIDs is useful for immunological purposes, as it makes it possible to dissect out the genetics of immunity in natural conditions — in the setting of a natural ecosystem governed by natural selection [5, 105–108]. Such studies are therefore an indispensable complement to animal studies, which benefit from being experimental but suffer from the inherent limitations of experimental assays. The dissection of PIDs is also extremely helpful for medical purposes, as illustrated throughout this review.

Conflict of interest statement

No conflict of interest was declared.

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