

Novel primary immunodeficiencies revealed by the investigation of paediatric infectious diseases

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Human primary immunodeficiencies impairing myeloid and/or lymphoid cellular responses to activating receptors other than antigen receptors have recently been described in children with various infectious diseases. Germline mutations in *NEMO* and *IKBA* impair NF- κ B-mediated signalling, at least in response to the stimulation of TLRs, IL-1Rs and TNFRs, and confer a broad predisposition to infections. Mutations in *IRAK4* selectively impair TLRs other than TLR3 and most IL-1R responses, and confer a predisposition to pyogenic bacterial diseases, including invasive pneumococcal disease in particular. Mutations in *TLR3* and *UNC93B1* impair TLR3 responses and confer a predisposition to herpes simplex encephalitis. Mutations in *STAT1* impair IFN- γ and/or IFN- α/β responses and predispose subjects to mycobacterial and viral diseases, respectively. Mutations in *IFNGR1* and *IFNGR2* impair IFN- γ responses and confer a predisposition to mycobacterial diseases. Mutations in *IL12B* and *IL12RB1* impair IL-12 and IL-23 responses and predispose subjects to infections caused by mycobacteria and *Salmonella*. Finally, mutations in *TYK2* and *STAT3* mostly impair IL-6R responses, conferring a predisposition to staphylococcal disease in particular. The infectious phenotypes associated with these novel leukocyte activation deficiencies are therefore collectively diverse, tightly dependent on the morbid gene and affected pathway, and individually narrow, often restricted to one or a few infectious diseases.

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Introduction

Primary immunodeficiencies (PIDs) cannot easily be divided into 'innate' and 'adaptive' conditions. Mutations in only a few genes would be predicted to have a direct and exclusive effect on T-cell or B-cell adaptive immunity, or both. These genes would include those specifically controlling the production or function of antigen receptors. Similarly, only a few known conditions are caused by genes expressed exclusively in innate cells. Indeed, most PID-causing mutations directly affect both innate and adaptive immunity. Moreover, the impairment of one type of immunity indirectly affects the other type of immunity. There is currently no ideal classification of PIDs, which may be classified on the basis of clinical phenotype, cellular phenotype or PID-causing genotype [1,2–5]. We review here a small but expanding group of PIDs with the following features in common: (i) seemingly normal development of the principal myeloid and lymphoid leukocyte subsets (CD4 and CD8 T cells, B cells, granulocytes, monocytes, NK cells, and NK-T cells, the status of blood DCs and T regs being undefined in most patients), (ii) apparently normal T-cell and B-cell responses to antigens, at least *in vitro*, (iii) impaired myeloid and/or lymphoid leukocyte activation by receptors other than antigen receptors, whether because of a lack of ligand, a lack of receptor, or a lack of signalling component, and (iv) predisposition to infectious disease, with few, if any, other clinical phenotypes. The infections occurred either in the context of a well-defined complex primary immunodeficiency – occasionally associated with developmental features – or as unexplained, 'idiopathic' infectious disease. The various infectious phenotypes observed led to the description of PIDs affecting various leukocyte-signalling pathways (Figure 1).

Inborn errors of NF- κ B-mediated immunity (*NEMO* and *IKBA*)

X-linked recessive anhidrotic ectodermal dysplasia with immunodeficiency (XR-EDA-ID) was found in 2001 to result from hypomorphic mutations in *IKBKG/NEMO*, encoding the regulatory subunit of the IKK complex [6–8]. In 2003, an autosomal dominant form of EDA-ID (AD-EDA-ID) was identified, caused by a hypermorphic heterozygous mutation of *IKBA*, impairing the phosphorylation and degradation of NF- κ B inhibitor α (I κ B α) [9] (Figures 1 and 2). This disease does not strictly belong to the group of diseases dealt with here, as it also involves severe impairment of TCR signalling. In both

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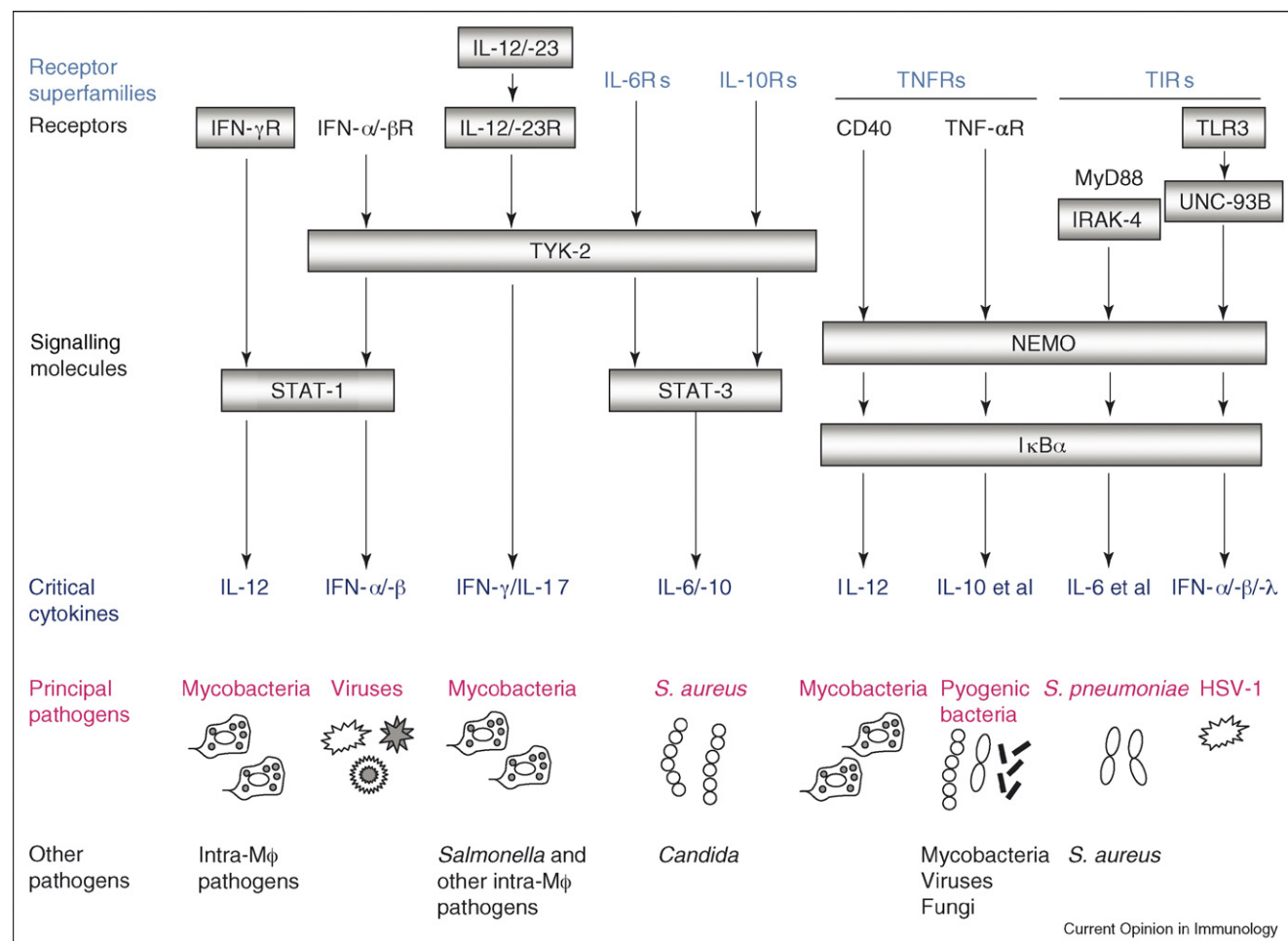
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Figure 1

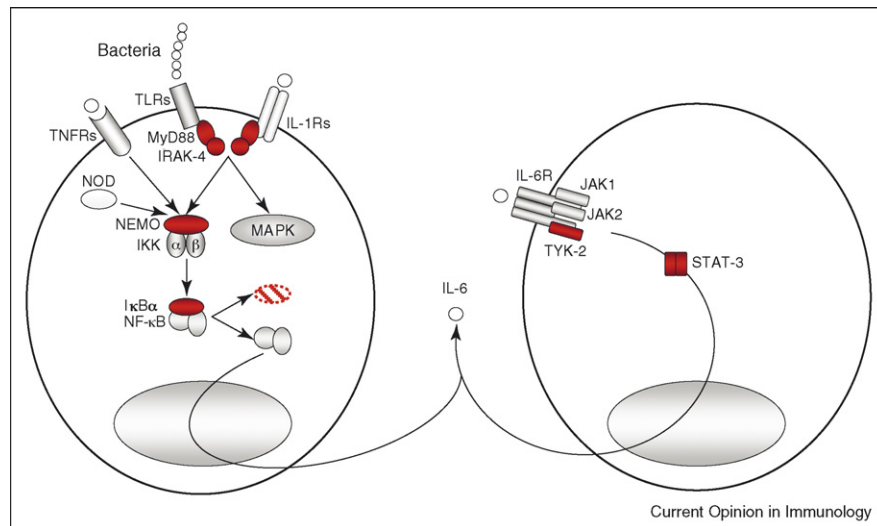


Summary of the various impaired signalling pathways associated with a specific increase in susceptibility to pathogens. The main actors of the relevant signalling pathways are presented, including receptors (IFN- γ R, IFN- α/β R, IL-12/-23R, CD40, TNF- α R, TLR3) or superfamily receptors (IL-6Rs, IL-10Rs, TNFRs, TIRs: TLRs/IL-1Rs), adaptors (MyD88, UNC-93B), kinases (IRAK-4, TYK-2), signal transducers and activators of transcription (STAT-1, STAT-3), regulatory subunits (NEMO) or inhibitors (I κ B α). The main cytokines secreted upon activation of these various pathways playing a critical role in the resistance to the pathogens are shown. The proteins for which mutations in the corresponding genes have been identified and responsible for various infectious phenotypes are indicated in shaded boxes. Finally, the most frequent and the secondary pathogens found associated with the various deficiencies are presented.

XR-EDA-ID and AD-EDA-ID, the mutations lead to impaired NF- κ B activation, and up to 57 patients have since been reported [6–28,29]. The developmental features range from EDA with osteopetrosis and lymphoedema [6,18,28] to a complete absence of phenotype [17,19,23,25]. Similarly, the spectrum of infectious diseases observed varies from case to case [6,22]. The most frequent pathogens observed include Gram-positive and Gram-negative pyogenic bacteria, *Streptococcus pneumoniae* and *Staphylococcus aureus* in particular. Some patients also presented mycobacterial diseases. Rare patients suffered from fungal and viral diseases, including herpes simplex virus encephalitis (HSE) [19,25]. Most patients presented multiple infections, but a few presented an apparently specific predisposition to pneumococcal disease [10] or

mycobacterial disease [29]. NF- κ B dimers are involved in several pathways, including those triggered by the many members of the TNFR, IL-1R, and TLR families. The success of haematopoietic stem cell transplantation in patients with EDA-ID suggests that impaired NF- κ B activation in haematopoietic cells plays a crucial role in the pathogenesis of infection [30,31]. The molecular pathogenesis of infections can be studied by searching for correlations between EDA-ID cellular phenotypes and infectious phenotypes. Studies of subtle mutations in NEMO showed that mycobacterial disease resulted at least partly from impaired CD40-dependent induction of IL-12 [29] (see below). A complementary approach would be to search for other patients with mutations in genes encoding products acting upstream or downstream from

Figure 2



Cells producing and responding to IL-6. Schematic representation of cytokine production and cooperation between phagocytes (polymorphonuclear neutrophils, monocytes and dendritic cells) and lymphocytes (T, B and NK): bacteria are recognised by TLRs at the surface of phagocytes. This recognition induces activation of the NF- κ B and MAPK pathways via MyD88 and IRAK-4. These activation pathways induce the production of several pro-inflammatory cytokines (IL-6, IL-1 β , TNF- α , etc.). IRAK-4 deficiency is associated with impaired induction of inflammation by TLR ligands, and impaired propagation of inflammation by IL-1 and IL-18. NEMO and I κ B α deficiencies are associated with impaired induction of inflammation by TLR ligands and TNFR ligands. IRAK-4, NEMO and I κ B α deficiencies are associated with impaired IL-6 production. The binding of IL-6 to IL-6R induces the phosphorylation of TYK-2, JAK1 and JAK2, thereby activating the signal-transducing protein STAT-3. STAT-3 homodimers translocate to the nucleus inducing the transcription of the target genes. TYK-2 and STAT-3 deficiencies are associated with impaired IL-6 responses, in particular. Proteins for which mutations in the corresponding genes have been identified and shown to be associated with greater susceptibility to staphylococcal diseases are shown in red.

NEMO and I κ B α . In this regard, studies of inherited IRAK-4 deficiency indicated that pneumococcal disease could be accounted for at least partly by impaired TLR and IL-1R responses [32] (see below).

Inborn errors of the TLR and IL-1R pathways (IRAK4, MYD88)

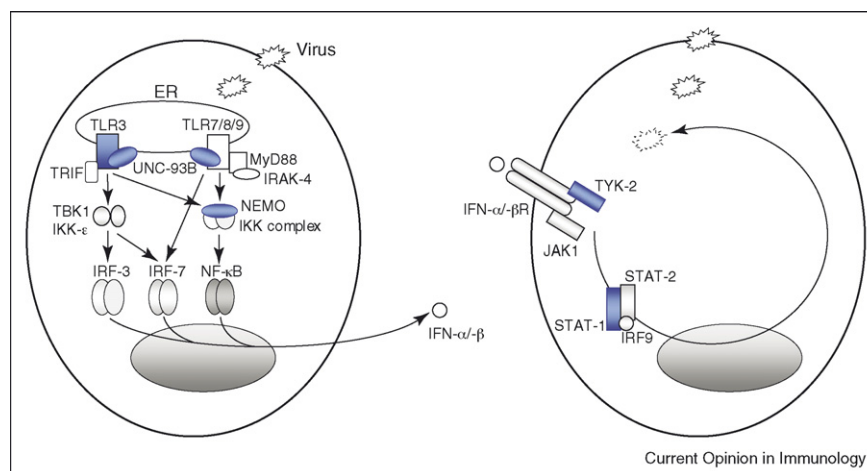
IRAK-4 is a serine-threonine kinase acting downstream from TLRs and IL-1Rs. Autosomal recessive IRAK-4 deficiency was first discovered in 2003 [32]. Up to 28 patients [10,32–45] have since been identified [46[•]]. Patients with autosomal recessive MyD88 deficiency have also recently been identified (von Bernuth H. *et al.*, in preparation). MyD88 is a key adaptor molecule in the TLR and IL-1R (TIR) pathway, connecting surface TLRs and IL-1Rs with IRAK-4 (Figures 1 and 2). Most patients with IRAK-4 deficiency present invasive bacterial diseases and/or peripheral infections, mostly caused by *S. pneumoniae* and, to a lesser extent, *S. aureus* in early childhood [46[•]]. Only a few IRAK-4-deficient patients have presented severe Gram-negative bacterial infections. None has presented unusually severe parasitic, fungal or viral disease. IRAK-4 deficiency is life-threatening in childhood, with about 40% mortality in the first eight years of life, but seems to become less severe with age; no death or invasive infection has been observed in patients over the ages of 8 and 14 years, respectively

[46[•]]. IRAK-4-deficient cells display strong impairment of NF- κ B- and MAPK-mediated induction of inflammatory cytokines in response to TIR agonists, but no effect on the TLR3 and TLR4 induction of IFN- α , IFN- β and IFN- λ [41]. Moreover, blood TLR responses in terms of the induction of multiple cytokines and TLR responses in purified individual leukocyte subsets have been shown to be impaired in patients with these deficiencies [46[•]]. The IRAK-4-dependent TIR pathway is therefore vital for protective immunity to selected pyogenic bacteria in early childhood. However, the narrow and transient infectious phenotype of the patients suggests that TLRs are largely redundant for host defence to most other microbes. It remains unclear whether the infections in these patients, including pneumococcal infections in particular, result from impaired responses to one or more TLRs or IL-1Rs [11]. The mechanisms ensuring immunity to other microbes, notably those threatening EDA-ID but not IRAK-4 patients, can also be dissected by forward genetics.

Inborn errors of the TLR3-IFN- α -IFN- β and IFN- λ pathway (TLR3, UNC93B1)

The role in host defences of the TLRs dependent on MyD88 and IRAK-4 remains to be clarified, but that of TLR3, which is independent of MyD88 and IRAK-4, has recently been defined. HSE is the most common cause of

Figure 3



Cells producing and responding to IFN- α - β . Schematic representation of type I IFN production by dendritic cells and type I IFN response in infected cells. Viruses enter the cells via specific receptors and viral nucleic acids are detected by the various TLRs expressed on the endoplasmic reticulum (ER). This recognition induces activation of the IRF-3, IRF-7 and NF- κ B pathways via UNC-93B, TRIF and MyD88, leading to type I IFN production. TLR3, UNC-93B and NEMO deficiencies are associated with impaired IFN production, particularly during herpes virus infection. The binding of type I IFN to its receptor induces the phosphorylation of JAK1 and TYK-2, activating the signal transduction proteins STAT-1, STAT-2 and IRF9. This complex translocates as a heterotrimer to the nucleus, where it acts as a transcriptional activator, binding to specific DNA response elements in the promoter region of IFN-inducible genes. TYK-2 and STAT-1 deficiencies are associated with impaired IFN responses. Proteins for which genetic mutations have been identified and associated with greater susceptibility to viral diseases are shown in blue.

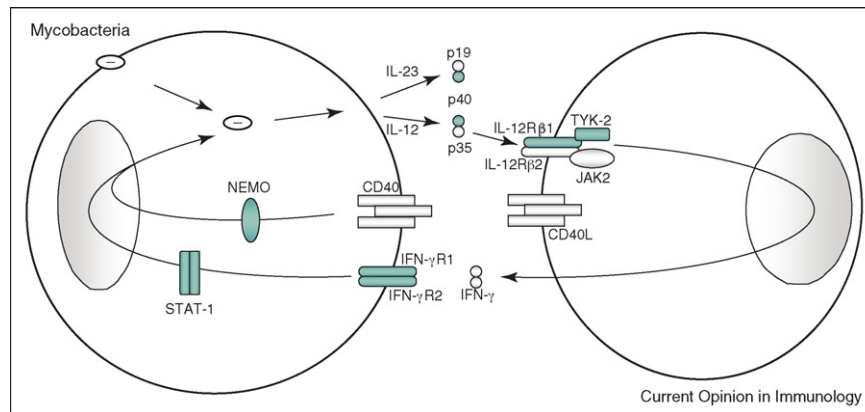
acute, sporadic viral encephalitis in the Western world [47]. In 2006, autosomal recessive UNC-93B deficiency was identified as the first genetic aetiology of HSE [48^{*}] (Figures 1 and 3). UNC-93B is a 12-transmembrane domain protein present in the endoplasmic reticulum. Physical interaction between mouse UNC-93B and TLR3, TLR7 and TLR9 has been documented [49]. The cells of patients with UNC-93B deficiency do not respond to TLR3, TLR7, TLR8 or TLR9, in terms of IFN- α , IFN- β and IFN- λ production in particular. Impaired TLR7, TLR8, and TLR9 responses probably play only a moderate role in the pathogenesis of HSE, as patients with IRAK-4 deficiencies do not respond to TLR7, TLR8 or TLR9 either, but do not suffer from HSE [41,46^{*}]. The importance of the TLR3 pathway in host defences against HSV-1 in the central nervous system (CNS) was established by the report of a second genetic aetiology of HSE: autosomal dominant TLR3 deficiency [50^{**}]. This observation provided further support for the hypothesis that the TLR7, TLR8, and TLR9 responses are largely redundant in host defence [51]. It also defined the first human TLR immunodeficiency, thereby providing the first validation that TLRs are not entirely redundant in host defence in the setting of a natural ecosystem [1,52,53^{*}]. A plausible mechanism of HSE pathogenesis, on the basis of *in vitro* data for fibroblasts, involves low levels of production of the anti-viral molecules IFN- α , IFN- β and IFN- λ by CNS resident cells in response to HSV-1 primary infection, leading to higher levels of viral replication and cell death

[48^{*},50^{**},54]. This observation suggests that HSE in a patient with EDA-ID may have resulted from the impaired production of IFN- α , IFN- β , or IFN- λ in response to TLR3 [19,25^{*},55]. Moreover, the involvement of IFN- α , IFN- β , and/or IFN- λ *in vivo* is suggested by the occurrence of HSE in a patient with STAT-1 deficiency and an impaired cellular response to these IFNs [55,56].

Inborn errors of the STAT-1-dependent, IFN- α , IFN- β , IFN- γ and IFN- λ pathways (STAT1)

The first disorder of human IFN- α / β -mediated immunity was described in 2003, with the discovery of two children with complete STAT-1 deficiency [56]. A few other patients have since been identified [57]. All these patients had homozygous *STAT1* mutations, leading to a complete absence of the protein. The patients' cells do not respond to type I IFNs (IFN- α and IFN- β) and to type II IFN (IFN- γ) in terms of ISGF-3 (STAT-1, STAT-2 and p48 complexes activated by IFN- α and IFN- β) and GAF (STAT-1 dimers) activation, respectively (Figures 1, 3 and 4). Impaired responses to type III IFNs (IFN- λ) were recently documented in cells from STAT-1-deficient children [58]. The children died from severe viral infection, including HSE in one patient, and the patients' cells were unable to control viral infections *in vitro*. The pathogenesis of viral illnesses, including HSE in particular, involves impaired IFN- α , IFN- β and/or IFN- λ responses. In contrast to what has been observed with

Figure 4



Cells producing and responding to IFN- γ . Schematic representation of cells producing and responding to IFN- γ during mycobacterial infection. The phagocytosis of mycobacteria by monocytes/macrophages or dendritic cells leads to the production of IL-23 and IL-12. The recognition of CD40L by CD40 via NEMO also induces IL-12 production. The binding of IL-12 to its specific receptor (composed of two subunits: IL-12R β 1 and IL-12R β 2), expressed only on T and NK cells, activates a transduction pathway (via TYK-2) culminating in the production of IFN- γ by these cells. NEMO, IL-12p40, IL-12R β 1 and TYK-2 deficiencies are associated with impaired IFN- γ production (primary or secondary). IFN- γ , via its ubiquitously expressed receptor (IFN- γ R1 and IFN- γ R2) and the transcription factor STAT-1, activates the antimycobacterial programme and increases IL-12 production, creating an amplification loop. IFN- γ R1, IFN- γ R2 and STAT-1 deficiencies are associated with an impaired response to IFN- γ . Proteins for which mutations in the corresponding genes have been identified and associated with greater susceptibility to mycobacterial diseases are shown in green.

UNC-93B- and TLR3-deficient fibroblasts, enhanced viral growth in STAT-1-deficient cells and cell death were not complemented by exogenous IFNs *in vitro* [48*,50**,55]. The contribution of individual types and species of IFN to HSE and other viral diseases remains to be determined. One approach to this question is to search for mutations in the genes encoding individual IFNs or their receptors in patients with viral diseases. The diagnosis of more STAT-1-deficient patients may also help us to delineate the spectrum of viral susceptibility in these patients, thereby defining the role of STAT-1 in anti-viral immunity [57]. Finally, the STAT-1-dependent genes triggered by IFN- α , IFN- β and IFN- λ that control viruses, including herpes virus in particular, may be revealed by the investigation of other patients. Patients with STAT-1 deficiency are not only vulnerable to viruses, they also suffer from severe mycobacterial diseases. Mycobacterial diseases result largely from the abolition of IFN- γ responses, as suggested by the occurrence of severe mycobacterial diseases in patients with mutations in the IFN- γ receptor [59].

Inborn errors of the IFN- γ pathway (*IFNGR1*, *IFNGR2*, *STAT1*)

Mendelian susceptibility to mycobacterial disease (MSMD) is characterised by a selective predisposition to infection by weakly virulent mycobacteria, such as BCG vaccines and environmental mycobacteria, in otherwise healthy patients (Figures 1 and 4). Since the discovery of the first genetic aetiology of this syndrome in 1996 – with mutations in *IFNGR1*, encoding the ligand-

binding chain of the IFN- γ receptor [60,61] – two related MSMD-causing genes have been identified: *IFNGR2*, encoding the accessory chain of the IFN- γ receptor [62] and *STAT1* [63]. Allelic heterogeneity at these loci defines nine genetic disorders, depending on the mode of transmission (recessive or dominant), the impact on function (complete or partial), the expression of the molecule (production of a non-functional molecule or no molecule produced), and the specific function affected (phosphorylation or DNA-binding, in the case of STAT-1) [59]. Recently described forms include complete IFN- γ R2 deficiency, with expression of the receptor at the surface [64]. Interestingly, the mutation creates a new glycosylation site, and the novel glycan is necessary and sufficient to abolish receptor function [64,65]. An *IFNGR2* mutation has also been reported to be dominant *in vitro* in a healthy heterozygous relative of an IFN- γ R2-deficient patient [66]. It remains unclear whether *IFNGR2* mutations can be dominant at the clinical level. Another recently described genetic form results from *STAT1* mutations impairing the DNA-binding domain [67*]. The previously described MSMD-causing *STAT1* mutation impaired phosphorylation [63]. Patients with either type of *STAT1* mutation present mycobacterial disease as the sole infectious phenotype, owing to the selective impairment of GAF activation. IFN- α responses are entirely normal, unlike in patients with complete STAT-1 deficiency. Finally, the level of IFN- γ responsiveness among patients with *IFNGR1*, *IFNGR2*, and *STAT1* mutations is correlated with clinical phenotype, patients with partial IFN- γ responses having milder dis-

ease [68,69]. Improvements in phenotypic definition are now required for patients with these disorders, as an ascertainment bias probably accounts at least partly for the narrow predisposition to mycobacterial diseases documented to date. For example, single patients with histoplasmosis [70] and listeriosis [71] have been reported. The STAT-1-dependent IFN- γ responsive genes controlling immunity to mycobacteria remain unknown. By contrast, the key IFN- γ -inducing genes were rapidly identified.

Inborn errors of the IL-12 and IL-23 pathways (*IL12B*, *IL12RB1*)

It was shown in 1998 that patients with MSMD might harbour mutations of the IL-12 and IL-23 pathways [72–74], indicating that these cytokines play a key role in controlling anti-mycobacterial IFN- γ levels. Mutations were found in *IL12B*, which encodes IL-12p40, common to both IL-12 and IL-23 [73], and in *IL12RB1*, which encodes the first chain of IL-12 receptor (IL-12R β 1), common to the IL-12 and IL-23 receptors [72,74]. IL-12R β 1 deficiency is the most common genetic aetiology of MSMD [59], and IL-12p40 and IL-12R β 1 deficiencies appear to be clinical phenocopies. Interestingly, about half of all IL-12R β 1-deficient patients have developed invasive salmonellosis [75]. There are actually ten times more cases of salmonellosis among patients with impaired IL-12/23 immunity than among patients with impaired IFN- γ immunity [76]. This suggests that the impairment of IFN- γ -independent pathways, such as IL-23-dependent IL-17 induction, may be involved in the pathogenesis of salmonellosis. Several patients presented with *bona fide* tuberculosis as their sole infectious phenotype, providing the first examples of Mendelian predisposition to tuberculosis [77–80]. Moreover, other infectious diseases, such as paracoccidioidomycosis [81] and leishmaniasis [82], were each reported in one patient, leading us to search for patients in regions of the world where these genetic conditions are currently underdiagnosed. Progress has also recently been made towards identifying the genes controlling IL-12 production, which is known to be positively regulated by two major pathways: a microbe-dependent, T cell-independent pathway, and a microbe-independent, T cell-dependent pathway. Specific mutations affecting the NEMO leucine zipper domain have been shown to be associated with X-linked recessive MSMD in three unrelated kindreds [29^{*}]. These hypomorphic recessive mutations in *NEMO* selectively impair the T cell-dependent, CD40-dependent, c-Rel-mediated NF- κ B pathway of IL-12 activation in myeloid cells. No MSMD-causing lesions affecting the microbe-dependent production of IL-12 have yet been reported. By contrast, a child with TYK-2 deficiency and impaired responses to IL-12 and IL-23 was found to be susceptible to mycobacteria and *Salmonella*, like IL-12p40- and IL-12R β 1-deficient patients. However, this child also suffered from hyper-IgE syndrome (HIES) and staphylococcal disease [83^{*}].

Inborn errors of the IL-6 pathway (*STAT3*, *TYK2*)

Insight into the pathogenesis of staphylococcal infections was recently provided by investigations of patients with HIES [84,85]. Autosomal dominant (AD) HIES is a distinct entity – a complex primary immunodeficiency associated with developmental traits and a poor inflammatory response [84] (Figures 1 and 2). By contrast, autosomal recessive (AR) HIES groups together patients with little in common, other than high serum IgE concentrations, and whose immunological phenotypes may range from profound T-cell immunodeficiency [86] to TYK-2 deficiency [83^{*}] – the first genetic aetiology of ‘HIES’ to be discovered. TYK-2 is a kinase involved in multiple receptor signalling. The patient with TYK-2 deficiency presented relatively mild BCG disease (regional BCG-itis) but invasive non-typhoidal salmonellosis, probably because of impaired IL-12 and IL-23 responses. Cutaneous viral diseases caused by the molluscum contagiosum virus and herpes simplex virus probably resulted from impaired IFN- α/β responses. However, the patient did not present HSE, whether because of TYK-2-independent IFN responses, incomplete clinical penetrance, or both. Salmonellosis and mycobacteriosis are exceedingly rare infections in patients with HIES [87–89], which principally confers predisposition to staphylococcal diseases and, to a lesser extent, candidiasis [84,86]. Consistent with this, the TYK-2-deficient patient also suffered from staphylococcal infections [83^{*}]. In an elegant investigation, dominant-negative mutations in the STAT-3 DNA-binding domain were recently reported in patients with AD-HIES [90^{**}]. These data were rapidly confirmed by another survey [91^{*}]. STAT-3 can be phosphorylated by TYK-2 and is involved in responses to several cytokines, including IL-6 and IL-10. Most pathways involving members of the IL-6 and IL-10 receptor superfamilies remain to be tested in TYK-2- and STAT-3-deficient patients. Nonetheless, studies of patients with TYK-2 and STAT-3 deficiencies strongly suggest that the signalling pathways downstream from IL-6Rs and/or IL-10Rs are essential for immunity to staphylococci. Suggestive evidence for the specific role of IL-6 in the pathogenesis of staphylococcal disease was recently provided by the description of neutralising, circulating anti-IL-6 autoantibodies in a child with staphylococcal disease [92]. These data also provide a plausible explanation for the occurrence of staphylococcal disease in NEMO-, IRAK-4- and MyD88-deficient patients, who display profound impairment of the induction of IL-6 by TLR and IL-1R agonists [6,46^{*}].

Concluding remarks

The past ten years have witnessed the emergence of a novel group of primary immunodeficiencies in patients with various infectious diseases, associated in some instances with a complex immunological and developmental syndrome involving predisposition to multiple

infections, such as EDA-ID or HIES, but in most cases isolated and 'idiopathic', such as MSMD and HSE in otherwise healthy children. In patients with such primary immunodeficiencies, myeloid and/or lymphoid cells fail to activate one or several receptors, because of a lack of ligand (e.g. IL-12), a lack of receptor (e.g. IL-12R), or a lack of a key signalling molecule (e.g. TYK-2 in the IL-12 pathway). These disorders were not discovered by the directed efforts of investigators specifically investigating the biology of any of these signalling pathways. Instead, they were discovered serendipitously, by the forward genetic dissection of various paediatric infectious diseases. These experiments of nature indicate that the TIR-IRAK-4-NEMO pathway is crucial for immunity to some pyogenic bacteria, including pneumococcus in particular, the TLR3-UNC-93B-NEMO-IFN- α / β -STAT-1 pathway is crucial for immunity to herpes simplex virus in the CNS, the NEMO-IL-12-TYK-2-IFN- γ -STAT-1 circuit is crucial for immunity to mycobacteria and the TYK-2-STAT-3 pathway is crucial for immunity to staphylococcus, possibly via IL-6 production (Figure 1). Surprisingly, with the possible exception of the IL-6 pathway, for which mutations in the genes encoding this cytokine and its receptor have not yet been reported, mutations often seem to result in a pathogen-specific disease predisposition, the molecules they encode appearing to be otherwise redundant in host defence. Of course, specificity is not absolute, and there is significant redundancy and promiscuity [1,53*]. For example, IRAK-4-deficient patients are susceptible to invasive pneumococcal disease, but about a third of these patients also suffer from staphylococcal disease, possibly because of impaired IL-6 production. Similarly, about half the known IL-12p40- and IL-12R β 1-deficient patients are vulnerable to *Salmonella*, perhaps because of impaired IL-23-mediated immunity. The genetic puzzle of immunity to infection *in natura* is only beginning to be assembled, and more primary immunodeficiencies affecting leukocyte activation are likely to be discovered in children with infectious diseases [1,53*].

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