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Human Inborn Errors of Immunity: an Expanding Universe

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Abstract

Molecular, cellular, and clinical studies of human inborn errors of immunity have revolutionized our understanding of their pathogenesis, considerably broadened their spectrum of immunological and clinical phenotypes, and enabled successful targeted therapeutic interventions. These studies have also been of great scientific merit, challenging a number of immunological notions initially established in inbred mice, while revealing previously unrecognized mechanisms of host defense by leukocytes and other cells, and of both innate and adaptive tolerance to self.

Introduction

Primary Immune Deficiencies (PIDs) have been classically characterized by increased susceptibility to infections, due to genetic defects affecting development and/or function of the immune system. The history of PIDs is typically dated back to 1952, when Bruton described a boy who had suffered from 19 episodes of pneumococcal infections, lacked serum gamma globulins, and recovered upon intramuscular administration of gamma globulins (1). Two years earlier, Glanzmann and Riniker had described an infant with severe lymphopenia and atrophy of lymphoid tissues who succumbed to infections early in life (2).

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Subsequently, Hitzig reported other infants with early-onset life-threatening infections who lacked both gamma globulins and lymphocytes (3). This condition, which was initially named Swiss-type agammaglobulinemia (4) (to distinguish it from Bruton's agammaglobulinemia), is now referred to as Severe Combined Immune Deficiency (SCID). Together, isolated agammaglobulinemia and SCID provided evidence of the critical role played by humoral and cellular immunity, respectively, in protection against infections, paving the way to the discovery of T and B cells few years later (5).

The first inborn errors of innate immunity defects were also reported in the 1950s. In 1950, Kostmann described the first patients with severe congenital neutropenia (6). While searching for other cases of hypogammaglobulinemia, Janeway et al. reported in 1954 a patient with recurrent infections and, paradoxically, elevated serum immunoglobulins (7). The patient was found in 1957 to suffer from a congenital defect of phagocyte function, designated as chronic granulomatous disease in 1957 (8). Inborn errors of complement were described from the 1960s onward. It was soon recognized that the nature of pathogens (viruses, bacteria, fungi, or parasites, "opportunistic" or not) causing infections in patients with PID is largely determined by the arm of immunity that is affected (T lymphocytes, B lymphocytes, phagocytes, complement). PIDs in any category have long been defined by susceptibility to a broad range of pathogens. Although clinically and immunologically homogeneous forms of PIDs (agammaglobulinemia, SCID, CGD) were evidently transmitted with different patterns (X-linked, autosomal recessive), too few immunological reagents were then available to distinguish different forms of PID in each category. Consequently, only a handful of distinct disorders were included in the first classification of PIDs in 1968, which, incidentally, did not include neutropenia as it was regarded by immunologists of the time as a hematological condition (9).

Over the years, it has been recognized that depending upon the specific nature of the disease, autoimmunity, autoinflammation, allergy, and malignancy can be common, and in some cases, predominant, clinical manifestations associated with monogenic defects of immunity (13). To capture this broad range of phenotypes associated with these disorders, the term "inborn errors of immunity" (IEI) has been proposed. Importantly, advances in molecular genetics and cellular immunology have allowed a much more precise definition of various forms of IEI (Fig. 1). Use of next generation sequencing (NGS) has permitted the identification of a growing number of IEI (Fig. 2A), whose number has now reached 431 in the 2020 classification from the International Union of Immunological Societies Committee on Inborn Errors of Immunity (10). At the molecular level, it has been shown that most PIDs can be caused by mutations in different genes (locus heterogeneity), which typically govern a certain pathway. More surprisingly, distinct pathogenic variants at the same locus have also been shown to cause different forms of IEI, usually but not necessarily because of different genotypes (allelic heterogeneity: mono-allelic vs. bi-allelic lesions, loss-of-function (or hypomorphic) vs. gain-of-function (or hypermorphic) variations, dominant-negative vs. haploinsufficient mode of dominance).

Following up on the surprising observation that patients with autosomal recessive (AR) defects in the terminal components of complement were selectively prone to *Neisseria* infections, it was gradually realized that many other IEI manifest as susceptibility to a

narrow group of pathogens (11). Furthermore, some of these PIDs have been shown to reflect genetic defects that are extrinsic to the hematopoietic system, reflecting instead functional abnormalities of cell types other than leukocytes (12).

Importantly, it has also been recognized that depending upon the specific IEI, autoimmunity, autoinflammation, allergy, and malignancy can be common, and in some cases, predominant, clinical manifestations (13). Finally, the in-depth characterization of the molecular, cellular, and immunological mechanisms of disease has permitted a shift from supportive (mostly focusing on prevention and treatment of infections or inflammation) to definitive (hematopoietic stem cell transplantation, gene therapy) care and to targeted pharmacological interventions (enzyme replacement therapy, cytokine administration, therapeutic antibodies, small molecule inhibitors) (14–16). Here, we will review recent advances in the study of IEI, and how this has been of both clinical and immunological importance.

The spectrum of IEI: Phenotypes and Genotypes

Combined immunodeficiencies: Uncovering Pathways to T Cell Development and Immune Regulation

Following the first descriptions of SCID in the 1950s, a growing number of patients with early-onset life-threatening infections and lymphopenia were described in the next decades. A first evidence of genetic heterogeneity came with the observation that SCID was inherited as an X-recessive (XR) (17) or autosomal recessive (AR) trait (3). After T and B lymphocytes (and later on, NK cells) were described, it was further found that SCID comprises different conditions, all of which are characterized by lack of autologous T cells, whereas B and/or NK cells may either be present or absent.

Eventually, cloning of SCID-causing genes revealed an even higher level of heterogeneity. The first SCID disorders that were defined at the molecular level were adenosine deaminase (ADA) and purine nucleoside phosphorylase (PNP) deficiency. The metabolic basis of these disorders was established by Eloise Giblett in 1972 and in 1975, respectively (18, 19), while *ADA* and *PNP* mutations were reported in 1985 and 1987. Along with mutations in *CYBB*, causing X-linked granulomatous disease (20), mutations underlying ADA deficiency were actually the first identified in the entire field of IEI.

The molecular pathogenesis of XR SCID was revealed in 1993, with mutations in the *IL2RG* gene (21). This gene was initially thought to code only for the γ chain of the IL-2 receptor; however, it was soon found that the γ chain is also a subunit of receptors for IL-4, IL-7, IL-9, IL-15, and IL-21 (and for this reason is also referred to as the common γ chain, γ_c), and that it is constitutively associated with the intracellular tyrosine kinase JAK3 (22). These observations led to the identification of JAK3 deficiency as an AR form of SCID, which is clinically and immunologically indistinguishable from XR SCID (23). Important differences emerged when comparing the immunological phenotype of patients and mice with genetic defects of γ_c signaling. In particular, γ_c and Jak3 defects in mice are associated with a T⁻ B⁻ NK⁻ SCID phenotype, whereas in humans they cause T⁻ B⁺ NK⁻ SCID. The discovery of patients with AR IL-7R deficiency as an etiology of T⁻ B⁺ NK⁺ revealed that abolished IL-7

signaling plays a critical role in the SCID phenotype of *IL2RG*- and *JAK3*-deficient patients, while it has no impact on B cell development in humans, unlike in mice (24). The more recent discovery that patients with AR IL-7 deficiency display a milder T cell deficiency suggests that abrogated responses to TSLP, which also engages the IL-7R, contributes to the SCID phenotype of AR IL-7R deficiency (25, 26).

Many other gene defects accounting for defects of T-cell development were identified from the late 1990s onward. In some cases, these studies revealed previously unappreciated molecules and mechanisms that govern T-cell development, preceding the generation of animal mutants. This was the case for ARTEMIS and Cernunnos/XLF defects that compromise V(D)J recombination and DNA repair (27–29), for AK2 deficiency that compromises mitochondrial function and cell survival in reticular dysgenesis (30, 31), as well as for various defects of transcription factors that account for HLA class II deficiency (32–35). In other cases, mutations were found in human orthologs of genes previously studied in mice, such as *RAG1* (36) and *RAG2* (37).

Advances in molecular genetics have enabled the identification of a growing number of genetic etiologies of combined immune deficiency (CID). At variance with SCID, CID disorders are characterized by a less severe numerical and/or functional T-cell defect. Furthermore, while early-onset, life-threatening infections are the hallmark of SCID, various forms of immune dysregulation (such as autoimmune cytopenias, organ-specific autoimmunity, and lymphoproliferation) are commonly seen in CID patients (38). This led to the identification of previously undescribed disorders of immune regulation, as in the case of calcium release-activated calcium (CRAC) channel defects due to ORAI1 and STIM1 deficiency (39, 40).

The most recent classification of IEI includes 64 disorders underlying SCID or CID (Fig. 2B). Mutations in the same gene can underlie a broad range of clinical and immunological phenotypes, as neatly exemplified by RAG deficiency (41). Different levels of V(D)J recombination activity driven by distinct gene mutations allow for the development of variable numbers of T and B cells. Patients with loss-of-function *RAG1* or *RAG2* mutations display a T⁻ B⁻ NK⁺ SCID phenotype, whereas severely hypomorphic mutations often underlie Omenn syndrome, in which oligoclonal T cells infiltrate the skin and other target tissues. By contrast, less severely hypomorphic *RAG* gene variants are typically associated with autoimmunity and granulomatous lesions (42). The immune dysregulation of RAG deficiency (and of other forms of CID) reflects perturbations in the mechanisms of negative selection of self-reactive T and B lymphocytes, and poor function (or restricted TCR repertoire) of regulatory T cells (41).

Major progress has been made in the screening of inherited T cell disorders. Measurement of T-cell receptor excision circles (TRECs), a by-product of VDJ recombination at the T cell receptor α/δ locus (43), in dried blood spots collected at birth can identify newborns with severe T-cell lymphopenia (TCL). Immunological and genetic studies are needed to diagnose SCID as opposed to other causes of TCL, such as prematurity, some syndromic conditions, chylothorax and other causes of T-cell loss, and use of some immunosuppressive drugs during pregnancy (44). The implementation of universal newborn screening (NBS) for SCID

in the USA has revealed an incidence of SCID of approximately 1:65,000, which is significantly higher than previously thought (44). By allowing early identification of SCID babies, NBS facilitates interventions aimed at preventing infections and rapid referral to hematopoietic stem cell transplantation (HSCT). This is especially important, because it has been shown that younger age and infection status at transplantation are key factors that determine improved outcome after HSCT for SCID (45, 46).

Monogenic errors of immune regulation

The understanding of immunological self-tolerance and autoimmunity greatly benefited from studies of monogenic inborn errors of T-cell tolerance, T-cell apoptosis, or regulatory T cells (Tregs), each presenting with distinctive immunological and clinical manifestations but unified by pathological self-reactive T-cell responses.

One of the longest-studied examples of such disorders, first reported by Leonard in 1929, as an AR condition known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED; also known as Type 1 autoimmune polyglandular syndrome, APS1) (reviewed in (47)). From a clinical standpoint, APECED is characterized by pleiotropic autoimmune manifestations and the presence of tissue- and cytokine-specific autoantibodies. The disease is caused by mutations in *AIRE*, a key transcription factor that regulates tissue-restricted self-antigen expression in medullary thymic epithelial cells, thereby governing negative selection of autoreactive T cells (48). In APECED patients, thymic escape of self-reactive TCR $\alpha\beta^+$ CD4 $^+$ T cells causes autoimmunity. Furthermore, an altered positive selection of thymic Tregs, increased autoreactive B cells and production of autoantibodies further aggravate the autoimmunity of the disease (49–51). Adoptive transfer experiments in mouse models of APECED support a predominant pathogenetic role of self-reactive T cells, whereas autoantibody formation appears largely secondary to, rather than causative of, tissue damage (52).

Patients with APECED typically suffer from hypoparathyroidism, adrenal insufficiency (Addison's disease), and chronic mucocutaneous candidiasis (CMC). Other autoimmune endocrine problems (hypothyroidism, ovarian and testicular failure hypopituitarism), as well skin lesions (urticarial eruption, alopecia, vitiligo), and pulmonary, gastrointestinal, liver, renal, and ocular manifestations are frequently seen (47). Neutralizing anti-IL-17A/F antibodies are often present in APECED patients and play a pathogenic role in CMC (53, 54). This is an example of increased susceptibility to infection due to an autoimmune mechanism. In addition to anti-IL-17A/F autoantibodies, APECED patients have anti-IFN- α and anti-IFN- ω autoantibodies, which are not known to be pathogenic, yet represent useful diagnostic biomarkers. As the defect is in the thymic epithelial cells and not in hematopoietic cells, there are currently no curative approaches for APECED, and patients with this disease have an increased mortality rate and a poor quality of life.

Autoimmune lymphoproliferative disease (ALPS) is another form of monogenic autoimmunity, which is caused by germline or somatic mutations in *TNFRSF6*, *TNFSF6*, and *CASP10*, coding for FAS/CD95, FAS ligand (FasL), and caspase 10, respectively. These defects impair FAS/CD95-mediated cell death of lymphocytes, leading to the main clinical

manifestations of lymphadenopathy, splenomegaly and autoimmune cytopenias (reviewed in (55, 56)). An unusual population of TCR $\alpha\beta$ ⁺ CD4⁻ CD8⁻ double negative T (DNT) cells infiltrates and accumulates within lymphoid organs. These DNT cells resemble TEMRA cells, as they express the naïve marker CD45RA but also activation and exhaustion markers. In some patients DNT cells are the only cell type carrying the mutation, supporting their important pathogenic role. B cells are also altered in ALPS, with decreased marginal zone and memory B cells, abundant plasma cells, and increased levels of IgG and IgA. Other diagnostic biomarkers include elevated serum levels of IL-10, soluble FasL, and vitamin B12. Although lymphoproliferation tends to improve in adulthood, ALPS patients usually require immunosuppression and have an increased risk of lymphoma. Related disorders of defective apoptosis are caused by Caspase-8 (57) or FADD deficiencies (56), or activating mutations in *NRAS/KRAS* (58, 59), which are associated with other immunological and clinical phenotypes.

A third form of monogenic autoimmune disorders is inborn errors of Tregs, collectively called Tregopathies (reviewed in (60)). Immune dysregulation - Polyendocrinopathy - Enteropathy X-linked (IPEX) syndrome (reviewed in (61)), affecting CD4⁺CD25^{hi}CD127^{lo} thymic derived Tregs, represents the prototype of this group of disorders. IPEX was first clinically described in 1982 by Powell (62), and its successful treatment with HSCT (proving the hematopoietic intrinsic nature of the disease) was reported in 2001 (63). Around the same time, three groups described mutations in human *FOXP3* (64–66). In 2003, several publications connected *Foxp3* mutations, defective Tregs, and autoimmunity in mice (67–69). Defective Treg function in patients with IPEX (with impaired capacity to suppress proliferation and cytokine production of T effector cells) was reported in 2006 (70), establishing Treg dysfunction as the primary pathogenic cause of IPEX. *FOXP3* mutated effector T cells have an increased proliferative capacity, and their cytokine expression profile is skewed toward Th2 and Th17 cells, which may contribute to the autoimmune pathology and probably to atopic disease as well (61, 71).

In most IPEX patients, the disease manifests within the first months of life (72), with severe enteropathy, type 1 diabetes and skin disease resembling atopic dermatitis. Cytopenias and autoimmune hepatitis are also very common. In some cases, however, *FOXP3* mutations are detected in adolescents with milder or atypical autoimmune manifestations, including thyroiditis, glomerulonephritis, alopecia, psoriasis or arthritis. An increased CD4:CD8 ratio, eosinophilia, and elevated serum IgE are typical biomarkers of the disease. Tissue-specific auto-Abs are frequently detected; in particular, anti-harmonin and anti-villin Abs are associated with enteropathy (73). Enumeration of circulating Treg cells and evaluation of *FOXP3* expression have limited diagnostic value, since some patients express fairly normal amounts of mutated *FOXP3* protein. DNA demethylation at the Treg-specific-region (TSDR) of the *FOXP3* gene promoter is a requirement for stable *FOXP3* expression (74). Increased TSDR demethylation (suggesting a possible compensatory mechanism) has been reported in IPEX patients, and may represent an important diagnostic aid (75). IPEX is a life-threatening disease, with limited response to immunosuppression and poor long-term disease-free survival. HSCT can be curative, although the clinical status of the patients at the time of transplant can negatively affect the outcome (72).

IPEX-like diseases are caused by mutations in genes encoding molecules involved in survival, development, signaling or function of Tregs, but also of T effector (Teff) cells (60, 76). This group of disorders comprises defects in several genes: i) *CD25*, encoding the α chain of the IL-2 receptor (IL-2R α) complex, which is essential for Treg peripheral survival, Teff expansion, and for sustaining Ag-specific T-cell immune responses. CD25 deficiency manifests with enteropathy, other autoimmune features, and increased susceptibility to infections, in particular to CMV. In a few cases, all carrying the same mutation, autoimmunity has been reported as the only clinical feature (77). Biallelic mutations in *CD122*, encoding for IL-2R β , cause similar clinical manifestations (78, 79), and mutations in *STAT5B*, which lead to growth hormone insensitivity and short stature, also impair IL-2 signaling and Treg fitness (80, 81); ii) *CTLA4*, encoding a negative regulator of T cell responses. CTLA-4 is constitutively expressed by Treg, and directly regulated by FOXP3, in contrast to its inducible expression in Teff cells. By competing with CD28 for binding to the costimulatory molecules CD80 and CD86, expressed on the surface of APCs, CTLA-4 blocks T cell activation. CTLA4 haploinsufficiency is characterized by lymphoproliferation (including lymphoid infiltrates in the lungs and in the CNS), increased susceptibility to infections, and autoimmunity (enteropathy, cytopenias, skin lesions) (82, 83). The disease has incomplete penetrance; iii) *LRBA*, encoding an anchor-protein involved in membrane recycling of CTLA-4 (84). LRBA deficiency is an AR disease with similar manifestations to CTLA4 haploinsufficiency, but with earlier clinical onset and complete penetrance (85). Recently, mutations in *DEF6*, also involved in CTLA-4 membrane trafficking, have been described (86); iv) *STAT3*, encoding a signaling mediator of many cytokine receptors. Gain-of-function (GOF) *STAT3* mutations are associated with reduced *STAT5B* signaling, and impaired *FOXP3* and *IL17A* expression. The clinical manifestations are heterogeneous, including autoimmune polyendocrinopathy, cytopenias, enteropathy and lung disease, as well as recurrent infections and short stature (87). Related to altered *STAT3* signaling are also *IL10*, *IL10RA*, and *IL10RB* mutations, which impact production of, and response to, the immunosuppressive cytokine IL-10. IL-10 antagonizes IFN- γ and is also important for gut immune homeostasis and for the induction of Type 1 regulatory T cells (88). Loss of IL-10 or IL-10 responsiveness causes a disease that manifests primarily with very early onset inflammatory bowel disease (89, 90). Together, this third group of Tregopathies illustrates the many pathways regulating this cell subset that is important for maintaining immune homeostasis and preventing autoimmunity.

Autoinflammatory disorders: IL-1 and Type I Interferon-associated diseases

Autoinflammatory diseases are defined by fever, skin rashes or other manifestations of inflammation, in the absence of autoimmunity and infection, or disproportionate to a precipitating infection (reviewed in (91)). Two major groups of monogenic autoinflammatory disorders are the IL-1 inflammasomopathies and the type I interferonopathies. In inflammasomopathies, overactivation of IL-1 β and related cytokines like IL-18, results from dysregulated inflammasome activation. Normally, various stimuli which cells interpret as danger or damage, including microbial products or microcrystals, trigger assembly of inflammasomes in the cytosol. The inflammasome is a multimeric signaling complex that brings together through homotypic interactions NLRP1, NLRP3, or NLRC4 sensor proteins with pyrin and ASC. Entry of procaspase-1 into this complex

promotes self-cleavage for activation. The activated caspase-1 in turn cleaves to activate the proinflammatory cytokines IL-1 β and IL-18, which unleashes a cascade of diverse biological effects including leukocyte extravasation into tissues, modulation of immune cell functions, and induction of fever, acute phase reactants, and other metabolic changes. Additionally, activated caspase-1 cleaves and activates gasdermin D, which forms pores in the membrane to cause pyroptotic cell death.

Monogenic autoinflammatory disorders caused by dysregulated inflammasome activation and/or hyperactivation of the IL-1 pathway are exemplified by Familial Mediterranean Fever due to mutations in *MEFV* encoding pyrin. However, inflammasomopathies have since broadened to include those stemming from GOF mutations in other inflammasome components (*NLRP3*, *NLRC4*, and *NLRP1*), or in molecules upstream that regulate inflammasome activation (*LPIN2*, *PSTPIP1*, *MVK*, *WDR1*). Additionally, inflammasomopathies include LOF mutations that decrease IL-1 antagonism (*IL1RN*). In contrast, genetic loss of human IL-18 antagonism (mutations in *IL18BP*) does not underlie autoinflammation, but excessive inflammation and liver destruction in response to hepatitis virus A infection (92). As would be expected from their shared pathogenic mechanism, most inflammasomopathies are amenable to primary or adjunctive treatments targeting production of or responsiveness to IL-1 (91).

By contrast, interferonopathies, which constitute a second group of monogenic autoinflammatory disorders, are caused by overactivation of type I IFNs and IFN-stimulated genes (ISG) or IFN-regulated genes (IRG) (93). Normally, the accumulation of virus products – such as nucleic acid structures not normally found in uninfected cells or found in inappropriate cellular compartments – are detected by various intracellular sensors. These sensors encompass the RIG-I-like receptors (RLRs), certain TLRs, and cyclic GMP-AMP synthase (cGAS). Their binding to virus products triggers the assembly of signaling platforms that turn on transcription of antiviral type I IFNs and proinflammatory cytokines. Interferonopathies can result from GOF mutations in the virus sensors or associated adaptors (*IFIH1*, *DDX58*, *TMEM173*), or LOF mutations in nucleases or in RNA-editing enzymes (*TREX1*, *SAMHD1*, *ADAR1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*) that lead to abnormal accumulation of endogenous nucleic acids. Alternatively, LOF mutations that negatively regulate the IFN responsive pathway (*USP18*, *ISG15*), or GOF mutations in the same pathway (*STAT1*, *STAT2*, *JAK2*), can also result in type I interferonopathy (94). The latter type of condition was recently shown to be controlled by a JAK inhibitor (95). Finally, LOF mutations that impair proteasomal function (*PSMB8*, *PBSM4*, *PSMA3*) and lead to accumulation of ubiquitinated proteins also result in inappropriate IFN induction through an unclear mechanism.

Interferonopathies tend to show more central nervous system and skin involvement, often leading to a picture resembling congenital infection or a diagnosis of Aicardi-Goutière syndrome during infancy. However, when vasculitis and other manifestations of systemic inflammation are prominent, treatment with JAK inhibitors aimed at interrupting IFN receptor-mediated signaling has been shown to ameliorate disease (96).

Finally, recently it has been recognized that autoinflammatory disorders can result from dysregulation of pathways that impact protein ubiquitination, a post-translational modification process (97). Ubiquitin is a small protein that is attached to substrate proteins usually through a lysine linkage, sometimes by itself and sometimes in chains, through a series of enzymatic reactions involving activation, conjugation, and ligation; this process is countered by deubiquitinases that remove ubiquitin from proteins. Normally, the ubiquitin tags mark substrate proteins for degradation via proteasomes. However, ubiquitination is also important for non-degradative functions involved in cellular homeostasis including intracellular signaling.

Autoinflammatory disorders of the third group of dysregulated ubiquitination can result from LOF mutations in components of the linear ubiquitin assembly complex (LUBAC) that is required for ubiquitination (*RNF31* encoding the catalytic HOIP, and *RBCK1* encoding HOIL-1 accessory protein). Alternatively, disease can arise from LOF mutations in genes whose products function as deubiquitinases (*TNFAIP3*, *OTULIN*). Collectively, these mutations result in the abnormal accumulation of signaling intermediates downstream of IL-1 or TNF, which effectively prolong their functional activities. Through effects on ubiquitinated targets including IKK γ and RIPK1, these mutations can contribute to hyperactivation of NF- κ B, mitogen-activated protein kinases (MAPK), and other signaling pathways to reinforce autoinflammatory effects. Furthermore, mutations in the ubiquitinated target RIPK1 can also phenocopy disease through complex effects that cause increased programmed cell death to secondarily promote inflammation (98). Interestingly, in the case of LUBAC deficiencies, NF- κ B is hyperactivated in monocytes, but simultaneously impaired in fibroblasts and B cells; this divergence can help explain the mixed picture of immunodeficiency with autoinflammation in such patients. Overall, this new group of autoinflammatory disorders reveals new molecular targets in the ubiquitin-proteasome system for potential future interventional therapies.

Inborn errors of immunity underlying allergy: the hyper IgE syndrome

Severe allergy can also be a manifestation of inborn errors of immunity. While it is now well established that many IEI can manifest with elevated serum IgE as a sign of immune dysregulation, in this review we will focus primarily on “the” hyper IgE syndrome (HIES), whose clinical and immunological features were described between 1966 and 1999 (99, 100). These patients suffer from severe eczema and show elevated serum IgE levels, which can show reactivity toward a variety of allergens. The patients also suffer from severe infections, especially chronic mucocutaneous candidiasis (CMC) and staphylococcal diseases of the skin and lungs, often with pneumatoceles that are prone to superinfection. Another characteristic feature of HIES is the poor clinical and biological inflammation, with cold abscesses of the skin and lungs. A fourth defining phenotype includes a range of extra-hematopoietic manifestations, including skeletal disorders in particular, such as bone fragility, scoliosis, and deciduous teeth retention. Two of these four cardinal features can be seen in similar but unrelated disorders: eczema, infection susceptibility, and elevated IgE are seen for example in patients with DOCK8 deficiency, while poor inflammation in the course of skin or systemic, but rarely pulmonary, staphylococcal infection is seen in patients with MyD88 or IRAK-4 deficiency. It is the combination of these four phenotypes that makes the

HIES a distinctive clinical entity. This by no means implies that all patients are closely similar. There is actually great inter-individual variability among HIES patients, even within a given family.

The first step toward the molecular and cellular dissection of the HIES came in 2007 with the discovery of heterozygous HIES-causing mutations in *STAT3* (101). The mutations are loss-of-function and dominant-negative. Even low amounts of *STAT3* can exert negative dominance. An autosomal recessive (AR) form of HIES was found in 2018 with bi-allelic mutations in *ZNF341*, a transcription factor that governs the baseline and inducible transcription of *STAT3*, thereby also regulating its expression and activity (102, 103). Severely hypomorphic mutations of the *IL6ST* gene, were reported to underlie a severe AR form of HIES (104). The *IL6ST* gene encodes for the gp130 co-receptor of IL-6 family cytokines, including IL-6, IL-11, IL-27, OSM and LIF; all of these receptors signal via *STAT3*. A complete form of gp130 deficiency underlies an even more severe condition, evoking Stüve-Wiedemann syndrome (105). A second genetic etiology of autosomal dominant (AD) HIES is due to heterozygous, dominant-negative mutations in *IL6ST*, which impair cellular responses to IL-6 and IL-11 to a greater extent than other IL-6 family cytokines (106).

The immunological and clinical phenotypes of the patients with these three genetic etiologies of HIES largely but not completely overlap, possibly reflecting differences in the biochemical pathways affected. Cells from HIES patients mutated in *STAT3*, *ZNF341*, or *IL6ST* respond poorly to IL-6 family cytokines. Cells mutated in *STAT3* or *ZNF341* also respond poorly to IL-21 and IL-23. The discovery of other inborn errors of immunity has shed light onto the molecular and cellular basis of each of the cardinal HIES phenotypes. Their staphylococcal disease results mostly from impaired responses to IL-6, as inferred from the discovery of patients with AR IL-6R deficiency (107). Interestingly, their eczema and elevated IgE levels, as well as their poor inflammation, also seems to result mostly from insufficient responses to IL-6. In contrast, IL-6R-deficient patients do not display skeletal phenotypes. The skeletal manifestations seen in patients with HIES result at least in part from the poor cellular responses to IL-11, as inferred from the discovery of patients with IL-11R deficiency and Crouzon-like skeletal anomalies (108). Some other shared features of HIES remain unexplained in molecular terms, e.g. vascular anomalies, lymphomas.

Although the four genetic etiologies of HIES seem to be broadly responsible for phenocopies, a detailed and systematic clinical survey would be useful. Anecdotally, it seems that *ZNF341*-deficient patients have a better inflammatory response and fewer somatic manifestations than *STAT3*-mutated patients, but the underlying mechanisms for this remain unknown. Moreover, *STAT3*- and *ZNF341*-mutated patients frequently have chronic mucocutaneous candidiasis (CMC), unlike *IL6R*- and *IL6ST*-mutated patients. The former patients display CMC because of impaired development of Th17 and perhaps other IL-17-producing lymphocytes, as inferred from inborn errors of IL-17. While isolated defects of IL-6R, IL21R, and IL-23R do not or rarely underlie CMC (109, 110), their combined deficiency via mutations in *STAT3* or *ZNF341*, but not *IL6ST*, commonly underlies CMC. Overall, core molecular deficiencies of these three groups of HIES patients involve an impaired *ZNF341*- and *STAT3*-dependent IL-6ST-mediated response to IL-6

(allergy and staphylococcal disease) and IL-11 (skeletal anomalies), while at least some specific features, such as CMC, are caused by ZNF341- and STAT3-dependent impairment of IL-17.

Inborn errors of immunity with increased susceptibility to Epstein-Barr virus (EBV) infection and malignancies

Some IEs result from genomic instability, apoptosis defects, and other abnormalities that predispose to cancer, without necessarily interfering with immune responses (111). However, other PIDs have an increased risk of cancers due to inadequate control by the immune system of oncogenic viruses such as human papillomaviruses, human herpes virus 8, and Epstein-Barr virus (EBV). Of these, EBV is illustrative because it infects nearly all adults (reviewed in (112)). PID patients can develop EBV-associated cancers such as Hodgkin's disease, non-Hodgkin lymphomas, and rare smooth muscle cancers, which reflect chronically increased virus loads due to impaired immune surveillance. EBV can be also associated in the general population with other cancers such as Burkitt's lymphoma, nasopharyngeal carcinomas, and gastric cancers.

Primary infection with EBV is usually asymptomatic during childhood but can sometimes cause an acute mononucleosis-like illness in adolescents and adults. Subsequently, EBV establishes a lifelong infection where the virus persists in latent form within B cells. It is periodically reactivated to be shed as infectious virus, and its increased replication can also drive lymphoproliferation. Control of both the primary infection and subsequent EBV reactivation requires robust T and NK cells immunity. This requirement has been demonstrated in conditions characterized by severe immunosuppression such as following HSCT, or in CID that have defective lymphocyte functions and broad susceptibility to different viruses and other microbes. Illustrative PIDs in this category include deficiencies in RAS guanyl releasing protein 1 (RASGRP1), CTP synthase 1 (CTPS1), WASP actin nucleation promoting factor (WAS), serine/threonine kinase 4 (STK4), dedicator of cytokinesis 8 (DOCK8), coronin 1A (CORO1A), IL-21R, GATA2, as well as activating mutations in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta (*PIK3CD*) or phosphoinositide-3-kinase-regulatory subunit 1 (*PIK3RI*) (113).

By contrast, several other PIDs display a narrower defect with a heightened susceptibility to EBV relative to other viruses. Studies into these latter disorders have revealed mechanisms that are particularly important for immunity against EBV (reviewed in (113)). In this category of PIDs are the X-linked lymphoproliferative diseases, caused by hemizygous loss-of-function mutations in *SH2D1A* encoding the signaling adaptor SLAM-associated protein (SAP), or in *XIAP* encoding the X-linked inhibitor of apoptosis protein. These, or several other mutations that impair cytotoxic function due to deficiency in perforin or molecules involved in lytic granule exocytosis, result in prolonged immune activation that however is ineffective in suppressing EBV replication, and/or can impair cell-cell interaction between EBV-infected B cells and cognate cytotoxic T lymphocytes. When initially infected with EBV, such patients typically present with hemophagocytic lymphohistiocytosis, characterized by life-threatening fulminant lymphoproliferation, macrophage activation and end-organ damage.

Finally, among PIDs that display a relatively selective susceptibility to EBV are those that impair proximal signaling molecules for T cell activation. Such PIDs include deficiencies in IL2 inducible T cell kinase (ITK), magnesium transporter 1 (MAGT1), CD70, CD27, and CD137 (4-1BB) (113). MAGT1 promotes T cell activation through magnesium second messenger signaling for calcium-dependent responses through its effects on ITK, and ITK activity is directly regulated by Mg^{2+} (114). Additionally, MAGT1 promotes NK cell cytotoxicity against EBV-infected cells through its ability to upregulate NKG2D on NK cells and CD8 T cells. Recent studies have identified that MAGT1 participates in an N-glycosylation complex, which is necessary for maturation of fully functional glycosylated NKG2D and CD70 (115, 116). CD70 is normally highly expressed on EBV-infected B cells, and this ligand engages the CD27 costimulatory molecule on T cells. Deficiency in either CD70 or CD27 impairs priming and expansion of EBV-specific CD8 T cells, as well as expression of NKG2D and other molecules important for such cells to interact with and respond to EBV-infected cells. The recent discovery of CD137-deficient patients with poor EBV control indicates that other costimulatory pathways can also contribute to anti-EBV immunity (117). Thus, the EBV susceptibility in this category of PIDs may reflect defects in multiple overlapping pathways.

Phenotypic and genetic heterogeneity of inborn errors of immunity: Converging pathways and allelic heterogeneity

Inborn errors of innate-adaptive immunity: MSMD and CMC

Inborn errors that selectively prevent the development of neutrophils are probably the only pure disorders of innate immunity, echoing the selective disorders of development of T and/or B cells that are pure disorders of adaptive immunity. Only a few inborn errors (such as reticular dysgenesis and telomeropathies) disrupt the development of both innate and adaptive cell types. Most other IEI affect leukocyte function, and typically impact both innate and adaptive leukocytes. Two good examples are the inborn errors of IFN- γ and IL-17A/F immunity (118). These are the prototypic type 1 and type 17 signature cytokines, and can be secreted by both innate and adaptive leukocytes. In particular, IFN- γ can be secreted by $\alpha\beta^+$ and $\gamma\delta^+$ T cells, and among $\alpha\beta^+$ T cells by NKT, mucosa-associated invariant T (MAIT) cells, and conventional CD4 $^+$ and CD8 $^+$ T cells. It is produced by memory CD4 $^+$ T cells in particular by the Th1 and Th1* subsets. However, IFN- γ is also produced by B cells, NK cells and some innate lymphoid cells (ILCs) (119). It serves as the macrophage-activating factor, more so than an anti-viral interferon. Indeed, patients with any of the 31 known inborn errors of IFN- γ affecting 16 distinct genes, are prone to mycobacterial disease and more rarely to related infections by intra-macrophagic microbes (120).

These inborn errors were discovered by forward genetics from the study of Mendelian susceptibility to mycobacterial disease (MSMD), a “Mendelian infection” characterized by severe disease caused by poorly virulent mycobacteria, e.g., BCG vaccines and environmental mycobacteria, in otherwise healthy individuals (118). There is genetic heterogeneity but physiological homogeneity, as all gene products are involved in IFN- γ immunity (Fig. 3). Interestingly, three IFN- γ -inducing monokines are each essential for

optimal production of IFN- γ , as AR IL-12R, IL-23R, and ISG15 deficiencies are all genetic etiologies of MSMD, albeit with incomplete penetrance, which is higher in patients unresponsive to both IL-12 and IL-23 (110, 118, 121). It is interesting that etiologies with low penetrance for MSMD led to the discovery of genetic etiologies of bona fide tuberculosis (122, 123). While the defects that impair responses to IFN- γ are most likely disorders of mononuclear phagocytes, in which mycobacteria reside, the cellular basis of inborn errors of IFN- γ production has proven much more difficult to decipher. A lack of NK, NKT, or B cells alone is not sufficient to be prone to mycobacterial disease, unlike a lack of all T cells. Patients with RORC deficiency have absent (NKT, MAIT) or defective ($\gamma\delta^+$ and Th1*) IFN- γ -producing cells (124). The discovery of additional genetic etiologies of MSMD is required to better delineate the cellular basis of anti-mycobacterial IFN- γ immunity in humans.

While IFN- γ is the classic Th1 signature cytokine, IL-17A/F is the prototypic Th17 signature cytokine. The role of human IL-17 cytokines in host defense was first suspected when it was shown that patients with autoimmune polyendocrinopathy type 1 (APS-1), whose only infectious disease is chronic mucocutaneous candidiasis (CMC), have neutralizing autoantibodies against IL-17A and IL-17F (53, 54). Patients with inborn errors of IL-17 immunity were discovered from the forward genetic study of isolated and familial forms of CMC (125). The study of patients harboring mutations in *IL17RA* and *IL17A/F* genes showed that IL-17 is required for mucocutaneous immunity to *Candida albicans*, while being redundant for host defense against other microbes, with the exception of *Staphylococcus aureus*, which can also cause peripheral lesions in the patients. Interestingly, gain of function (GOF) mutations in *STAT1* underlie CMC by impairing the production of IL-17A/F- by CD4⁺ cells, and perhaps by other lymphocytes, probably because of enhanced responses to interferons (IFNs)-producing T cells (126).

IL-17A and IL-17F multimerize to signal via IL-17RA and IL-17RC. Interestingly, patients with IL-17RC deficiency are prone to CMC but not staphylococcal disease, perhaps because responses to IL-25 (IL-17E) are maintained (127). Mutations downstream of the IL-17RA/RC receptor include ACT1 deficiency and JNK1 haploinsufficiency (128). The latter defect also impairs the homeostasis of connective tissues, probably in part by disrupting cellular responses to TGF- β . The nature of the cells that are responsible for the CMC phenotype in patients with inborn errors of the IL-17-responsive pathway remains unclear, as IL-17A/F can activate a variety of conjunctive and epithelial cells in the skin and mucosae, promoting their secretion of chemo-attractants for leukocytes and also inducing the production of effector genes against fungi. As a matter of fact, the nature of the IL-17-producing lymphocytes that are required for mucocutaneous immunity to *Candida* is also elusive, as IL-17A/F can be secreted by $\alpha\beta^+$ and $\gamma\delta^+$ T cells, including at least the Th17 and Th1* subsets, as well as innate lymphocytes. The discovery of additional genetic etiologies of isolated or syndromic CMC will shed light onto the cellular basis of human CMC, including the roles of IL-17-producing leukocyte subsets and that of IL-17-responding cells other than leukocytes.

Inborn errors of non-hematopoietic cell-intrinsic immunity: from EV to HSE

The study of inborn errors of immunity has also revealed the importance of non-hematopoietic cell-intrinsic immunity for host defense (12). The importance of cells other than leukocytes was already established from the study of thymic disorders, which were shown from DiGeorge onward to be stromal phenocopies of T cell-intrinsic severe combined immunodeficiency (129). The discovery of the importance of non-hematopoietic cell-intrinsic immunity to viruses came from the study of patients with monogenic infections, whether Mendelian or not. Epidermodysplasia verruciformis (EV) was with hindsight the first described inborn error of immunity, in 1946 (130). It is precisely the lack of leukocytic phenotype that prevented its inclusion in the international list of inborn errors of immunity until 2004. These patients are prone to flat warts and pityriasis-like skin lesions that evolve into non-melanoma skin cancer. The lesions are caused by defective beta-human papillomaviruses (HPV), which lack the E5 and E8 virulence genes present in other, more pathogenic HPVs. HPVs have an exclusive tropism for keratinocytes. Infection by beta-HPV is common and asymptomatic, except in patients with EV.

Typical or isolated EV is defined by a lack of other infections (which are seen in patients with T cell deficits underlying atypical or syndromic EV) (131). The first two genetic etiologies were discovered in 2002, with mutations in *TMC6* and *TMC8*, encoding for EVER1 and EVER2, respectively (132). A third genetic etiology was discovered more recently, with mutations in *CIB1* (133). The three proteins form a complex; in the absence of EVER1 or EVER2, the expression of CIB1 is dramatically reduced in keratinocytes. Moreover, this complex interacts with E5 and E8, suggesting that it behaves like a human restriction factor for HPVs. A plausible model is therefore that keratinocytes lacking EVER1, EVER2, or CIB1, become permissive to β -HPVs that lack the corresponding virulence factor E5 and E8, and cannot cause lesions in humans with a functional EVER-CIB1 complex. It has proven challenging to test this model experimentally, as it has not been yet possible to establish an *in vitro* model of the full HPV cycle across all layers of skin keratinocytes.

Another condition that also revealed the importance of cell-intrinsic immunity to viruses by resident, non-hematopoietic cells in specific tissues or organs is herpes simplex virus 1 (HSV-1) encephalitis (HSE) (134). In the course of primary infection by HSV-1, children rarely cannot prevent the virus from reaching the forebrain via the olfactory bulb or the brainstem via the trigeminal nerves. Until the advent of acyclovir, HSE was almost invariably lethal, and survivors continue to suffer from severe neurological sequelae. Despite its severity, HSE is restricted to the central nervous system: there are no lesions elsewhere and the virus cannot even be found in the bloodstream. A forward genetic approach of forebrain HSE found germline mutations in various components of the TLR3 signaling pathway (135). More recently, mutations were found also in *SNORA31* gene, encoding a small nucleolar RNA, that do not affect the TLR3-responsive pathway (136). Finally, mutations in the only known RNA debranching enzyme DBR1 were found in patients with brainstem infection caused by HSV-1, influenza virus, or norovirus (137). Different anatomical territories of the central nervous system (CNS) therefore seem to rely on different mechanisms of host defense against viruses.

Leukocytes from patients with inborn errors of the TLR3 pathway do not display any detectable phenotype. In contrast, their fibroblasts and induced pluripotent stem cell (iPSC)-derived cortical neurons and oligodendrocytes show impaired immunity to HSV-1, which can be rescued by exogenous type I IFN (138). Consistent with this, the occurrence of HSE has been reported also in a patient with AR STAT1 deficiency, a condition that impairs cellular response to type I IFN. iPSC-derived trigeminal neurons lacking TLR3 are not more vulnerable than control cells, further suggesting that the cellular basis of disease involves an impairment of CNS-resident cortical neurons (139). The mechanisms by which SNORA31 haploinsufficiency impairs cortical neuron immunity remain to be deciphered. Likewise, neither brainstem neurons (nor any other CNS resident cell) from DBR1-deficient patients have been tested. Yet, their dermal fibroblasts showed enhanced RNA lariat accumulation and impaired cell-intrinsic immunity to the viruses tested, including HSV-1. The patients' fibroblasts have only 1–3% residual activity, accounting for the massive accumulation of RNA lariats. The mechanism by which these lariats disrupt cell-intrinsic immunity is a topic of intensive study. Overall, the study of HSE and other types of viral encephalitis has revealed the essential role of human CNS-resident, non-hematopoietic cell-intrinsic immunity to viruses.

Advances in treatment (from supportive care to precision medicine)

The study of the cellular and molecular IEI has led to major contributions in the treatment of human diseases (Fig. 4). Upon characterization of the cellular phenotype of SCID, and shortly after the initial description of HLA in 1967 (140), allogeneic HSCT was successfully used for the first time in a baby with XR-SCID in 1968 (14). Initially, results were only successful when there was an HLA-identical sibling, as otherwise fatal graft-versus-host disease would develop. Development of methods that allow T-cell depletion from the bone marrow enabled the first successful application of an HLA-mismatched HSCT in a patient with SCID in 1983 (141), paving the way for the application of HSCT to a large number of severe hematological and metabolic disorders. Use of chemotherapy or irradiation is typically used to deplete the recipient's hematopoietic stem and progenitor cells, but carries significant risks of toxicity. As an alternative approach to conditioning, injection of anti-CD117 mAb targeting hematopoietic stem cells (142) has recently been started ([NCT02963064](#)). Finally, some forms of severe T-cell lymphopenia are of extra-hematopoietic origin. Identification of the thymic nature of the immune deficiency has permitted development of thymic transplantation for complete DiGeorge syndrome and other congenital thymic defects (143).

Moreover, identification of the molecular bases of IEI has allowed development of targeted therapeutic approaches, based on replacement of the missing product, targeted pharmacological manipulation of the signaling pathway involved or correction of the gene defect. In 1987, Hershfield reported that enzyme replacement treatment (ERT) with polyethylene glycol-conjugated bovine ADA led to metabolic and immunological improvement in patients with ADA-SCID (144). In 1990, ADA-SCID became the first genetically-determined metabolic condition for which ERT was approved by the Food and Drug Administration.

Inborn errors of immune regulation have emerged as an important group of disorders in which newer therapeutic agents are being tested, often with promising initial results (see also Table 1). One example is the use of jakinibs to treat disease due to heterozygous gain-of-function (GOF) mutations in *STAT1* or *STAT3*. These diseases cause combinations of infection susceptibility, autoimmunity, inappropriate inflammatory responses, and lymphoproliferation, which have been historically difficult to treat. *STAT1* and *STAT3* are transcription factors that normally become activated upon stimulation of various cytokine receptors, with IFN receptors activating *STAT1*, and IL-6, γ c, IL-10, or IL-23 receptors activating *STAT3*. Since GOF mutations confer augmented activity upon cytokine receptor stimulation, which can exert complex downstream effects on immunity, disease should be amenable to inhibition of JAK adaptors that couple cytokine receptor activation to *STAT* activation. Indeed, efficacy of JAK inhibition in treating both *STAT1* and *STAT3* GOF patients has been recently demonstrated (145).

A second example where knowledge of the molecular etiology of PIDs has led to targeted therapies in immunodysregulatory disorders is *CTLA-4*-haploinsufficiency. While treatment with mTOR inhibitors in these patients can inhibit the increased costimulatory signals, *CTLA-4*-Fc fusion proteins such as abatacept can alternatively replace the missing *CTLA-4* function (146). This new modality seems to be helpful in cases of refractory disease, and a clinical trial is planned for formal testing (NCT03733067). Additionally, *CTLA-4*-Fc fusion proteins may be useful in *LRBA* and *DEF6* deficiencies which phenocopy *CTLA4*-haploinsufficiency by increasing *CTLA-4* degradation within lysosomes (84).

A third example is the use of small molecule inhibitors of PI3K in activated phosphoinositide 3-kinase δ syndrome (APDS), a condition characterized by lymphoproliferation and immunodeficiency, with hypogammaglobulinemia with elevated serum IgM, accumulation of senescent T cells and increased proportion of transitional B cells. In this disease, treatment with leniolisib, a selective PI3K δ inhibitor, was recently shown in a 12-week open-label dose-escalation safety/efficacy trial to suppress the hyperactive PI3K δ pathway in patients, normalize abnormal immune biomarkers, and improve lymphoproliferation and autoimmune cytopenias (147). A randomized placebo-controlled study is currently in progress to validate these exciting findings (NCT02435173).

A final example of a disease where extrinsic targeted therapy is being tested is *CD55* deficiency with early-onset protein-losing enteropathy and thrombosis. Loss of *CD55* results in complement overactivation that is critical for disease pathogenesis, which is supported by anecdotal observations of improved disease upon treatment with the terminal complement inhibitor eculizumab (148). A randomized double-blind, placebo-controlled study is currently in progress to test the efficacy of a pozelimab, a fully human inhibitor of C5 (NCT04209634).

Ultimately, correction of the gene defect could provide definitive cure to patients with IEI (15). A first indication in this sense was provided by the observation of somatic mutations (reversions) that restore expression and function of the mutant protein in a clonal lineage, as first demonstrated in 1996 by Rochelle Hirschhorn for *ADA* deficiency (149). When the reversion event occurs in an early lymphoid progenitor, it confers a strong selective

advantage to T-cell progenitors, and may even lead to apparent normalization of the immunological phenotype and clinical improvement, as observed in XR-SCID (150).

In the early 1990s gene therapy was attempted for ADA-SCID patients, initially using gene modified autologous T cells (151). In 1992, two ADA-SCID patients were treated with combined autologous T cells and hematopoietic stem cell precursors (HSPCs) carrying two distinct gamma-retroviral vectors expressing the wild-type *ADA* gene. This pioneering trial provided seminal demonstration of the selective advantage of cells with restored function, and also showed that while gene-modified T cells can be beneficial in the short term, long-term reconstitution is derived from gene-modified hematopoietic stem and progenitor cells (HSPCs) (152). Gamma-retroviral-mediated transfer of wild-type *ADA* cDNA under a constitutive promoter (to ensure persistent transgene expression) led to random but stable integration into the genome. The clinical success and safety of this approach, combined with ERT discontinuation and nonmyeloablative conditioning, was further confirmed in 10 patients (153). In 2016, this ex-vivo HSPC gene therapy designed to cure ADA-SCID (Strimvelis, Orchard Therapeutics), was approved by the European Medicines Agency, becoming the first gene therapy product approved for commercialization (154).

A similar therapeutic strategy, based on first-generation γ -retroviral vectors, led to successful and rapid reconstitution of T-cell immunity in infants with XR-SCID (155). However, six patients developed T cell acute lymphoblastic anemia due to insertion of the transgene into an oncogene (*LMO2* in most cases), resulting in transactivation of the oncogene (156). Similar serious adverse events (SAEs) were reported also after initial attempts to treat Wiskott-Aldrich syndrome (WAS) by gene therapy (157). This prompted investigators to develop safer vector delivery systems. First, second-generation γ -retroviral vectors were generated, that were devoid of the potent transactivating long-term repeats of the viral vector and used a cellular promoter to drive expression of the transgene. Use of such self-inactivating (SIN) γ -retroviral vectors led to robust T-cell reconstitution, without occurrence of leukemic events, in patients with XR-SCID (158). Then, SIN-lentiviruses (SIN-LV) emerged as the most efficient and safest gene delivery vectors for both T cells and HSPCs. Gene therapy with SIN-LV vectors has now been used for numerous monogenic IEIs, including ADA-SCID, XR-SCID, WAS, CGD and LAD (reviewed in (15)). Furthermore, addition of reduced-toxicity conditioning regimens has allowed more robust engraftment of gene-corrected HSCs and multilineage immune reconstitution, overcoming the lack of B-cell and NK-cell reconstitution that has been observed after gene therapy for XR-SCID, when no chemotherapy had been used (159, 160).

However, addition of wild-type copies of the relevant cDNAs would not cure disorders due to GOF and possibly dominant-negative mutations. Furthermore, use of constitutive cellular promoters driving expression of the transgene could be deleterious in the treatment of disease due to mutations of genes whose expression is tightly regulated, such as *CD40LG* and *FOXP3*. In this regard, a recent major advancement in the curative potential of gene therapy has been the development of “gene editing”. Here, a single nucleotide variant is replaced, or the entire gene coding sequence is inserted precisely at the endogenous locus, using a nuclease-mediated DNA break and subsequent repair by homologous recombination (161). Gene correction by editing preserves spatiotemporal regulated gene expression, which

is important for genes that are differentially expressed during development and lineage differentiation, or that are only expressed upon cell activation. In addition, gene editing is particularly attractive for the correction of dominant-negative mutations. The use of different nucleases has been explored, with the CRISPR/Cas9 nuclease system combined with AAV-mediated delivery of the donor template, demonstrating the clearest translational efficacy. Although already in the clinic for the treatment of genetic blood disorders, CRISPR/Cas9 gene editing is still in pre-clinical phase for correction of IEI. However, feasibility and efficacy have been demonstrated both *in vitro* and *in vivo* in mice and in humanized mice models for XR-SCID (162), X-linked hyper-IgM (163), and IPEX (164). Collectively this work confirms that IEI offer an ideal model system for the exploration and advancement of innovative curative approaches, and supports the view that development of gene editing may lead to dramatic improvement in the life of affected patients. Yet, affordability of gene therapy remains a major financial and ethical challenge (165).

Conclusions

The last ten years have witnessed a gigantic progress in the field of IEI. The number of disorders being discovered is literally growing exponentially, including not only rare but also common genetic defects. The range of clinical phenotypes attributed to IEI is also diversifying at full speed, with an unsuspected diversity of infectious, malignant, autoimmune, autoinflammatory, and allergic phenotypes being caused by monogenic lesions. There is every reason to believe that we have only seen the tip of the iceberg, and that countless more IEI will be discovered. Vast areas of medicine, refractory to large population-based association studies, are being slowly but surely transformed by the family- and patient-based search for new types of IEI. The next ten years may very well see conditions as diverse as life-threatening COVID-19 and systemic lupus erythematosus each deciphered into a myriad of IEI. Noteworthy, an emerging feature of IEI is that their high level of genetic heterogeneity is typically associated with a high level of physiological homogeneity. Patients and their families have benefited the most from this avalanche of genetic and immunological studies. Indeed, these patient-based, basic studies ushered other types of studies, aimed at better diagnosing patients and better describing their clinical features, thereby improving genetic counseling. Progress in the molecular genetics and cellular immunology of IEI has also resulted in the development of innovative preventive and therapeutic approaches, in line with a long tradition. Indeed, enzyme replacement, hematopoietic transplantation, and gene therapy were also pioneered for IEI. Last, but not least, the field of IEI is also of great benefit to the scientific community for the basic knowledge it reveals. With the recent advent of many path-breaking genetic and immunological technologies, the extraordinary genetic and phenotypic diversity of the 7 billion living humans, which was previously seen as an insurmountable obstacle to scientific research, now provides a unique opportunity to delineate, for the first time, the essential and redundant functions of genes involved in one or another aspect of immunity.

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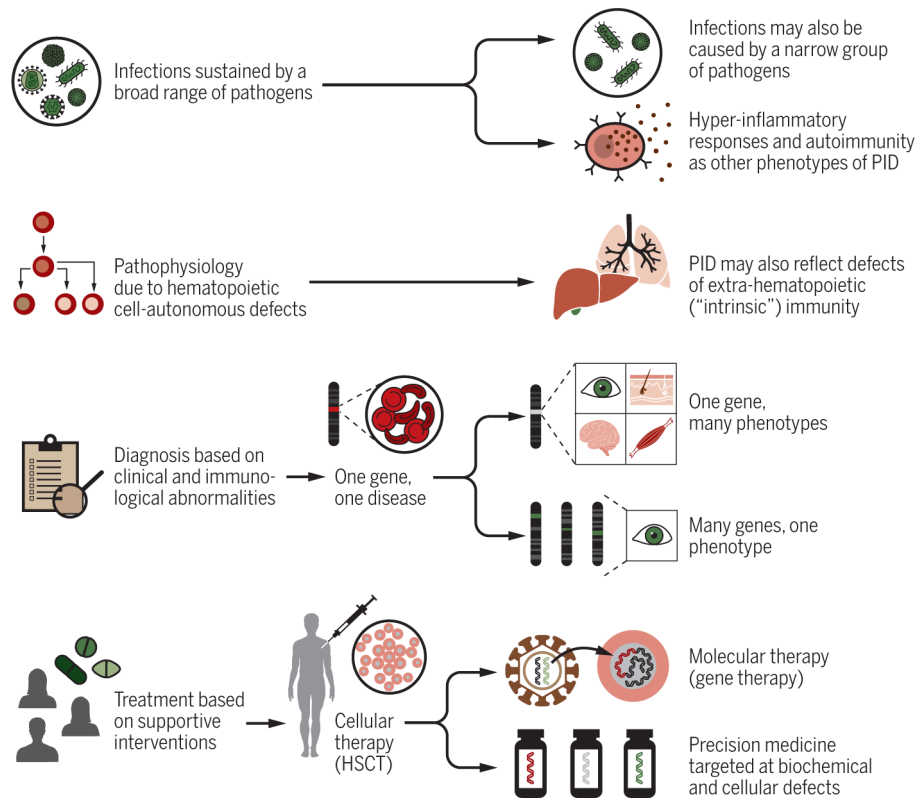


Figure 1. Evolution of clinical, pathophysiological diagnostic and therapeutic approach to inborn errors of immunity.

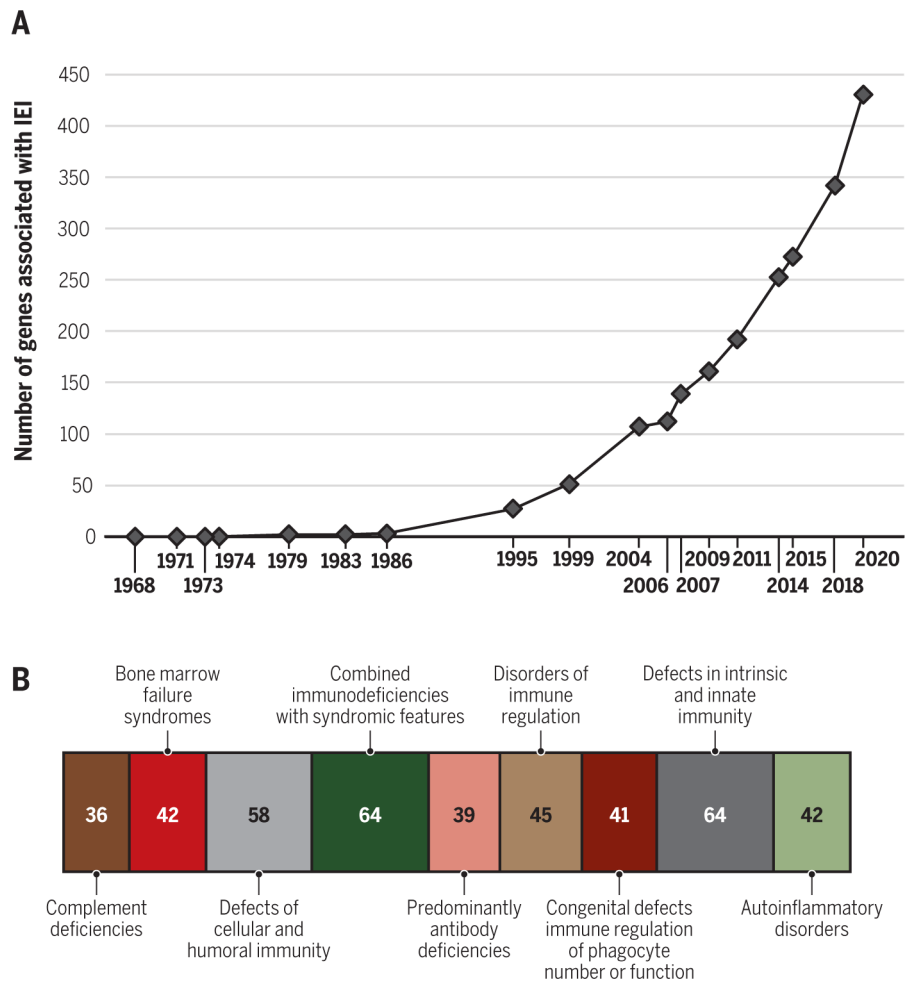


Figure 2. History and current classification of monogenic inborn errors of immunity. (A) Number of genes associated with inborn errors of immunity known at the time of various editions of the classification of these disorders; (B) Number of genes responsible for each category of inborn errors of immunity, as reported in the 2020 classification (10).

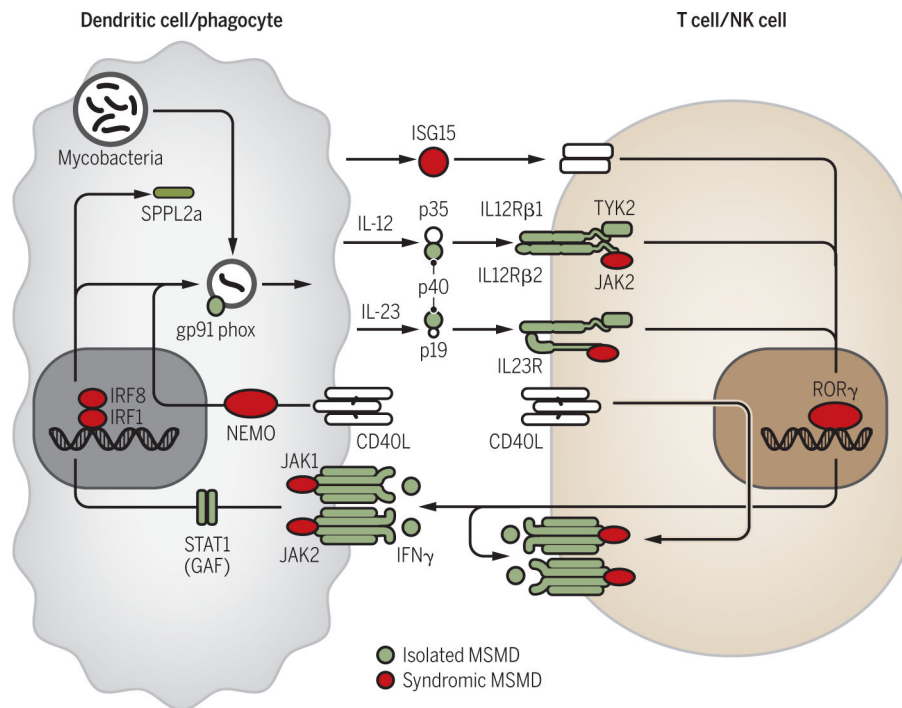


Figure 3. Genetic etiologies of Mendelian susceptibility to mycobacterial disease (MSMD). Interactions between cells involved in the production of (T cells/NK cells) and in the response to IFN- γ (dendritic cells, phagocytes). Proteins whose mutations in the corresponding gene cause isolated MSMD are depicted in green, while those responsible for syndromic MSMD are depicted in red.

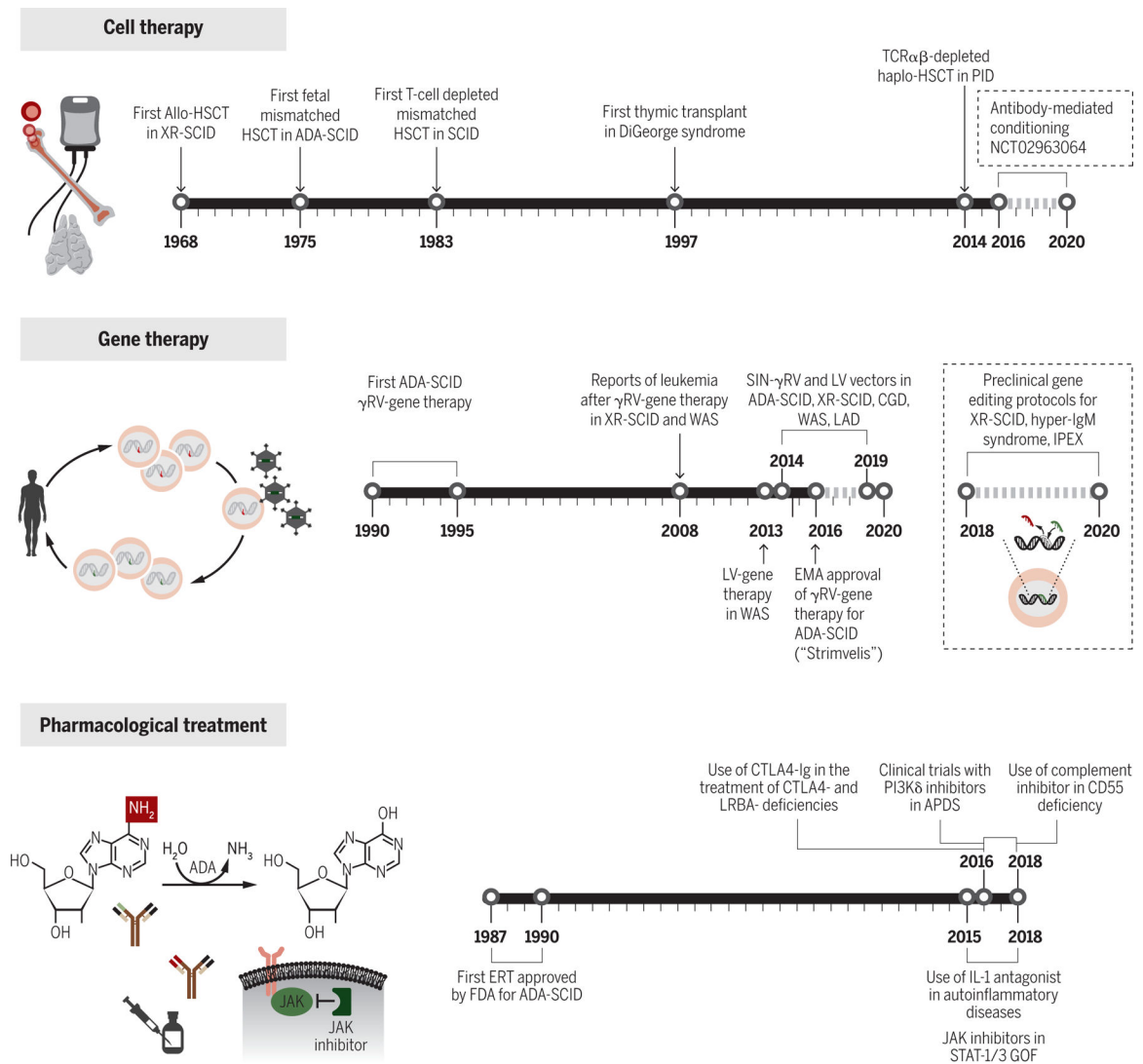


Figure 4. Progress in the treatment of inborn errors of immunity. Three separate timelines display milestone events in the evolution of cell therapy, gene therapy and pharmacological treatment to address inborn errors of immunity.

Table 1.

Targeted therapies for treatment of selected monogenic immune dysregulatory conditions.

Immune dysregulatory condition	Molecular pathogenic pathway targeted	Treatment	References
<i>STAT1</i> GOF	STAT1 hyperactivation	JAK inhibition (ruxolitinib)	(145)
<i>STAT3</i> GOF	STAT3 hyperactivation	JAK inhibition (ruxolitinib, tofacitinib)	(145)
CANDLE syndrome (proteasome complex component LOF)	Type I IFN hyperactivation	JAK inhibition (baricitinib)	(93)
SAVI (<i>STING</i> GOF)	Type I IFN hyperactivation	JAK inhibition (baricitinib)	(93)
CTLA-4 haploinsufficiency	T cell costimulatory pathway hyperactivation	CTLA-4-Fc fusion protein (abatacept, belatacept)	(146)
LRBA deficiency	Increased CTLA-4 degradation leading to T cell costimulatory pathway hyperactivation	CTLA-4-Fc fusion protein (abatacept)	(84)
APDS (PASLI) (<i>PIK3CD</i> or <i>PIK3R1</i> GOF)	PI3K pathway hyperactivation	PI3K inhibition (leniolisib)	(147)
CHAPLE (CD55 deficiency)	Complement hyperactivation	Eculizumab, pozelimab (in testing)	(148)
Inflammasomopathies (<i>NLRP1</i> , <i>NLRP3</i> , <i>PSTPIP1</i> GOF; LPIN2, MEVK, WDR1, DIRA or IL1RN deficiencies, etc.)	IL-1 hyperactivation	IL-1 antagonists (anakinra, canakinumab, rilonacept)	(91)