

From Infectious Diseases to Primary Immunodeficiencies

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The field of primary immunodeficiencies (PIDs) is expanding in many directions, including the genetic dissection of infectious diseases [1,2]. PIDs typically confer predisposition to multiple infections, but an increasing number of PIDs have been found to confer a more specific predisposition to one or several infections [3]. Examples include susceptibility to viruses, such as predisposition to Epstein-Barr virus in patients who have X-linked lymphoproliferative syndrome [3–5], predisposition to oncogenic papillomaviruses in patients who have epidermodysplasia verruciformis [6,7], and susceptibility to bacteria, such as predisposition to *Neisseria* in patients who have mutations in the properdin gene or in the genes encoding the terminal components of complement [8]. The authors review here how the exploration of patients who have a selective predisposition to weakly virulent mycobacteria led to the discovery of a new group of PIDs involving impairment of the

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interleukin (IL)-12-interferon (IFN)- γ circuit, how the exploration of children with a predisposition to invasive pneumococcal disease (IPD), either isolated or associated with a predisposition to other infections, led to the discovery of disorders of nuclear factor kappa B (NF- κ B), and how the investigation of children with herpes simplex virus (HSV) encephalitis led to the description of disorders of the Toll-like receptor (TLR) 3 pathway.

Mendelian susceptibility to mycobacterial diseases

Mendelian susceptibility to mycobacterial diseases (MSMD) (MIM 209,950) [9] is a rare syndrome characterized by the occurrence of clinical disease caused by weakly pathogenic mycobacteria, such as bacillus Calmette-Guérin (BCG) vaccines and nontuberculous environmental mycobacteria (EM), in otherwise healthy individuals [10]. Patients are also vulnerable to the more virulent species, *Mycobacterium tuberculosis* [11]. They are resistant to most other infections, with the notable exception of systemic nontyphoidal salmonellosis, which is commonly observed [12]. Other infectious diseases have been reported only rarely, mostly in single patients. This syndrome is clinically heterogeneous; the clinical features cover a spectrum ranging from local recurrent to disseminated mycobacterial diseases. In most familial cases, inheritance is autosomal and recessive, but in some kindreds, the syndrome segregates into an autosomal dominant or X-linked recessive (XR) inheritance [13,14]. In recent years, five autosomal genes have been found to be mutated in children with this mendelian genetic disorder: *IFNGR1* [15–19], *IFNGR2* [20,21], *STAT1* [22,23], *IL12B* [24], and *IL12RB1* (Fig. 1) [25,26]. All are involved in interleukin (IL)-12/23–dependent, IFN- γ mediated immunity. Mutations in *IFNGR1*, *IFNGR2*, and *STAT1* impair the cellular responses to IFN- γ , whereas mutations in *IL12B* and *IL12RB1* impair the IL-12/23–dependent production of IFN- γ . Mutations in *NEMO* have also been identified as responsible for XR form of MSMD (see Fig. 1) [27]. The high level of allelic heterogeneity at these seven loci accounted for the existence of 13 different inheritance disorders, according to the mode of transmission (recessive or dominant), the impact on function (complete or partial), association with a lack of protein expression or the expression of an abnormal protein, and the specific function affected (phosphorylation or DNA binding in the case of STAT-1). However, no genetic cause has yet been identified for about half the patients who have MSMD [28].

Recessive complete IFN-gamma receptor (IFNGR) 1 deficiency was first identified in 1996, in a patient who had a lack of receptor expression [15,19]. Mutations conferring autosomal recessive complete IFNGR1 deficiency with [16] or without cell surface receptor expression have since been reported [15]. A lack of cellular responses to IFN- γ stimulation in vitro has been reported in these patients, who also have high plasma IFN- γ

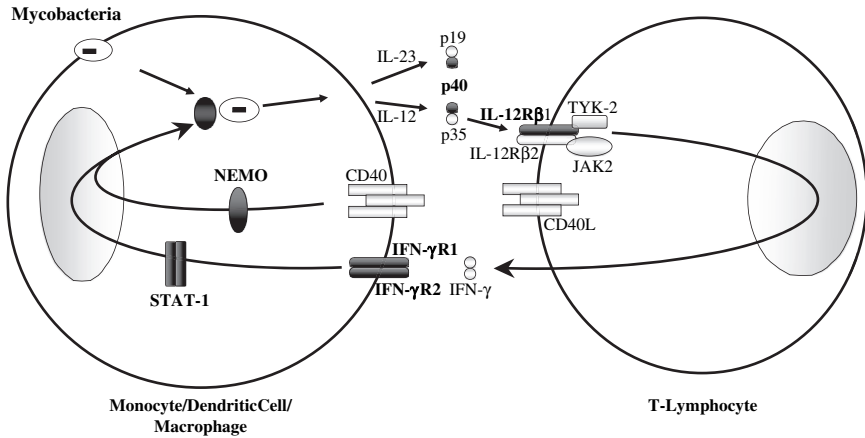


Fig. 1. MSMD-causing gene products in the IL-12/23–IFN- γ pathway. Cytokine production and cooperation between monocytes/macrophages/dendritic cells and natural killer or T cells. Proteins for which mutations in the corresponding genes have been identified and associated with particular susceptibility to mycobacterial diseases are shown in gray. Allelic heterogeneity of the seven genes results in the definition of 13 genetic disorders. The IL-12/23–IFN- γ loop and the CD40L-activated CD40 pathway, mediating cooperation between T cells and monocytes, are crucial for protective immunity to mycobacterial infection in humans. The *NEMO* mutations in the leucine zipper (LZ) domain mostly impair CD40–NEMO-dependent pathways.

concentrations [29]. Mycobacterial infections in patients who have complete IFNGR1 deficiency are associated with an early onset of severe and fatal infectious diseases, lepromatous-like and multibacillary granulomas [30], and a poor prognosis. No asymptomatic patients over the age of 3 years have been reported. *Mycobacterium bovis*–BCG and other EM (eg, *Mycobacterium fortuitum* [16,31], *Mycobacterium chelonae* [18], *Mycobacterium smegmatis* [32,33], *Mycobacterium peregrinum* [34], *Mycobacterium scrofulaceum* [13,35]) frequently cause disease in these patients. All patients vaccinated with BCG developed disseminated BCG infection. Salmonellosis was reported only rarely [15,19,31]. Viral infections caused by human herpes virus 8 [36], cytomegalovirus [37], and other bacterial infections, caused by *Listeria monocytogenes* [38], were documented in single patients. A diagnosis of complete IFNGR1 deficiency should be considered for children with several episodes of mycobacterial disease (BCG, EM) occurring before the age of 3 to 5 years. The outcome is spontaneously fatal and the only potential cure is offered by hematopoietic stem cell transplantation, which is, however, associated with a high rate of graft rejection [39,40], because of the high plasma IFN- γ concentrations in these patients [41]. The oldest surviving patient is now 19 years old and has experienced at least five episodes of mycobacterial disease, caused by five microbial species [35].

Partial IFNGR1 deficiency may be caused by recessive or dominant *IFNGR1* alleles. The recessive form of partial IFNGR1 deficiency results

from a specific mutation, I87T [17,42]. Cells from the patients who have partial deficiency respond to high (but not low) concentrations of IFN- γ in vitro. Clinically, this defect is associated with BCG [17] or EM disease [42]. Affected children had well-delimited granulomas and a favorable outcome. One patient, not vaccinated with BCG, had clinical tuberculosis [11,17]. Dominant partial deficiency in *IFNGR1* is typically associated with the 818del4 mutation, associated with a hotspot for microdeletions, leading to the insertion of a premature stop codon in the proximal intracellular domain [18]. The cellular response to IFN- γ stimulation in vitro is intermediate between that of cells from patients who have complete IFNGR1 deficiency and healthy controls. The severity of the clinical features of patients who have dominant partial IFNGR1 deficiency appears to be intermediate between those of patients who have recessive complete and partial IFNGR1 deficiencies. Patients are susceptible to infections with BCG vaccines and EM (*M peregrinum*, *M kansasii*, *M chelonae*, *M fortuitum*, and *M asiaticum*), although the mycobacterial pathogen most frequently isolated from these patients is *M avium* complex [31,43]. Unifocal or multifocal mycobacterial osteomyelitis is common, and the overall prognosis is good. Some patients were initially diagnosed incorrectly as having Langerhans' cell histiocytosis [44]. In rare cases, these patients present other infections, such as salmonellosis [31]. Viral infection with varicella zoster virus [37] and fungal infection with *Histoplasma capsulatum* have each been observed in one patient [45]. Treatment is based principally on antibiotics and the use of recombinant IFN- γ .

A few patients who have MSMD with autosomal recessive, complete IFNGR2 deficiency have been reported. Two forms of complete IFNGR2 deficiency with [21] and without [20] receptor expression at the cell surface have been documented. The T168N missense mutation in *IFNGR2* creates a new N-glycosylation site caused by the addition of a new glycan branch on the IFNGR2 chain. An *IFNGR2* mutation has also been reported to be dominant in vitro in a healthy heterozygous relative of a patient who had IFNGR2 deficiency [46]. It remains unclear as to whether some *IFNGR2* mutations are clinically dominant in vivo. The criteria for suspicion of complete IFNGR2 deficiency are similar to those for complete IFNGR1 deficiency. Patients who have complete IFNGR2 deficiency display early-onset mycobacterial diseases and have a poor prognosis. No mature granulomas have been observed in these patients. The pathogens causing the infectious diseases included *M bovis* BCG [21], *M avium* [20,21], and *M fortuitum* [20]. The only curative treatment is hematopoietic stem cell transplantation. Partial recessive IFNGR2 deficiency has been reported in only one patient who had infections caused by BCG and *M abscessus* and a relatively mild clinical presentation, similar to that of children with partial recessive IFNGR1 deficiency [47]. Treatment is based on antibiotics and, when needed, recombinant IFN- γ . Overall, the genetic disorders of IFNGR1 and IFNGR2 strongly suggest a tight correlation between the

level of IFN- γ -mediated immunity and the clinical severity of mycobacterial disease [48].

STAT-1 is a critical transducer of cellular responses to type I (IFN- α/β) and type II (IFN- γ) IFNs, and to the less well characterized type III IFNs (IFN- λ) [49]. Patients who have complete STAT-1 deficiency present a syndrome of susceptibility to mycobacteria and viruses because of impaired cellular responses to antimycobacterial IFN- γ and antiviral IFN- α/β and - λ [50,51]. This clinical syndrome, therefore, clearly differs from that of patients who have MSMD, who are normally resistant to most viruses, with a few possible exceptions, as discussed earlier [50,51]. However, some germline mutations in *STAT1* have been shown to be responsible for mycobacterial disease as the sole infectious phenotype in selected patients, owing to the selective impairment of IFN- γ responses mediated by STAT-1 homodimers (gamma-activating factor) activation [22,23]. In these patients, IFN- α responses mediated by STAT-1-STAT-2-interferon regulatory factor (IRF)-9 trimers (interferon-stimulated gamma factor 3), unlike those in patients who have complete STAT-1 deficiency, were entirely normal. Patients who have partial STAT-1 deficiency are heterozygous for these subtle mutations that are intrinsically loss-of-function for IFN- γ and IFN- α/β responses, but dominant for IFN- γ responses only. As a result, these patients have mild clinical features characterized by mycobacterial disease without susceptibility to viruses, resembling those in patients who have partial IFNGR1 deficiency, with a good prognosis. Two types of *STAT1* mutations are dominant, depending on whether the mutation impairs STAT-1 phosphorylation [23] or DNA-binding activity [22]. Clinically, the patients suffered from disseminated BCG infection or *M. avium* infection [22,23]. One patient was reported to have *M. tuberculosis* infection [22]. Treatment is based on antibiotics and recombinant IFN- γ .

The first genetic defect of the human IL-12 and IL-23 pathways was described in 1998 [24] and indicated that these cytokines were critical for controlling the levels of the antimycobacterial molecule, IFN- γ . Mutations in the *IL12RB1* gene encoding the first chain of the IL-12 receptor (IL-12R β 1), common to the IL-12 and IL-23 receptors, and the *IL12B* gene encoding IL-12p40, common to IL-12 and IL-23, have been reported (see Fig. 1) [25,52]. All mutations in *IL12B* and *IL12RB1* cause a complete, autosomal recessive defect because they are loss-of-function. IL12RB1 deficiency is the most frequent genetic cause of MSMD affecting families from many different countries [13]. Mycobacterial disease and salmonellosis are the most common infectious diseases for both deficiencies [13]. The clinical phenotype of IL12RB1-deficient patients is similar to that of IL12p40-deficient patients. About one half of all IL12B- and IL12RB1-deficient patients have developed *Salmonella* infection at some time, in contrast to MSMD patients who have mutations affecting IFN- γ signaling immunity [53,54]. These observations suggest that IL-12/-23 plays a key role in the

pathogenesis of salmonellosis, possibly through IL-23-dependent IL-17 induction. Several patients who had *IL12RB1* defects were found to have susceptibility to *M tuberculosis* as their sole infectious phenotype, and one patient who had IL12B deficiency, who had been vaccinated with BCG, had *M tuberculosis* infection, providing the first conclusive evidence that tuberculosis can result from a mendelian predisposition [11,55–57]. Other infectious diseases, such as paracoccidioidomycosis [58], leishmaniasis [59], and nocardiosis [54], have been reported in isolated cases, suggesting that the clinical features of these disorders may expand with the diagnosis of new cases. Treatment is based on antibiotics and IFN- γ .

The recent identification of specific mutations in *NEMO* revealed XR-MSMD-causing gene. *NEMO* encodes the NF- κ B essential modulator, also known as IkappaB kinase (IKK)- γ , a regulatory unit of the IKK complex. Mutations in this gene are responsible for various diseases: null mutations lead to incontinentia pigmenti [60] and hypomorphic mutations result in XR anhidrotic ectodermal dysplasia with immunodeficiency, osteopetrosis, and noninflammatory lymphedema (XR-EDA-ID-OL) [61], XR anhidrotic ectodermal dysplasia with immunodeficiency, and osteopetrosis (XR-EDA-ID-O) [61–63], XR anhidrotic ectodermal dysplasia with immunodeficiency (XR-EDA-ID) [61], XR-mild-EDA [64,65], or immunodeficiency (ID) only without ectodermal dysplasia (EDA) [66]. The range of infections varies considerably, and includes viral, fungal, and common pyogenic infections [67]. Specific mutations affecting the leucine zipper domain of NEMO, E315A, and Q319R were recently shown to be associated with mycobacterial infections in three unrelated kindreds with MSMD (XR-MSMD-type 1) [27]. Two mycobacteria were isolated: *M avium* in most patients and *M tuberculosis* in one patient [68]. Another patient probably had tuberculosis [27]. One patient presented mild signs of EDA, limited to conical decidal incisors, whereas the other patients had no overt developmental abnormality. These subtle mutations affect the T-cell-dependent, CD40-dependent activation of c-Rel, resulting in impaired IL-12 induction in monocytes and dendritic cells [27]. The prognosis seems to be unpredictable, varying considerably among patients. Treatment is based on antibiotics and, possibly, IFN- γ .

Mendelian predisposition to invasive pneumococcal disease

IPD is defined by the infection of normally sterile compartments of the body by *Streptococcus pneumoniae* (Fig. 2). In most individuals with IPD, colonization of the upper respiratory tract with *S pneumoniae* is a prerequisite for IPD. Thus, in most cases, IPD is caused by bacteria crossing the mucosal epithelia of the upper respiratory tract and reaching the blood stream. IPD may thus present as sepsis, meningitis, osteomyelitis, or arthritis. The colonization of the upper respiratory tract with *S pneumoniae*

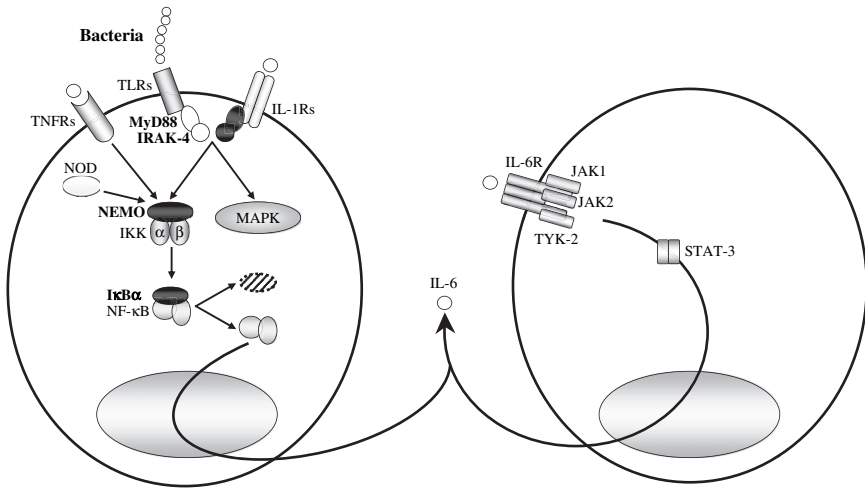


Fig. 2. Mendelian susceptibility to IPDs. Cytokine production and cooperation between phagocytes (polymorphonuclear neutrophils, monocytes, and dendritic cells) and lymphocytes (T, B, and natural killer) recognized by TLRs at the surface of phagocytes. This recognition induces activation of the NF- κ B and mitogen-activated protein (MAP) kinase pathways by way of myeloid differentiation factor 88 (MyD88) and interleukin receptor-associated kinase-4 (IRAK-4). These activation pathways induce the production of several proinflammatory cytokines (IL-6, IL-1 β , and tumor necrosis factor [TNF]- α). IRAK-4 deficiency is associated with the impaired induction of inflammation by TLR ligands, and the impaired propagation of inflammation by IL-1 and IL-18. NEMO and I κ B α deficiencies are associated with the impaired induction of inflammation by TLR ligands and TNF receptor ligands. IRAK-4, NEMO, and I κ B α deficiencies are associated with impaired IL-6 production. Proteins for which mutations in the corresponding genes have been identified and shown to be associated with particular susceptibility to IPD are shown in gray.

reaches a peak at the age of 3 years, when more than 50% of children are colonized. Colonization then declines to about 10% by the age of 10 years [69,70]. Before the introduction of a protein-conjugated vaccine against *S pneumoniae*, the prevalence of IPD among children under the age of 2 years ranged from 14/100,000 in Germany, more than 90/100,000 in Spain, and 188/100,000 in the United States [71–73] to estimates as high as 1741/100,000 in sub-Saharan Africa [74]. The introduction of the protein-conjugated vaccine in 2000 has greatly decreased the number of cases of IPD, but the prevalence of this disease remains substantial in children [75–77]. An intact respiratory tract epithelium usually prevents *S pneumoniae* invasion. Having crossed this barrier, opsonization by complement and antibodies is crucial for phagocytosis by neutrophilic granulocytes, monocytes, and, in particular, splenic macrophages. T cells seem to be crucial for the maintenance of a humoral antipneumococcal response. The importance of these components of the immune system is demonstrated by the greater susceptibility to IPD of patients who have mucosal epithelia damaged by flu [78], of patients who have defects of early components of the

classic complement pathway (C1, C4, C2), C3, factors I and D or antibody formation, and of patients who have asplenia or HIV infection [79,80]. Several primarily nonimmunologic conditions also predispose patients to IPD: kidney failure, liver failure, heart failure, sickle cell anemia, leukemia, and fistulae in the cerebroarachnoidal space [80,81]. However, although some cases may be accounted for by these conditions, the cause of IPD remains unknown in most patients.

XR-EDA-ID is a recently defined PID conferring predisposition to multiple infections, including IPD in particular, which has been documented in most patients. In 2001, XR-EDA-ID was shown to be caused by hypomorphic mutations in the gene encoding the NF- κ B essential modulator (NEMO) [61–63]. NEMO is a scaffold protein essential for the formation of a protein complex (IKK) catalyzing the phosphorylation of NF- κ B-inhibitor proteins (I κ Bs). I κ Bs control the balance between the nuclear and cytosolic activities of NF- κ B by binding to NF- κ B, which is present in the cytosol when bound to I κ B. The phosphorylation of I κ Bs leads to the dissociation of I κ Bs from NF- κ B and an increase in the nuclear activity of NF- κ B. Because IKK is the convergence point for several pathways controlling the development of skin appendages (dependent on the receptor for ectodysplasin) and for many pathways mediating immunologic responses (eg, dependent on receptors such as those of the tumor necrosis factor- α -receptor superfamily, the B-cell receptor, and the those of the Toll-like and IL-1 receptor [IL-1R] family [TIR]), most patients who have NEMO deficiency present a clinical combination of ectodermal dysplasia and immunodeficiency (EDA-ID) [61–63], an entity first described by Abinun and colleagues [82,83]. The features of EDA-ID comprise a typical facies (frontal bossing, saddle nose), aberrant development of skin appendages, such as hair (sparse or missing hair and sparse or missing eye brows), teeth (hypodontia, anodontia, conical incisors or delayed eruption of teeth), and sweat glands (anhidrosis and heat intolerance), and strong susceptibility to IPD and other infectious diseases [61–63,82–84].

The ectodermal and immunologic phenotypes of individual patients who have NEMO deficiency may be extremely variable. The degree of EDA ranges from XR-EDA-ID-OL [61,85,86], through XR-EDA-ID-O [63,92], “classic” XR-EDA-ID [61–63,82–84,88–95], and XR-mild-EDA [64,65], to ID only [13,66,84,96,97]. The infectious phenotype is similarly broad. In addition to IPD [61,63–65,83–85,87,90,91], NEMO-deficient patients may present sepsis, meningitis, osteomyelitis, and pneumonia due to other pyogenic bacteria (*S aureus*, *Streptococcus bovis*, *L monocytogenes*, *Streptococcus equii*, *Salmonella enteritidis*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Pseudomonas fluorescens*, *Klebsiella pneumoniae*, *Escherichia coli*) [8,61,64,84,86,87,89,90,93–95,97]; lymphadenitis, sepsis, osteomyelitis, and pneumonia caused by mycobacteria (*M abscessus*, *M avium*, *M bovis*, *M kansasii*) (see earlier discussion) [13,61,63,66,84–89,92,96,97]; infections caused by various viruses (chronic molluscum contagiosum; HSV stomatitis; sepsis,

colitis or retinitis due to cytomegalovirus; nonspecified viral meningitis; HSV encephalitis) (see later discussion) [61,63,66,84,86,87,92,96]; sepsis or pneumonia caused by fungi (*Candida albicans*, *Pneumocystis carinii*, *Pneumocystis jirovecii*) [61,84,85,87,93]; or enteritis caused by *Giardia lamblia* [84]. Severe infections may be accompanied by surprisingly low signs of inflammation [84,85,87,93]. In addition to the diversity of possible pathogens, considerable interindividual variation is observed in the frequency and severity of infections, with some patients having a course of disease justifying a bone marrow transplant [85,95] and others doing well on antibiotic prophylaxis only (von Bernuth and Casanova, unpublished data). If the severity of the clinical course justifies a bone marrow transplant, reduced-intensity conditioning and graft-versus-host disease prophylaxis should be considered because severe liver toxicity has been observed [85,95].

Patients who have NEMO deficiency may present a number of comorbid features at an early age, including intractable diarrhea and failure to thrive [84,85,93]. In one family, all patients were reported as born small for gestational age [93]. Some NEMO-deficient patients may present autoimmune phenomena [84,93,96] and impaired natural killer cell-mediated cytotoxicity [84,87,92,95]. In routine immunologic workup, most NEMO-deficient patients present low, high, or fluctuating serum concentrations of the three subtypes of immunoglobulin, in all possible combinations [63,64,83–86,89–93,95,99], leading to the suggested “diagnosis” of “common variable immunodeficiency.” Low levels of IgG and IgA combined with high levels of IgM may lead to the “diagnosis” of “Hyper-IgM syndrome” [62,63,66,84,87,93,94,96,99,100]. In some patients, low levels of CD27⁺, IgD[−] (“class-switched somatically mutated memory”) B cells have been observed [66,96,99]. This feature probably results from defective V(D)J recombination in individuals who have hypomorphic mutations in the C-terminal region of the zinc-finger motif [101]. The proliferation of lymphocytes in response to mitogens and antigens may appear normal, but mild impairment of mitogen-dependent and, in particular, T-cell-dependent or antigen-dependent proliferation has been reported in some patients [64,84,85,92,96]. The most consistent immunologic finding among patients who have NEMO deficiency seems to be the absence of antibodies against glycans, such as those of *S pneumoniae*, despite infection or vaccination, and of allohemagglutinins in children over the age of 2 years [63,64,66,83,85,90,91,96].

The discovery that XR EDA-ID was caused by hypomorphic mutations in *NEMO* paved the way for the discovery, in 2003, that a hypermorphic mutation in *IKBA* was the cause of autosomal dominant AD-EDA-ID [102]. A heterozygous dominant-negative missense mutation, S32I, in *IKBA* prevents IκBα phosphorylation at the mutated site, maintaining NF-κB in its IκBα-bound form restricted to the cytosol [102]. The same mutation was described in a second patient who had AD-EDA-ID [103]. A third patient, who had a heterozygous mutation creating a premature

stop codon, W11X, leading to haploinsufficiency of $\text{IkB}\alpha$, was recently reported [104]. The clinical phenotypes of the first two patients were similarly severe, with chronic diarrhea and failure to thrive, recurrent bronchopneumonia, meningitis, and enteritis caused by gram-positive bacteria (*S aureus*, *Streptococcus pyogenes*), gram-negative bacteria (*Pseudomonas* spp, *K pneumoniae*, *Serratia* spp, *Salmonella typhimurium*), and fungi (*P jiroveci*). Both patients had a “hyper-IgM phenotype” with low serum concentrations of IgG and IgA, a high serum concentration of IgM, and no antibodies against glycans. Unlike patients who have NEMO deficiency, these patients also showed marked signs of an aberrant T-cell development and impaired T-cell function, with no detectable γ/δ T cells, almost all α/β T cells having the naive CD45RA phenotype, and no antibodies detected in the serum in response to recall antigens, despite vaccination, together with a complete lack of in vitro proliferation in response to CD3-specific antibodies (OKT 3) and recall antigens. Pronounced lymphocytosis was also a typical feature in both patients [102,103]. The third patient described also suffered from multiple bronchopneumonia but with no bacteremia documented to date. In further contrast to the first two patients who had the S32I mutation in *IKBA*, this patient had normal serum IgG and low IgM levels and a less pronounced T-cell phenotype. Antibody responses and in vitro proliferation to recall antigens were normal, as were the percentages of T and B cells, despite marked lymphocytosis [104]. Hematopoietic stem cell transplantation is a curative option for patients who have autosomal dominant EDA-ID [105].

Because NEMO mutations impair multiple pathways and render patients susceptible to a broad range of infections including IPD, the authors hypothesized that a deficiency in one particular pathway upstream from NEMO and IKK might be responsible for cases of IPD without EDA or infections with other pathogens. One obvious candidate was the TIR-dependent pathway, because the extracellular domain of TLRs consists of leucine-rich repeats that sense components of various pathogens, and because the extracellular domain of IL-1Rs consists of immunoglobulin-like domains that recognize IL-1. All human TLRs (1–10) and IL-1Rs (TIRs) signal by way of a structurally similar intracellular domain, the so-called “TIR domain.” TIRs, which have no kinase domain, transmit their signal by way of several adapter molecules that bind to the receptors by way of the TIR domain and recruit other molecules to the receptor. One of these adapter molecules, myeloid differentiation factor 88 (MyD88), is used by all TLRs except TLR3 and by all IL-1Rs with a TIR domain. After MyD88, the next molecule to be recruited is interleukin receptor-associated kinase-4 (IRAK-4). Upon binding to MyD88, this kinase is phosphorylated. It then phosphorylates interleukin receptor-associated kinase-1 (IRAK-1), resulting in the degradation of this protein. IRAK-1 activation is essential for the subsequent transmission of the signal to several pathways, including those controlled by mitogen-activated protein (MAP) kinases and IKK,

eventually leading to the translocation of transcription factors activator protein (AP)-1 and NF- κ B to the nucleus.

The authors' hypothesis that IPD was caused by defects in this pathway was confirmed by the identification of the first three patients who had a strong, almost specific susceptibility to IPD caused by autosomal recessive complete IRAK-4 deficiency in 2003 [106]. Because IRAK-4 deficiency leads to an isolated impairment of TIR signaling, IRAK-4-deficient patients display no EDA. Despite the major role initially proposed for TLRs in human immunity [107] and the almost complete impairment of TIR signaling (with the exception of TLR3-IFN- β and TLR4-IFN- α/β pathways) in all cell types tested, patients who have IRAK-4 deficiency are not particularly susceptible to mycobacteria, viruses, fungi, or parasites [108,109]. In contrast, IRAK-4 deficiency predisposes patients exclusively to infections caused by pyogenic bacteria, *S pneumoniae* in particular. Meningitis, arthritis, osteomyelitis, and abscess formation in internal organs and just below the skin are the most frequently observed infections. The pyogenic bacteria other than *S pneumoniae* known to have caused severe infections in patients who had IRAK-4 deficiency to date are *S aureus* and *Pseudomonas aeruginosa*, with less frequent infections caused by *Clostridium septicum*, *Streptococcus parasanguis*, *Streptococcus milleri*, *E coli*, *Neisseria Meningitidis*, and *Shigella sonnei* [65,106,108–118]. Most patients suffer from IPD and invasive infections caused by other pyogenic bacteria in infancy and early childhood. The prognosis of IRAK-4 deficiency improves significantly with age. No deaths have been reported in patients over the age of 8 and no invasive infection was reported in six patients over the age of 14, even in the absence of antibiotic prophylaxis [108,110,111,114,116]. In most cases, routine immunologic workup gave normal findings for levels of immunoglobulins, antibodies against recall antigens and glycans, percentages of lymphocyte subpopulations, and lymphocyte proliferation assays. Only a few cases of IRAK-4 deficiency associated with low serum levels of antibodies against recall antigens [112] or glycans [108,112] have been reported. A characteristic, but not specific, clinical feature of IRAK-4 deficiency is the prolonged period required for the umbilical cord to detach after birth (>30 days) [118]. As previously reported for a NEMO-deficient patient, most patients who have IRAK-4 deficiency have a delayed or weak inflammatory response (low fever, low C-reactive protein levels), even during severe invasive infection [98,113]. In most patients who have IRAK-4 deficiency, the immunologic routine workup does not reveal any anomaly. Only a few patients displayed low levels of serum antibodies against recall antigens [52] or glycans [52,108]. A defect in TIR-dependent pathways can be suspected in patients whose whole blood cells do not produce IL-6 or whose granulocytes do not shed CD62L after stimulation by TLR agonists [119]. The authors recommend treating patients who have IRAK-4 deficiency with an antibiotic prophylaxis that is directed against pyogenic bacteria, in particular, *S pneumoniae*. Vaccinations against *S pneumoniae* and *N meningitidis* should

be performed and in selected cases, the administration of immunoglobulins may be considered.

Mendelian predisposition to herpes simplex encephalitis

Herpes simplex encephalitis (HSE), which is typically caused by HSV type 1 (HSV-1) in patients older than 3 months [120–122], is the most common sporadic viral encephalitis in the Western world (Fig. 3) [123]. The estimated incidence of HSE is between two and four individuals per million per year [124–126], with approximately one third of all HSE cases caused by primary infections (mostly in children, because about 90% of people are seropositive by the age of 18 years) [122,126,127–129]. The first child with HSE was described in 1941 [130], and the first adult in 1944 [131]. This disease was almost invariably lethal until the advent of acyclovir in the 1980s. Most patients now survive HSE, although many, including young children in particular, present neurologic sequelae [127]. HSE is a devastating disease of unclear pathogenesis, because HSV-1 is widespread and readily transmitted from person to person, with more than 85% of adults between the ages of 20 and 40 serologically positive for HSV-1 in a survey of more than 20 countries [132,133]. Moreover, HSV-1 is benign in most

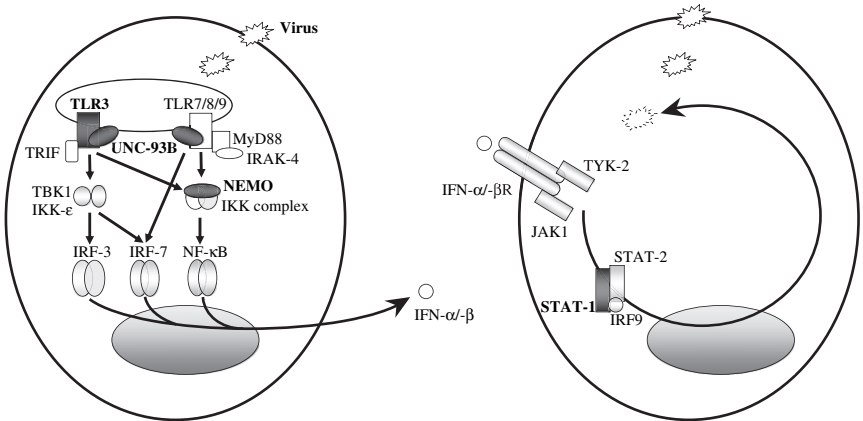


Fig. 3. Mendelian predisposition to HSE. Production and response to IFN- α/β during virus infections. Viruses enter the cells by way of specific receptors, and viral nucleic acids are detected by the various TLRs. This recognition induces activation of the IRF-3, IRF-7, and NF- κ B pathways by way of 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 is translocated 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. STAT-1 deficiencies are associated with impaired IFN responses. Proteins for which genetic mutations have been identified and associated with particular susceptibility to viral diseases have been identified and associated with particular susceptibility to viral diseases are shown in gray.

individuals, infecting the oral mucosa, establishing latency in the trigeminal ganglia, and resulting in asymptomatic infection or recurrent herpes labialis. The pathogenesis of HSE, which affects a few HSV-1-infected individuals, has therefore long remained unclear. No particular risk factors have been definitively demonstrated to be associated with the variation of individual HSV-1 [134–137] or other environmental factors [126,128,129]. The role of human genetic susceptibility in HSE was first suggested by the reports of four unrelated multiplex HSE kindreds [138–141]. Although HSE is sporadic in most cases, the patients from these families belonged to one or two generations and suffered from HSE at several years apart [138–141]. A high incidence of parental consanguinity (14%) was recently documented in French kindreds with HSE [127]. These clinical observations suggest that HSE may result from mendelian predisposition, in at least some children.

The first attempt to document human genetic predisposition to HSV-1 infection was reported in 2001, with apolipoprotein E genotypes associated with HSE in one study [142] but not another [143]. HSE was not reported in patients who had bona fide mendelian PIDs until 2003, when a few patients were reported to lack STAT-1, a critical protein downstream from the receptors to IFN- α/β and IFN- γ [51]. STAT-1-deficient patients suffered from mycobacterial disease caused by their impaired response to IFN- γ [10], and were susceptible to viral diseases, including recurrent HSE in one child [51], presumably because of their impaired IFN- α/β responses [144]. This finding provided the first suggestion that isolated HSE might be caused by inherited immunodeficiencies involving IFN- α/β -mediated immunity. Consistent with this hypothesis, one patient who had a mutation in *NEMO* [66,96] presented recurrent mycobacterial disease and recurrent and lethal HSE. NEMO not only regulates NF- κ B activation, it is also involved in the activation of IRF3 after viral infections or virus-associated stimulation [145]. In this patient who had NEMO deficiency, the production of IFN- α , - β , and - λ was impaired and may account for the occurrence of HSE. Although HSE has not been observed in other PIDs, the occurrence of HSE in the STAT1- and NEMO-deficient patients also presenting mycobacterial disease strongly suggests that the human innate immune system is involved in protective immunity to HSV-1 in the central nervous system (CNS), and indicates that the production of, or response to, IFN- α , - β , and - λ is probably important in HSE.

The first genetic cause of isolated HSE was described in 2006, with the identification of homozygous germline mutations in *UNC93B1*, in two unrelated and otherwise healthy patients suffering from HSE, from different consanguineous kindreds [146]. The human and mouse UNC-93B proteins contain 12 transmembrane domains and are found mostly in the endoplasmic reticulum [147,148]. In the mouse, UNC-93B binds to the transmembrane domains of TLR3 and TLR9 [147], and is required for the signaling of intracellular, nucleic acid-sensing TLRs (TLR3, TLR7, and TLR9)

because UNC-93B-deficient mouse macrophages display impaired responses to these TLRs [148]. The identification of human UNC-93B deficiency confirmed the requirement for UNC-93B in human TLR3, TLR7, TLR8, and TLR9 signaling [146]. The 1034del4 and 781G>A mutations in the coding region of *UNC93B1* result in a premature termination codon and lead to a complete loss of UNC-93B expression (caused by nonsense-mediated mRNA decay) and function. TLR3 signaling was abolished in the patients' fibroblasts, as shown by the impaired IFN- β and - λ production following stimulation with poly(I:C). TLR7, TLR8, and TLR9 are expressed in peripheral blood mononuclear cells (PBMCs), and the PBMCs from UNC-93B-deficient patients did not respond to the stimulation of TLR7, TLR8, or TLR9, in terms of the production of IFN- α , - β , and - λ , and other cytokines tested. TLR7-, TLR8-, and TLR9-mediated IFN- α , - β , and - λ production seems to be largely redundant in human antiviral immunity; the IRAK-4-deficient patients [108] displayed impaired IFN- α , - β , and - λ production following the activation of TLR7, TLR8, and TLR9 but were resistant to most common viral infections, HSE in particular. The identification of human UNC-93B deficiency thus provided the first evidence that HSE can result from a monogenic trait, and that impaired TLR3-triggered, UNC-93B-dependent, IFN- α , - β , and - λ induction may be involved in HSE.

In 2007, a germline heterozygous *TLR3* mutation was identified in two other unrelated and otherwise healthy children with HSE from nonconsanguineous families [149]. The identification of the second genetic cause of isolated HSE established that the TLR3-UNC-93B-IFN- α , - β , and - λ signaling pathway is essential for protective immunity to HSV-1 in the CNS, at least in some children, during primary infection. TLR3, one of the 10 members of the human TLR family, recognizes dsRNA, an almost universal viral intermediate potentially generated during most viral infections, and induces IFN production. TLR3 was therefore thought to play a broad role in antiviral immunity. In the two children with autosomal dominant TLR3 deficiency, the same heterozygous 1660C>T mutation (P554S) was found [145]. The 1660C>T mutant allele is loss-of-function and dominant negative for the response to poly(I:C) in fibroblasts, in terms of IFN- β and - λ induction. Different types of TLR3-expressing cells, including fibroblasts, from patients displayed an impaired response to poly(I:C). The production of IFN- β and - λ by fibroblasts was impaired following stimulation with poly(I:C), HSV-1, and vesicular stomatitis virus (VSV), as in UNC-93B-deficient fibroblasts. Moreover, higher viral titers and higher levels of cell death following HSV-1 and VSV infection were observed in TLR3-heterozygous fibroblasts and UNC-93B-deficient fibroblasts complemented with IFN- α and - β , and, less efficiently, with IFN- λ . Impaired TLR3 signaling thus results in abnormally weak IFN- α , - β , and - λ production, enhanced viral replication, and enhanced cell death in patients' fibroblasts. By inference, this provides a plausible mechanism for HSE in the CNS. Indeed, TLR3 is

the most abundantly and widely expressed TLR in human CNS-resident cells, including neurons [150], microglia [151,152], astrocytes [151,152], and oligodendrocytes [151]. HSV-1 replication has been documented *in vitro* in these cells [150,153,154], and human neurons [150], astrocytes [152], and microglia also produce IFN- β in response to dsRNA.

These findings have provided conclusive evidence that isolated HSE results from a new group of single-gene immunodeficiencies, at least in some children. The production of IFN- α , - β , and - λ by way of TLR3-UNC-93B is critical for protective immunity to HSV-1 in the CNS. These results have important therapeutic implications, because at least some HSE patients would probably benefit from recombinant IFN- α treatment in addition to acyclovir [146]. An interesting unresolved question concerns the role of different IFN- α , - β , and - λ subtypes in anti-HSV-1 immunity. The subtype may be of importance, and may provide further indications for the treatment of HSE patients who have IFNs. HSE patients, including the reported UNC-93B- and TLR3-deficient patients [146,149], are typically not susceptible to other infections, or even to HSV-1 infections outside the CNS [155]. TLR3-independent IFN responses to dsRNA in some cell types, including dendritic cells [149], and TLR3-independent IFN responses to other viral intermediates may confer protection against a wide range of viruses in TLR3- and UNC-93B-deficient patients [156,157]. However, limited by the small number of UNC-93B- and TLR3-deficient patients studied, which resulted in probable strong ascertainment bias, no definitive conclusion can be made concerning the infectious phenotypes of UNC-93B- and TLR3-deficient patients. Five of the seven TLR3-deficient individuals and one of the three UNC-93B-deficient individuals did not develop HSE, despite proved HSV-1 infection [149]. The incomplete clinical penetrance of HSE in TLR3- and UNC-93B-deficient individuals provides an explanation for the sporadic occurrence of HSE. It may be that age at infection is a key factor governing the development of HSE in genetically predisposed individuals, as suggested by the genetic epidemiologic survey of French cases [127]. Finally, the lack of identified genetic deficiencies in most other HSE patients, including adult HSE patients, in whom the pathogenesis of HSE may be different from that in pediatric cases [158], makes it interesting to explore the possible genetic disorders in these patients, whether they concern the TLR3-UNC-93B-IFN- α , - β , and - λ signaling pathway, or other systems. Future genetic studies based on positional cloning, and biologic studies based on functional screens, will undoubtedly provide additional insight into the pathogenesis of HSE, by better defining the molecules and cells involved in immunity to HSV-1 in the CNS.

Summary

From the 1950s onwards, patients who had a selective predisposition to infections caused by weakly virulent mycobacteria (MSMD) were thought

to have a PID, given the occurrence of similar infections in patients who had multiple infections and severe PIDs, such as severe combined ID [159]. It was not until 1996 that the first molecular defects were found, and now we know of 14 genetic causes of MSMD, resulting from mutations in seven genes. Many more genetic causes of MSMD remain to be discovered, and their discovery may help us decipher the genetic basis of pediatric tuberculosis, as suggested by the occurrence of this disease in children with IL12RB1 deficiency [11]. Children with recurrent IPD were also thought, from the 1950s onwards, to suffer from PIDs, because PIDs affecting pneumococcal opsonization, such as X-linked agammaglobulinemia, predispose patients to invasive disease caused by encapsulated bacteria, including pneumococcus [80]. It was not until 2003, with the description of children with IRAK-4 deficiency, based on the prior discovery of *NEMO* and *IKBA* mutations in patients who had a complex PID associated with multiple infections including IPD as the dominant trait, that the first specific genetic cause of recurrent IPD was documented. Most patients who have recurrent IPD and most patients who have a single episode of IPD still have no identified genetic cause. Finally, HSE was not thought to result from a PID until the first two patients who had HSE and mycobacterial disease were identified in 2003, and until a genetic cause of isolated HSE was discovered in 2006 [160]. Most children with a single episode or recurrent HSE still have no identified genetic cause. Research into PIDs will undoubtedly advance through the identification of new genetic causes of MSMD, IPD, and HSE. This expansion may become a paradigm, because other pediatric infectious diseases are also likely to result from novel PIDs.

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References

- [1] Casanova JL, Abel L. Inborn errors of immunity to infection: the rule rather than the exception. *J Exp Med* 2005;202:197–201.
- [2] Casanova JL, Abel L. Primary immunodeficiencies: a field in its infancy. *Science* 2007;317:617–9.
- [3] Picard C, Casanova JL, Abel L. Mendelian traits that confer predisposition or resistance to specific infections in humans. *Curr Opin Immunol* 2006;18:383–90.
- [4] Ma CS, Nichols KE, Tangye SG. Regulation of cellular and humoral immune responses by the SLAM and SAP families of molecules. *Annu Rev Immunol* 2007;25:337–79.

- [5] Rigaud S, Fondaneche MC, Lambert N, et al. XIAP deficiency in humans causes an X-linked lymphoproliferative syndrome. *Nature* 2006;444:110–4.
- [6] Lazarczyk M, Pons C, Mendoza JA, et al. Regulation of cellular zinc balance as a potential mechanism of EVER-mediated protection against pathogenesis by cutaneous oncogenic human papillomaviruses. *J Exp Med* 2008;205:35–42.
- [7] Orth G. Genetics of epidermodysplasia verruciformis: insights into host defense against papillomaviruses. *Semin Immunol* 2006;18:362–74.
- [8] Mathew S, Overturf GD. Complement and properdin deficiencies in meningococcal disease. *Pediatr Infect Dis J* 2006;25:255–6.
- [9] Hamosh A, Scott AF, Amberger JS, et al. Online Mendelian Inheritance in Man (OMIM), a knowledgebase of human genes and genetic disorders. *Nucleic Acids Res* 2005;33: D514–7.
- [10] Casanova JL, Abel L. Genetic dissection of immunity to mycobacteria: the human model. *Annu Rev Immunol* 2002;20:581–620.
- [11] Alcais A, Fieschi C, Abel L, et al. Tuberculosis in children and adults: two distinct genetic diseases. *J Exp Med* 2005;202:1617–21.
- [12] MacLennan C, Fieschi C, Lammas DA, et al. Interleukin (IL)-12 and IL-23 are key cytokines for immunity against *Salmonella* in humans. *J Infect Dis* 2004;190:1755–7.
- [13] Filipe Santos O, Bustamante J, Chapgier A, et al. Inborn errors of the IL-12/23 and IFN- γ mediated immunity: molecular, cellular and clinical features. *Semin Immunol* 2006;18: 347–61.
- [14] Bustamante J, Picard C, Fieschi C, et al. A novel X-linked recessive form of Mendelian susceptibility to mycobacterial disease. *J Med Genet* 2007;44:e65.
- [15] Jouanguy E, Altare F, Lamhamedi S, et al. Interferon-gamma-receptor deficiency in an infant with fatal bacille Calmette-Guerin infection. *N Engl J Med* 1996;335: 1956–61.
- [16] Jouanguy E, Dupuis S, Pallier A, et al. In a novel form of complete IFN γ R1 deficiency, cell-surface receptors fail to bind IFN γ . *J Clin Invest* 2000;105:1429–36.
- [17] Jouanguy E, Lamhamedi-Cherradi S, Altare F, et al. Partial interferon-gamma receptor 1 deficiency in a child with tuberculous bacillus Calmette-Guerin infection and a sibling with clinical tuberculosis. *J Clin Invest* 1997;100:2658–64.
- [18] Jouanguy E, Lamhamedi-Cherradi S, Lammas D, et al. A human IFNGR1 small deletion hotspot associated with dominant susceptibility to mycobacterial infection. *Nature Genet* 1999;21:370–8.
- [19] Newport MJ, Huxley CM, Huston S, et al. A mutation in the interferon-gamma-receptor gene and susceptibility to mycobacterial infection. *N Engl J Med* 1996;335:1941–9.
- [20] Dorman SE, Holland SM. Mutation in the signal-transducing chain of the interferon-gamma receptor and susceptibility to mycobacterial infection. *J Clin Invest* 1998;101: 2364–9.
- [21] Vogt G, Chapgier A, Yang K, et al. Gains of glycosylation comprise an unexpectedly large group of pathogenic mutations. *Nat Genet* 2005;37:692–700.
- [22] Chapgier A, Boisson-Dupuis S, Jouanguy E, et al. Novel STAT1 alleles in otherwise healthy patients with mycobacterial disease. *PLoS Genet* 2006;2:e131.
- [23] Dupuis S, Dargemont C, Fieschi C, et al. Impairment of mycobacterial but not viral immunity by a germline human STAT1 mutation. *Science* 2001;293:300–3.
- [24] Altare F, Lammas D, Revy P, et al. Inherited interleukin 12 deficiency in a child with bacille Calmette-Guérin and *Salmonella* enteritidis disseminated infection. *J Clin Invest* 1998;102: 2035–40.
- [25] Altare F, Durandy A, Lammas D, et al. Impairment of mycobacterial immunity in human interleukin-12 receptor deficiency. *Science* 1998;280:1432–5.
- [26] Fieschi C, Dupuis S, Catherinot E, et al. Low penetrance, broad resistance, and favorable outcome of interleukin 12 receptor beta1 deficiency: medical and immunological implications. *J Exp Med* 2003;197:527–35.

- [27] Filipe-Santos O, Bustamante J, Haverkamp MH, et al. X-linked susceptibility to mycobacteria is caused by mutations in NEMO impairing CD40-dependent IL-12 production. *J Exp Med* 2006;203:1745–59.
- [28] Newport M, Holland SM, Levis M, et al. Inherited disorders of the IL-12-IFN γ axis. In: Ochs HD, Smith CIE, Puck J, editors. *Primary immunodeficiencies: a molecular and genetic approach*. 2nd edition. New York: Oxford University Press; 2007.
- [29] Fieschi C, Dupuis S, Picard C, et al. High levels of interferon gamma in the plasma of children with complete interferon gamma receptor deficiency. *Pediatrics* 2001;107:E48.
- [30] Emile JF, Patey N, Altare F, et al. Correlation of granuloma structure with clinical outcome defines two types of idiopathic disseminated BCG infection. *J Pathol* 1997;181:25–30.
- [31] Dorman SE, Picard C, Lammas D, et al. Clinical features of dominant and recessive interferon gamma receptor 1 deficiencies. *Lancet* 2004;364:2113–21.
- [32] Altare F, Jouanguy E, Lamhamedi-Cherradi S, et al. A causative relationship between mutant IFN γ R1 alleles and impaired cellular response to IFN γ in a compound heterozygous child. *Am J Hum Genet* 1998;62:723–6.
- [33] Pierre-Audigier C, Jouanguy E, Lamhamedi S, et al. Fatal disseminated Mycobacterium smegmatis infection in a child with inherited interferon gamma receptor deficiency. *Clin Infect Dis* 1997;24:982–4.
- [34] Koscielniak E, de Boer T, Dupuis S, et al. Disseminated Mycobacterium peregrinum infection in a child with complete interferon-gamma receptor-1 deficiency. *Pediatr Infect Dis J* 2003;22:378–80.
- [35] Noordzij JG, Hartwig NG, Verreck FA, et al. Two patients with complete defects in interferon gamma receptor-dependent signaling. *J Clin Immunol* 2007;27:490–6.
- [36] Camcioglu Y, Picard C, Lacoste V, et al. HHV-8-associated Kaposi sarcoma in a child with IFN γ RI deficiency. *J Pediatr* 2004;144:519–23.
- [37] Dorman SE, Uzel G, Roesler J, et al. Viral infections in interferon- γ receptor deficiency. *J Pediatr* 1999;135:640–3.
- [38] Roesler J, Kofink B, Wendisch J, et al. Recurrent mycobacterial and listeria infections in a child with interferon γ receptor deficiency: mutational analysis and evaluation of therapeutic options. *Exp Haematol* 1999;27:1368–74.
- [39] Chantre CF, Bruwier A, Brichard B, et al. Successful hematopoietic stem cell transplantation in a child with active disseminated Mycobacterium fortuitum infection and interferon-gamma receptor 1 deficiency. *Bone Marrow Transplant* 2006;38:75–6.
- [40] Roesler J, Horwitz ME, Picard C, et al. Hematopoietic stem cell transplantation for complete IFN-gamma receptor 1 deficiency: a multi-institutional survey. *J Pediatr* 2004;145:806–12.
- [41] Rottman M, Soudais C, Vogt G, et al. IFN- γ mediates the rejection of haematopoietic stem cells in IFN- γ R1-deficient hosts. *Plos Med* 2008;5:e26.
- [42] Remiszewski P, Roszkowska-Sliz B, Winek J, et al. Disseminated Mycobacterium avium infection in a 20-year-old female with partial recessive IFN γ RI deficiency. *Respiration* 2006;73:375–8.
- [43] Glosli H, Stray-Pedersen A, Brun AC, et al. Infections due to various atypical mycobacteria in a Norwegian multiplex family with dominant interferon-gamma receptor deficiency. *Clin Infect Dis* 2008;46:e23–7.
- [44] Edgar JD, Smyth AE, Pritchard J, et al. Interferon-gamma receptor deficiency mimicking Langerhans' cell histiocytosis. *J Pediatr* 2001;139:600–3.
- [45] Zerbe CS, Holland SM. Disseminated histoplasmosis in persons with interferon-gamma receptor 1 deficiency. *Clin Infect Dis* 2005;41:e38–41.
- [46] Rosenzweig SD, Dorman SE, Uzel G, et al. A novel mutation in IFN-gamma receptor 2 with dominant negative activity: biological consequences of homozygous and heterozygous states. *J Immunol* 2004;173:4000–8.

- [47] Döffinger R, Jouanguy E, Dupuis S, et al. Partial interferon gamma receptor signalling chain deficiency in a patient with bacille Calmette-Guérin and Mycobacterium abscessus infection. *J Infect Dis* 2000;181:379–84.
- [48] Dupuis S, Doffinger R, Picard C, et al. Human interferon-gamma-mediated immunity is a genetically controlled continuous trait that determines the outcome of mycobacterial invasion. *Immunol Rev* 2000;178:129–37.
- [49] Renauld JC. Class II cytokine receptors and their ligands: key antiviral and inflammatory modulators. *Nat Rev Immunol* 2003;3:667–76.
- [50] Chapgier A, Wynn RF, Jouanguy E, et al. Human complete Stat-1 deficiency is associated with defective type I and II IFN responses in vitro but immunity to some low virulence viruses in vivo. *J Immunol* 2006;176:5078–83.
- [51] Dupuis S, Jouanguy E, Al-Hajjar S, et al. Impaired response to interferon-alpha/beta and lethal viral disease in human STAT1 deficiency. *Nat Genet* 2003;33:388–91.
- [52] de Jong R, Altare F, Haagen IA, et al. Severe mycobacterial and Salmonella infections in interleukin-12 receptor-deficient patients. *Science* 1998;280:1435–8.
- [53] Fieschi C, Casanova JL. The role of interleukin-12 in human infectious diseases: only a faint signature. *Eur J Immunol* 2003;33:1461–4.
- [54] Picard C, Fieschi C, Altare F, et al. Inherited interleukin-12 deficiency: IL12B genotype and clinical phenotype of 13 patients from six kindreds. *Am J Hum Genet* 2002;70:336–48.
- [55] Altare F, Ensser A, Breiman A, et al. Interleukin-12 receptor beta1 deficiency in a patient with abdominal tuberculosis. *J Infect Dis* 2001;184:231–6.
- [56] Caragol I, Raspall M, Fieschi C, et al. Clinical tuberculosis in 2 of 3 siblings with interleukin-12 receptor beta1 deficiency. *Clin Infect Dis* 2003;37:302–6.
- [57] Ozbek N, Fieschi C, Yilmaz BT, et al. Interleukin-12 receptor beta 1 chain deficiency in a child with disseminated tuberculosis. *Clin Infect Dis* 2005;40:e55–8.
- [58] Moraes-Vasconcelos D, Grumach AS, Yamaguti A, et al. Paracoccidioides brasiliensis disseminated disease in a patient with inherited deficiency in the beta1 subunit of the interleukin (IL)-12/IL-23 receptor. *Clin Infect Dis* 2005;41:e31–7.
- [59] Sanal O, Turkmani G, Gumruk F, et al. A case of interleukin-12 receptor beta-1 deficiency with recurrent leishmaniasis. *Pediatr Infect Dis J* 2007;26:366–8.
- [60] Smahi A, Courtis G, Vabres P, et al. Genomic rearrangement in NEMO impairs NF-kappaB activation and is a cause of incontinentia pigmenti. The International Incontinentia Pigmenti (IP) Consortium. *Nature* 2000;405:466–72.
- [61] Doffinger R, Smahi A, Bessia C, et al. X-linked anhidrotic ectodermal dysplasia with immunodeficiency is caused by impaired NF-kappaB signaling. *Nat Genet* 2001;27:277–85.
- [62] Jain A, Ma CA, Liu S, et al. Specific missense mutations in NEMO result in hyper-IgM syndrome with hypohidrotic ectodermal dysplasia. *Nat Immunol* 2001;2:223–8.
- [63] Zonana J, Elder ME, Schneider LC, et al. A novel X-linked disorder of immune deficiency and hypohidrotic ectodermal dysplasia is allelic to incontinentia pigmenti and due to mutations in IKK-gamma (NEMO). *Am J Hum Genet* 2000;67:1555–62.
- [64] Ku CL, Dupuis-Girod S, Dittrich AM, et al. NEMO mutations in 2 unrelated boys with severe infections and conical teeth. *Pediatrics* 2005;115:e615–9.
- [65] Ku CL, Picard C, Erdos M, et al. IRAK4 and NEMO mutations in otherwise healthy children with recurrent invasive pneumococcal disease. *J Med Genet* 2007;44:16–23.
- [66] Puel A, Reichenbach J, Bustamante J, et al. The NEMO mutation creating the most-upstream premature stop codon is hypomorphic because of a reinitiation of translation. *Am J Hum Genet* 2006;78:691–701.
- [67] Puel A, Picard C, Ku CL, et al. Inherited disorders of NF-kappaB-mediated immunity in man. *Curr Opin Immunol* 2004;16:34–41.
- [68] Frucht DM, Holland SM. Defective monocyte costimulation for IFN-gamma production in familial disseminated Mycobacterium avium complex infection: abnormal IL-12 regulation. *J Immunol* 1996;157:411–6.

- [69] Abdullahi O, Nyiro J, Lewa P, et al. The descriptive epidemiology of *Streptococcus pneumoniae* and *Haemophilus influenzae* nasopharyngeal carriage in children and adults in Kilifi district, Kenya. *Pediatr Infect Dis J* 2008;27:59–64.
- [70] Bogaert D, De Groot R, Hermans PW. *Streptococcus pneumoniae* colonisation: the key to pneumococcal disease. *Lancet Infect Dis* 2004;4:144–54.
- [71] Jefferson T, Ferroni E, Curtale F, et al. *Streptococcus pneumoniae* in western Europe: serotype distribution and incidence in children less than 2 years old. *Lancet Infect Dis* 2006;6: 405–10.
- [72] Reinert RR, van der Linden M, Seegmuller I, et al. Molecular epidemiology of penicillin-non-susceptible *Streptococcus pneumoniae* isolates from children with invasive pneumococcal disease in Germany. *Clin Microbiol Infect* 2007;13:363–8.
- [73] Usen S, Adegbola R, Mulholland K, et al. Epidemiology of invasive pneumococcal disease in the Western Region, The Gambia. *Pediatr Infect Dis J* 1998;17:23–8.
- [74] Brent AJ, Ahmed I, Ndiritu M, et al. Incidence of clinically significant bacteraemia in children who present to hospital in Kenya: community-based observational study. *Lancet* 2006;367:482–8.
- [75] Poehling KA, Talbot TR, Griffin MR, et al. Invasive pneumococcal disease among infants before and after introduction of pneumococcal conjugate vaccine. *JAMA* 2006;295: 1668–74.
- [76] Roush SW, Murphy TV. Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. *JAMA* 2007;298:2155–74.
- [77] Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med* 2003;348: 1737–46.
- [78] McCullers JA. Insights into the interaction between influenza virus and pneumococcus. *Clin Microbiol Rev* 2006;19:571–82.
- [79] Carneiro-Sampaio M, Coutinho A. Immunity to microbes: lessons from primary immunodeficiencies. *Infect Immun* 2007;75:1545–55.
- [80] Picard C, Puel A, Ku CL, et al. Primary immunodeficiencies associated with pneumococcal disease. *Curr Opin Allergy Clin Immunol* 2003;3:451–9.
- [81] Mason EO Jr, Wald ER, Tan TQ, et al. Recurrent systemic pneumococcal disease in children. *Pediatr Infect Dis J* 2007;26:480–4.
- [82] Abinun M. Ectodermal dysplasia and immunodeficiency. *Arch Dis Child* 1995;73:185.
- [83] Abinun M, Spickett G, Appleton AL, et al. Anhidrotic ectodermal dysplasia associated with specific antibody deficiency. *Eur J Pediatr* 1996;155:146–7.
- [84] Orange JS, Jain A, Ballas ZK, et al. The presentation and natural history of immunodeficiency caused by nuclear factor kappaB essential modulator mutation. *J Allergy Clin Immunol* 2004;113:725–33.
- [85] Dupuis-Girod S, Corradini N, Hadj-Rabia S, et al. Osteopetrosis, lymphedema, anhidrotic ectodermal dysplasia, and immunodeficiency in a boy and incontinentia pigmenti in his mother. *Pediatrics* 2002;109:e97.
- [86] Mansour S, Woffendin H, Mitton S, et al. Incontinentia pigmenti in a surviving male is accompanied by hypohidrotic ectodermal dysplasia and recurrent infection. *Am J Med Genet* 2001;99:172–7.
- [87] Schmid JM, Junge SA, Hossle JP, et al. Transient hemophagocytosis with deficient cellular cytotoxicity, monoclonal immunoglobulin M gammopathy, increased T-cell numbers, and hypomorphic NEMO mutation. *Pediatrics* 2006;117:e1049–56.
- [88] Frix CD 3rd, Bronson DM. Acute miliary tuberculosis in a child with anhidrotic ectodermal dysplasia. *Pediatr Dermatol* 1986;3:464–7.
- [89] Sitton JE, Reimund EL. Extramedullary hematopoiesis of the cranial dura and anhidrotic ectodermal dysplasia. *Neuropediatrics* 1992;23:108–10.
- [90] Carrol ED, Gennery AR, Flood TJ, et al. Anhidrotic ectodermal dysplasia and immunodeficiency: the role of NEMO. *Arch Dis Child* 2003;88:340–1.

- [91] Nishikomori R, Akutagawa H, Maruyama K, et al. X-linked ectodermal dysplasia and immunodeficiency caused by reversion mosaicism of NEMO reveals a critical role for NEMO in human T-cell development and/or survival. *Blood* 2004;103:4565–72.
- [92] Orange JS, Brodeur SR, Jain A, et al. Deficient natural killer cell cytotoxicity in patients with IKK- gamma/NEMO mutations. *J Clin Invest* 2002;109:1501–9.
- [93] Orstavik KH, Kristiansen M, Knudsen GP, et al. Novel splicing mutation in the NEMO (IKK-gamma) gene with severe immunodeficiency and heterogeneity of X-chromosome inactivation. *Am J Med Genet A* 2006;140:31–9.
- [94] Smythe WR, Bridges ND, Gaynor JW, et al. Bilateral sequential lung transplant for ectodermal dysplasia. *Ann Thorac Surg* 2000;70:654–6.
- [95] Tono C, Takahashi Y, Terui K, et al. Correction of immunodeficiency associated with NEMO mutation by umbilical cord blood transplantation using a reduced-intensity conditioning regimen. *Bone Marrow Transplant* 2007;39:801–4.
- [96] Niehues T, Reichenbach J, Neubert J, et al. A NEMO-deficient child with immunodeficiency yet without anhidrotic ectodermal dysplasia. *J Allergy Clin Immunol* 2004;114:1456–62.
- [97] Orange JS, Levy O, Brodeur SR, et al. Human nuclear factor kappa B essential modulator mutation can result in immunodeficiency without ectodermal dysplasia. *J Allergy Clin Immunol* 2004;114:650–6.
- [98] von Bernuth H, Puel A, Ku CL, et al. Septicemia without sepsis: inherited disorders of nuclear factor-kappa B-mediated inflammation. *Clin Infect Dis* 2005;41:S436–9.
- [99] Jain A, Ma CA, Lopez-Granados E, et al. Specific NEMO mutations impair CD40-mediated c-Rel activation and B cell terminal differentiation. *J Clin Invest* 2004;114:1593–602.
- [100] Lee WI, Torgerson TR, Schumacher MJ, et al. Molecular analysis of a large cohort of patients with the hyper immunoglobulin M (IgM) syndrome. *Blood* 2005;105:1881–90.
- [101] Souto-Carneiro MM, Fritsch R, Sepulveda N, et al. The NF- κ B canonical pathway is involved in the control of the exonucleolytic processing of coding ends during V(D)J recombination. *J Immunol* 2008;180:1040–9.
- [102] Courtois G, Smahi A, Reichenbach J, et al. A hypermorphic IkappaBalpha mutation is associated with autosomal dominant anhidrotic ectodermal dysplasia and T cell immunodeficiency. *J Clin Invest* 2003;112:1108–15.
- [103] Janssen R, van Wengen A, Hoeve MA, et al. The same IkappaBalpha mutation in two related individuals leads to completely different clinical syndromes. *J Exp Med* 2004;200:559–68.
- [104] McDonald DR, Mooster JL, Reddy M, et al. Heterozygous N-terminal deletion of IkappaBalpha results in functional nuclear factor kappaB haploinsufficiency, ectodermal dysplasia, and immune deficiency. *J Allergy Clin Immunol* 2007;120:900–7.
- [105] Dupuis-Girod S, Cancrini C, Le Deist F, et al. Successful allogeneic hemopoietic stem cell transplantation in a child who had anhidrotic ectodermal dysplasia with immunodeficiency. *Pediatrics* 2006;118:e205–11.
- [106] Picard C, Puel A, Bonnet M, et al. Pyogenic bacterial infections in humans with IRAK-4 deficiency. *Science* 2003;299:2076–9.
- [107] Janeway CA Jr, Medzhitov R. Innate immune recognition. *Annu Rev Immunol* 2002;20:197–216.
- [108] Ku CL, von Bernuth H, Picard C, et al. Selective predisposition to bacterial infections in IRAK-4-deficient children: IRAK-4-dependent TLRs are otherwise redundant in protective immunity. *J Exp Med* 2007;204:2407–22.
- [109] Yang K, Puel A, Zhang S, et al. Human TLR-7-, -8-, and -9-mediated induction of IFN-alpha/beta and -lambda is IRAK-4 dependent and redundant for protective immunity to viruses. *Immunity* 2005;23:465–78.
- [110] Chapel H, Puel A, von Bernuth H, et al. *Shigella sonnei* meningitis due to interleukin-1 receptor-associated kinase-4 deficiency: first association with a primary immune deficiency. *Clin Infect Dis* 2005;40:1227–31.

- [111] Comeau JL, Lin TJ, Macken MB, et al. Staphylococcal pericarditis, and liver and paratracheal abscesses as presentations in two new cases of interleukin-1 receptor associated kinase 4 deficiency. *Pediatr Infect Dis J* 2008;27:170–4.
- [112] Day N, Tangsinmankong N, Ochs H, et al. Interleukin receptor-associated kinase (IRAK-4) deficiency associated with bacterial infections and failure to sustain antibody responses. *J Pediatr* 2004;144:524–6.
- [113] Enders A, Pannicke U, Berner R, et al. Two siblings with lethal pneumococcal meningitis in a family with a mutation in interleukin-1 receptor-associated kinase 4. *J Pediatr* 2004;145: 698–700.
- [114] Lavine E, Somech R, Zhang JY, et al. Cellular and humoral aberrations in a kindred with IL-1 receptor-associated kinase 4 deficiency. *J Allergy Clin Immunol* 2007;120:948–50.
- [115] McDonald DR, Brown D, Bonilla FA, et al. Interleukin receptor-associated kinase-4 deficiency impairs Toll-like receptor-dependent innate antiviral immune responses. *J Allergy Clin Immunol* 2006;118:1357–62.
- [116] Medvedev AE, Lentschat A, Kuhns DB, et al. Distinct mutations in IRAK-4 confer hyporesponsiveness to lipopolysaccharide and interleukin-1 in a patient with recurrent bacterial infections. *J Exp Med* 2003;198:521–31.
- [117] Medvedev AE, Thomas K, Awomoyi A, et al. Cutting edge: expression of IL-1 receptor-associated kinase-4 (IRAK-4) proteins with mutations identified in a patient with recurrent bacterial infections alters normal IRAK-4 interaction with components of the IL-1 receptor complex. *J Immunol* 2005;174:6587–91.
- [118] Takada H, Yoshikawa H, Imaizumi M, et al. Delayed separation of the umbilical cord in two siblings with interleukin-1 receptor-associated kinase 4 deficiency: rapid screening by flow cytometer. *J Pediatr* 2006;148:546–8.
- [119] von Bernuth H, Ku CL, Rodriguez-Gallego C, et al. A fast procedure for the detection of defects in Toll-like receptor signaling. *Pediatrics* 2006;118:2498–503.
- [120] Aurelius E, Johansson B, Skoldenberg B, et al. Encephalitis in immunocompetent patients due to herpes simplex virus type 1 or 2 as determined by type-specific polymerase chain reaction and antibody assays of cerebrospinal fluid. *J Med Virol* 1993;39:179–83.
- [121] Dennett C, Cleator GM, Klapper PE. HSV-1 and HSV-2 in herpes simplex encephalitis: a study of sixty-four cases in the United Kingdom. *J Med Virol* 1997;53:1–3.
- [122] Nahmias AJ, Whitley RJ, Visintine AN, et al. Herpes simplex virus encephalitis: laboratory evaluations and their diagnostic significance. *J Infect Dis* 1982;145:829–36.
- [123] Whitley RJ, Kimberlin DW. Herpes simplex encephalitis: children and adolescents. *Semin Pediatr Infect Dis* 2005;16:17–23.
- [124] Najioullah F, Bosshard S, Thouvenot D, et al. Diagnosis and surveillance of herpes simplex virus infection of the central nervous system. *J Med Virol* 2000;61:468–73.
- [125] Puchhammer-Stockl E, Presterl E, Croy C, et al. Screening for possible failure of herpes simplex virus PCR in cerebrospinal fluid for the diagnosis of herpes simplex encephalitis. *J Med Virol* 2001;64:531–6.
- [126] Skoldenberg B, Forsgren M, Alestig K, et al. Acyclovir versus vidarabine in herpes simplex encephalitis. Randomised multicentre study in consecutive Swedish patients. *Lancet* 1984;2:707–11.
- [127] Abel L, Plancoulaine S, Jouanguy E, et al. Submitted for publication, 2008.
- [128] Whitley RJ, Gnann JW. Viral encephalitis: familiar infections and emerging pathogens. *Lancet* 2002;359:507–13.
- [129] Whitley RJ, Soong SJ, Linneman C Jr, et al. Herpes simplex encephalitis. Clinical assessment. *JAMA* 1982;247:317–20.
- [130] Smith M, Lennette EH, Reames HR. Isolation of the virus of herpes simplex and the demonstration of intranuclear inclusions in a case of acute encephalitis. *Am J Pathol* 1941;17:55–69.
- [131] Zarafonetis CJD, Smodel MCJWA, Haymaker W, et al. Fatal herpes simplex encephalitis in man. *Am J Pathol* 1944;20:429–45.

- [132] Nahmias AJ, Francis KL, Beckman-Nahmias S. The natural history and epidemiology of herpes simplex viruses. New York: Taylor & Francis Group; 2006.
- [133] Nahmias AJ, Lee FK, Beckman-Nahmias S. Sero-epidemiological and -sociological patterns of herpes simplex virus infection in the world. *Scand J Infect Dis Suppl* 1990;69:19–36.
- [134] Bergstrom T, Alestig K, Svennerholm B, et al. Neurovirulence of herpes simplex virus types 1 and 2 isolates in diseases of the central nervous system. *Eur J Clin Microbiol Infect Dis* 1990;9:751–7.
- [135] Izumi KM, Stevens JG. Molecular and biological characterization of a herpes simplex virus type 1 (HSV-1) neuroinvasiveness gene. *J Exp Med* 1990;172:487–96.
- [136] Norberg P, Bergstrom T, Rekabdar E, et al. Phylogenetic analysis of clinical herpes simplex virus type 1 isolates identified three genetic groups and recombinant viruses. *J Virol* 2004;78:10755–64.
- [137] Sivadon V, Lebon P, Rozenberg F. Variations of HSV-1 glycoprotein B in human herpes simplex encephalitis. *J Neurovirol* 1998;4:106–14.
- [138] Gazquez I, Jover A, Puig T, et al. Familial herpes encephalitis. *Lancet* 1996;347:910.
- [139] Jackson AC, Melanson M, Rossiter JP. Familial herpes simplex encephalitis. *Ann Neurol* 2002;51:406–7.
- [140] Koskiniemi M, Saarinen A, Klapper PE, et al. Familial herpes encephalitis. *Lancet* 1995;346:1553.
- [141] Lerner AM, Levine DP, Reyes MP. Two cases of herpes simplex virus encephalitis in the same family. *N Engl J Med* 1983;308:1481.
- [142] Lin WR, Wozniak MA, Esiri MM, et al. Herpes simplex encephalitis: involvement of apolipoprotein E genotype. *J Neurol Neurosurg Psychiatry* 2001;70:117–9.
- [143] Nicoll JA, Martin L, Stewart J, et al. Involvement of apolipoprotein E in herpes simplex encephalitis. *Neuroreport* 2001;12:695–8.
- [144] Rudd BD, Smit JJ, Flavell RA, et al. Deletion of TLR3 alters the pulmonary immune environment and mucus production during respiratory syncytial virus infection. *J Immunol* 2006;176:1937–42.
- [145] Zhao T, Yang L, Sun Q, et al. The NEMO adaptor bridges the nuclear factor-kappaB and interferon regulatory factor signaling pathways. *Nat Immunol* 2007;8:592–600.
- [146] Casrouge A, Zhang SY, Eidenschenk C, et al. Herpes simplex virus encephalitis in human UNC-93B deficiency. *Science* 2006;314:308–12.
- [147] Brinkmann MM, Spooner E, Hoebe K, et al. The interaction between the ER membrane protein UNC93B and TLR3, 7, and 9 is crucial for TLR signaling. *J Cell Biol* 2007;177:265–75.
- [148] Tabeta K, Hoebe K, Janssen EM, et al. The Unc93b1 mutation 3d disrupts exogenous antigen presentation and signaling via Toll-like receptors 3, 7 and 9. *Nat Immunol* 2006;7:156–64.
- [149] Zhang SY, Jouanguy E, Ugolini S, et al. TLR3 deficiency in patients with herpes simplex encephalitis. *Science* 2007;317:1522–7.
- [150] Prehaud C, Megret F, Lafage M, et al. Virus infection switches TLR-3-positive human neurons to become strong producers of beta interferon. *J Virol* 2005;79:12893–904.
- [151] Bsibsi M, Ravid R, Gveric D, et al. Broad expression of Toll-like receptors in the human central nervous system. *J Neuropathol Exp Neurol* 2002;61:1013–21.
- [152] Jack CS, Arbour N, Manusow J, et al. TLR signaling tailors innate immune responses in human microglia and astrocytes. *J Immunol* 2005;175:4320–30.
- [153] Bello-Morales R, Fedetz M, Alcina A, et al. High susceptibility of a human oligodendroglial cell line to herpes simplex type 1 infection. *J Neurovirol* 2005;11:190–8.
- [154] Lokensgard JR, Hu S, Sheng W, et al. Robust expression of TNF-alpha, IL-1beta, RANTES, and IP-10 by human microglial cells during nonproductive infection with herpes simplex virus. *J Neurovirol* 2001;7:208–19.
- [155] Whitley RJ. Herpes simplex encephalitis: adolescents and adults. *Antiviral Res* 2006;71:141–8.

- [156] Meylan E, Tschopp J. Toll-like receptors and RNA helicases: two parallel ways to trigger antiviral responses. *Mol Cell* 2006;22:561–9.
- [157] Zhang SY, Jouanguy E, Sancho-Shimizu V, et al. Human Toll-like receptor-dependent induction of interferons in protective immunity to viruses. *Immunol Rev* 2007;220:225–36.
- [158] De Tieg X, Rozenberg F, Heron B. The spectrum of herpes simplex encephalitis in children. *Eur J Paediatr Neurol* 2007;12:72–81.
- [159] Reichenbach J, Rosenzweig S, Doffinger R, et al. Mycobacterial diseases in primary immunodeficiencies. *Curr Opin Allergy Clin Immunol* 2001;1:503–11.
- [160] Sancho-Shimizu V, Zhang SY, Abel L, et al. Genetic susceptibility to herpes simplex virus 1 encephalitis in mice and humans. *Curr Opin Allergy Clin Immunol* 2007;7:495–505.