Chapter 6
Pulmonary Manifestations of Defects in Innate Immunity

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6.1 Introduction

The immune response consists of mechanisms involved in innate immunity and, when necessary, in adaptive immunity. The innate response is phylogenetically older, of a nonspecific nature, and rapid and is coded within the germline, while the adaptive response is antigen specific, has been first described in vertebrates, is slower and of longer duration, and results from somatic DNA recombination.

Examples of the innate immunity components are epithelial barriers, antimicrobial peptides, soluble factors (chemokines and proteins of the complement system), and cell elements (neutrophils, monocytes, and natural killer cells). The humoral and cellular components of the innate immune system are diverse, and their responses are initiated by pattern recognition receptors (PRR) such as Toll-like receptors (TLRs) and NOD-like receptors (NLR, NOD), which recognize the pathogen-associated molecular patterns (PAMPs).

The innate immune responses play a fundamental role in the control of infections by interfering with the replication and/or viability of the pathogen, in addition to favoring the development of adaptive immunity [1]. The important role of innate immunity in the defense against infections can be clearly seen by the presence of severe infections secondary to the intrinsic defects of this immunity sector.

The way the innate immune system detects and responds to infections has been clarified at the molecular level; and the function of the system in the defense against various types of pathogens, as well as its importance in the physiopathology of PIDs, is currently being revealed [2].

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This chapter will deal with the main respiratory manifestations occurring in the presence of each innate immunity defect according to the molecular changes involved.

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6.2 Anhidrotic Ectodermal Dysplasia with Immunodeficiency

Anhidrotic ectodermal dysplasia with immunodeficiency (AED-ID) is a rare syndrome characterized by changes in the differentiation of ectoderm-derived structures such as the teeth, hair, and sweat glands and by impaired immunological function. The main clinical abnormalities are conical teeth and teeth present in reduced numbers, scarcity of body and scalp hair, reduced or absent sweating, and severe repeated infections.

According to genetic inheritance, AED-ID can be classified into recessive X-linked and autosomal dominant (AD) forms.

X-linked AED-ID is caused by hypomorphic mutations of the gene that codes for the kinase κB inhibitor gene (*IKBKG*), also known as NF-κB essential modulator (*NEMO*), a regulatory component of the IκB (IKK) complex necessary for the activation of the κB nuclear transcription factor (NF-κB) [3]. NF-κB is a regulatory protein of the immunoglobulin gene expression in B lymphocytes, immune response, inflammatory reactions, and protection against apoptosis, among other functions [4].

Members of the NF-κB family are present in the cell cytoplasm, linked to NF-κB inhibitors (IκB). During cellular activation, signals are generated that lead to the activation of IKK, which phosphorylates IκB in specific serine residues, promoting their ubiquitination and degradation by the proteasome, permitting translocation of the NF-κB complex to the nucleus for the activation of its target genes [3].

Approximately 43 mutations that impair NF-κB activation have been reported thus far [5].

The main disorder detected in X-linked AED-ID is related to the NEMO-dependent NF-κB activation by TLR and interleukin 1 (TIR: TLR, IL-1R, and IL-18R) and by tumor necrosis factor receptors (TNF-R: TNF-αR and CD40) [3].

The immunological investigation of patients with this disease may reveal various changes such as deficiency of specific anti-polysaccharide antibodies, low serum IgG levels [3], and variable IgA, IgM, and IgE levels, as well as increased IgM in some cases. Abnormal CD40-CD40L signaling is observed in some individuals [6] and reduced natural killer cell activity in others, causing these patients to be more

susceptible to mycobacterial infections. Patients usually have normal numbers of naive and memory T-cells [3].

The degree of impairment of the various pathways of NEMO activation depends on the type of mutation. In general, patients fail to produce IL-10 in response to activation with TNF-α, and many of them show an impaired antibody response, especially glycans, including pneumococcal capsules. These characteristics are the result of defective signaling by the signaling pathway of the ectodysplasin receptor (EDA-R). More recently, mutations in the leucine zipper domain of the *NEMO* gene have been diagnosed as the X-linked form of Mendelian susceptibility to mycobacterial diseases (MSMD), demonstrating the important role of NEMO in the IL-12/IFNγ pathway.

The AD form of AED-ID, also known as IκBα gain-of-function (GOF) mutation, is caused by a hypermorphic heterozygous *IKBA* mutation that prevents the phosphorylation and degradation of the NF-κB α inhibitor (IκBα), resulting in partial retention of NF-κB dimers in the cytoplasm. These dimers are involved in various pathways, including those triggered by members of the TNF-R, IL-1R, TLR, T-cell receptor (TCR), and B-cell receptor (BCR) families [5]. The quantity of mutant IκBα inside the cell, its binding affinity for NF-kB, and its resistance to degradation determine the degree of GOF and consequently the levels of NF-kB inhibition in heterozygous cells [7].

IκBα deficiency involves a severe impairment of TCR signaling. The patients exhibit hypogammaglobulinemia with the absence of production of specific antibodies. Some patients also have low proportions of CD4 and CD8 memory T-cells and of memory B-cells, few or no T γ/δ cells, and severe impairment of T-cell proliferation in response to anti-CD3 [5].

Children with both X-linked and AD forms of AED-ID suffer recurrent infections by variable pathogens such as capsulated pyogenic bacteria, mycobacteria, viruses, and fungi [3], with respiratory manifestations being the most frequent consequences.

Pneumococcal infections are the most frequent ones in these patients, probably due to the impaired responses related to TLR and IL-1R [5, 8], followed by *Haemophilus influenzae* and *Staphylococcus aureus* infections causing recurrent pneumonias and bronchiectasia [5].

Patients with AD mutations in *IKBA* suffer from severe pyogenic bacterial infections, especially pneumonias, due to β hemolytic type A streptococcus, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Serratia marcescens*.

Infections with atypical mycobacteria such as *Mycobacterium avium*, *Mycobacterium bovis*, and *Mycobacterium kansasii* are also frequent in patients with *NEMO* mutations with defects of CD40-CD40L signaling and changes in the immunity mediated by the IL-12/IFNγ pathway [3, 8], with consequent recurrent pneumonias, bronchiectasis, and pulmonary fibrosis. These patients also can present viral respiratory infections, especially those induced by cytomegalovirus and adenovirus, as well as respiratory infections caused by opportunistic fungi such as

Pneumocystis jirovecii [8]. About one-third of *NEMO*-deficient patients can die from invasive infections.

6.3 LUBAC Deficiency

The linear ubiquitin chain assembly complex (LUBAC), consisting of SHANK-associated RH domain-interacting protein (SHARPIN), heme-oxidized IRP2 ubiquitin ligase-1 (HOIL-1), and HOIL-1-interacting protein (HOIP), is an important regulator of inflammation and of the innate response signaling [9]. HOIL-1 L and SHARPIN are accessory HOIP proteins.

Ubiquitination was initially described as a mechanism of protein labeling as targets for degradation by proteasome. However, today we know that ubiquitination is involved in several other cell functions such as activation of the canonic NF-κB pathways, which occurs in a relatively rapid manner through stimuli from proinflammatory cytokines and PAMPs, such as lipoproteins and bacterial liposaccharides (LPS).

The stimulation of retinoic acid-inducible gene (RIG)-like receptors, TLRs, and NOD-like receptors induces NF-κB activation of type I IFN production. Recent studies have indicated that LUBAC regulates the responses of the immune system via TLR, NOD, and RIG.

Rats with spontaneous SHARPIN deficiency, denoted as carriers of chronic proliferative dermatitis in mice (CPDM), exhibit, in addition to dermatitis, splenomegaly, defects of secondary lymphoid organs, and significantly low serum IgG, IgA, and IgE levels. On this basis, it was discovered that SHARPIN is a physiological LUBAC component interacting with HOIP and that the lack of SHARPIN in rats with CPDM causes LUBAC destabilization resulting in impaired NF-κB signaling. The severe immunodeficiency detected in rats with CPDM resembles that of patients with X-linked AED-ID caused by mutation of the *NEMO* gene [10].

The immunological investigation of patients with LUBAC deficiency reveals lymphopenia, memory B-cell deficiency, deficient production of specific antibodies, and hypogammaglobulinemia [11].

Thus, patients with LUBAC deficiency mainly suffer recurrent respiratory infections, especially pneumonias caused by pyogenic bacteria and *Streptococcus pneumoniae*, due to deficient production of specific antibodies against pneumococcal glycans [12].

6.4 IRAK-4 and MyD88 Deficiencies

IRAK-4 is a kinase protein that plays a fundamental role in the signaling of the TLR family (except for TLR3). After recognizing the pathogens, TLRs trigger intracellular signaling pathways resulting in the induction of inflammatory cytokines and

type I INF. TLRs share with members of the IL-1R family an intracellular domain denoted Toll-interleukin-1 receptor (TIR) domain. MyD88 is a cytosolic adaptor molecule that connects TLRs and IL-1Rs to the IRAK complex. The MyD88- and IRAK-4-dependent TIR pathways lead to the production of proinflammatory cytokines.

IRAK deficiency is an autosomal recessive (AR) immunodeficiency caused by homozygous or heterozygous *IRAK4* gene mutations.

MyD88 deficiency is an AR immunodeficiency caused by homozygous or heterozygous *MyD88* gene mutations.

The immunological investigation of patients with IRAK4 and MyD88 deficiency does not reveal changes in leukocyte development or in the proliferative responses of B and T-cells to specific antigens. However, patients can show impairment of neutrophil migration, markedly reduced marginal zone B ($IgM^+IgD^+CD27^+$) cells, and impairment of specific IgG and IgM antibody responses to pneumococcal infections and isohemagglutinins (in up to half the patients). Some patients also exhibit increased serum IgE and IgG4 concentrations, although no association with allergic asthma occurs in these individuals [5].

The clinical signs and symptoms of affected patients are variable, with greater susceptibility to severe and invasive infections caused by pyogenic bacteria, but with normal resistance to viruses, fungi, parasites, and other bacteria. The main invasive bacterial infections of these patients are caused by *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. In more than 90% of patients, the first bacterial infection occurs at 2 years of age, with high lethality.

These patients also have noninvasive infections by pyogenic bacteria that affect the upper respiratory tract, manifesting as otitis, sinusitis, tonsillar abscess, necrotizing epiglottitis, pharyngitis, palatine infection, and pneumonia. The principal bacteria involved in this type of infection are also *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Streptococcus pneumoniae*.

Both immunodeficiencies tend to improve with age, with the patients no longer suffering invasive infections by pyogenic bacteria after adolescence. However, all patients continue to have noninvasive infections such as sinusitis and pneumonia even during adult life [5].

6.5 Herpes Simplex Encephalitis (TLR3, UNC93B1, TRAF3, TRIF, TBK1, IRF3 Deficiencies)

This group of inherited deficiencies involves defects of TLR3 signaling and susceptibility to herpes simplex encephalitis (HSE) caused by herpes simplex virus-1 (HSV-1) during childhood, a rare and potentially fatal manifestation [13].

The affected patients carry mutations in the *TLR3*, *UNC93B1*, *TRAF3*, *TRIF*, *TBK1*, or *IRF3* genes. The signaling pathway controlled by TRIF is mediated by TLR3 and TLR4 and leads to activation of the transcription factors IRF3 and NF-kB. TRIF recruits TRAF6, activates TAK1 for NF-kB activation, and also

recruits a signaling complex consisting of TBK1 and IKKε via TRAF3 for IRF3 activation. This signaling pathway results in the production of inflammatory cytokines and type I and III IFN with an important antiviral response [8].

Single-gene inborn errors of TLR3 immunity such as TLR3, UNC93B1, TRAF3, TRIF, TBK1, and IRF3 deficiencies predispose some individuals to HSE [14]. Heterozygous mutations of *TLR3* have been reported to cause HSE in children. The AD form is the most common trait. AR UNC93B deficiency has been identified as the first genetic etiology of isolated HSE. AD TRAF3 deficiency and HSE have been described in a French patient 7 years ago. TRIF deficiency associated with HSE was recently described in two kindreds (the first patient with a homozygous nonsense mutation resulting in complete absence of protein and the other with a heterozygous missense mutation). TBK1 deficiency associated with HSE has been reported in two kindreds that carried different heterozygous mutations, both associated with an AD trait. In a 2015 report, heterozygous mutation of *IRF3* was found to be associated with HSE, leading to impaired signaling trough the TLR3-TRIF pathway [15].

The peripheral blood mononuclear cells of patients with TLR3, UNC93B1, TRAF3, TRIF, TBK1, and IRF3 deficiency do not produce type I or III IFN (especially IFNα, β, and λ) [8, 16] in an appropriate manner or fibroblasts after infection with HSV-1 or vesicular stomatitis virus. Deficient IFN production by fibroblasts and induced pluripotent stem cells (iPSC) derived from the central nervous system (CNS) results in viral replication and increased cell death [13].

Despite their multiple affected TLRs, patients with UNC93B1, TLR3, TRAF3, TRIF, TBK1, and TRF3 deficiency seem to suffer only herpes simplex encephalitis, with no systemic or cutaneous HSV-1 and without any other severe viral infections [8]. Some patients are asymptomatic, while others may have neurological sequelae such as blindness and epilepsy.

6.6 Mendelian Susceptibility to Mycobacterial Diseases (IFNγ Receptor 1/2 Deficiencies, IL-12/23 Receptor β1 Chain Deficiency, IL-12p40 Deficiency, AD STAT1 Deficiency, LZ-NEMO Deficiency, Macrophage-Specific CYBB Deficiency, AD IRF8 Deficiency, ISG15 Deficiency)

Most PIDs exhibit Mendelian inheritance, with mutation in single genes. However, many factors contribute to the phenotypic expression of Mendelian PIDs in addition to gene mutations, such as possible mitochondrial and somatic mutations and the infectious environment.

The MSMD is a rare genetic syndrome that predisposes to infections caused by mycobacteria of low virulence such as strains of the BCG vaccine and nontuberculous environmental mycobacteria (EM). However, compromised individuals are also vulnerable to more virulent species such as *Mycobacterium tuberculosis*. On the

other hand, most patients are resistant to infections caused by all other pathogens, except for isolated cases of disease caused by intracellular bacteria such as *Nocardia* and *Listeria*, intracellular fungi such as *Paracoccidioides* and *Histoplasma*, intracellular parasites such as *Leishmania*, and some viruses such as herpes virus [8]. Some of these infections must share pathogenic mechanisms with MSMD because of their similar tropism for macrophages and clinical manifestations [17].

After contact with these intracellular mechanisms, macrophages secrete IL-12, which binds to its receptors (IL-12Rβ1 and IL-12Rβ2) on the surface of T and NK cells, culminating with the secretion of IFNγ by these cells. IFNγ, in turn, binds to its receptors (IFNγR1 and IFNγR2) on macrophages, activating genes such as IL-12 and respiratory burst NADPH oxidase, which permit the macrophages to destroy the pathogen. On this basis, IFNγR1 and IFNγR2, STAT1, IL-12B, and IL-12Rβ1 are involved in the immunity mediated by the IFNγ-dependent pathway of IL-12/23. Mutations in *IFNGR1*, *IFNGR2*, and *STAT1* impair the cellular response to IFNγ, while mutations in *IL12B* and *IL12Rβ1* impair the production of IL-12-/23-dependent IFNγ.

In addition, *IRF8* mutations have been reported to impair IL-12 secretion by monocytes and dendritic cells. Furthermore, *CYBB* mutations are responsible for X-linked MSMD [18].

6.6.1 IFNγR1 Deficiency

The high frequency of parental consanguinity and the occurrence of MSMD among siblings born to unaffected parents are more probably inherited as an AR trait, although there are cases of AD IFNγR1 deficiency.

The AR complete IFNγR1 deficiency was the first genetic etiology of MSMD to be identified at the molecular level in patients with lack of receptor expression. The lack or dysfunction of IFNγR1 does not permit the recognition of IFNγ, which is detected at high levels in the cytoplasm of affected patients. Patients with AR complete IFNγR1 deficiency suffer early, severe, and fatal infections with BCG and EM pathogens such as *Mycobacterium fortuitum*, *Mycobacterium chelonae*, *Mycobacterium smegmatis*, and *Mycobacterium peregrinum*, which are the most frequent among these patients. Other infections caused by viruses such as herpes virus 8, cytomegalovirus, respiratory syncytial virus, and *Listeria monocytogenes* have been separately detected in patients.

Patients with AR partial IFNγR1 deficiency, in turn, have residual responses to high IFNγ concentrations and for this reason have less severe clinical manifestations.

Patients with dominant IFNγR1 deficiency commonly suffer from recurrent EM and BCG infections with less severe clinical signs and symptoms than patients with complete deficiency. In addition, mycobacterial infection usually occurs later, and the intervals between infections are longer. Other infections caused by pathogens such as *Histoplasma capsulatum* have been detected as isolated infections in patient with this type of alteration [17].

6.6.2 IFNγR2 Deficiency

Based on the cellular response to IFNγ, IFNγ2R deficiency may be complete (undetectable response to IFNγ) or partial (residual response to IFNγ).

The clinical manifestations are similar to those of patients with AR IFNγR1 deficiency, and the major pathogens detected include *Mycobacterium bovis* of BCG, *Mycobacterium avium*, and *Mycobacterium fortuitum* [17].

6.6.3 IL-12/23 Receptor β1 Chain Deficiency

IL-12 comprises two subunits, p35 and p40, respectively, encoded by the *IL12A* and *IL12B* genes. IL-23 also comprises the p40 subunit. Both IL-12 and IL-23 bind to the IL-12 receptor β-subunit chain (IL-12Rβ1).

IL-12 binding to IL-12Rβ1 in T lymphocytes and NK cells induces the production of IFNγ, while IL-23 binding to IL-12Rβ1 and IL-23R promotes the production of IL-17.

IL-12Rβ1 deficiency is the most frequent known genetic cause of MSMD and can be seen in about 40% of the patients. The mutations are of the loss-of-function type and cause complete recessive deficiency [18, 19]. The activated T and NK lymphocytes of affected patients do not express IL-12Rβ1 on their surface.

BCG diseases and salmonellosis are the infections most frequently affecting these patients. Severe tuberculosis conditions may also appear in affected patients. Granulomas can still be formed in the lungs but are often multibacillary.

Other infections such as leishmaniasis and paracoccidioidomycosis have been detected in isolated cases [17].

6.6.4 IL-12p40 Deficiency

Deficiency of the *IL12B* gene, which codes for the IL-12p40 subunit, causes greater predisposition to BCG, *Mycobacterium tuberculosis*, and EM infections. Fungal *Candida* infections and infections with bacteria such as *Klebsiella* and *Nocardia* appear in isolated cases [17, 19]. The clinical picture is similar to that of IL-12Rβ1 deficiency but is mostly more severe.

6.6.5 AD STAT1 Deficiency

STAT1 is required for cellular responses to both type I (IFNα/β) and type II (IFNγ) interferons. Heterozygous missense mutations in *STAT1* cause partial dominant STAT1 deficiency. These mutations mostly compromise IFNγ. Thus, the patients

show predisposition only to mycobacterial infections, without increased susceptibility to severe viral infections.

The disease resembles that induced by partial forms of AR IFNγR1 and IFNγR2 deficiencies, and the patients may exhibit conditions ranging from atypical mycobacterial infections to more severe types of pulmonary tuberculosis [17].

6.6.6 LZ-NEMO Deficiency

Mutations in the leucine zipper domain of the *NEMO* gene (LZ-NEMO) were identified in the 1990 decade in male patients of the same family with *Mycobacterium avium* infections and no other opportunistic infections, defining a recessive X-linked cause of MSMD [17].

Patients selectively exhibit reduction of CD40-dependent IL-12 induction in mononuclear cells [20] resulting in deficient IFNγ production.

Most of the infections detected in these patients are limited to mycobacteria, especially *Mycobacterium avium*. Infection with *Haemophilus influenzae* b has been described in isolated cases [17].

6.6.7 Macrophage-Specific CYBB Deficiency

Chronic granulomatous disease (CGD) is characterized by the failure of phagocyte NADPH oxidase to generate superoxides in order to fight the pathogens and is due to mutations in the *CYBB* gene. Patients with mutations in this gene are more susceptible to infection with various catalase-positive pathogens, mainly in the mucocutaneous and respiratory systems.

One of the mutations in the *CYBB* gene causes an impaired respiratory burst in monocyte-derived macrophages, but not in granulocytes. Patients with this alteration only exhibit mycobacterial infections, without the remaining infections characteristic of patients with CGD. Therefore, this mutation selectively affects the respiratory burst in macrophages, which is a crucial mechanism for protective immunity to tuberculous mycobacteria [21].

6.6.8 AD IRF8 Deficiency

The interferon regulatory factor 8 (IRF8) is a member of the family of IFN regulator factors that is expressed in high levels in mononuclear phagocytes and regulates the differentiation of macrophages and granulocytes and the development of dendritic cells. It can activate or suppress gene transcription under stimulation by IFNγ, lipopolysaccharides (LPS), and other microbial stimuli. Thus, it plays an important role

in the defense against intracellular pathogens, activating IL-12 production in response to IFNγ.

Patients with AD IRF8 deficiency suffer recurrent infections related to BCG, as well as pulmonary tuberculosis due to *Mycobacterium tuberculosis*, with a rapid development of granulomas [22].

6.6.9 ISG15 Deficiency

The ISG15 (interferon-stimulated gene 15) is an intracellular protein produced by neutrophils, monocytes, lymphocytes, and granulocytes, which acts on T and NK cells, inducing IFNγ production.

Thus, its deficiency impairs the synthesis of IFNγ, rendering ISG15-deficient patients susceptible to mycobacterial infections [23].

6.7 AR STAT1 and STAT2 Deficiency

Signal transducer and activator of transcription-1 (STAT-1) is a protein involved in the transduction of cell responses to IFNα/β, λ, and γ and IL-27 through the formation of two transcriptor factor complexes: the interferon-stimulated gamma factor 3 (ISGF3) composed of STAT1-STAT2-p48/IRF9 trimers and the gamma-activated factor (GAF) comprised of STAT1 homodimers.

Complete AR mutations of *STAT1* lead to a full loss of the STAT1 proteins, and, as a consequence, there is no STAT-dependent response to IFNα/β, λ, and γ. This favors infections with several viruses [8] such as HSV-1, CMV, and respiratory syncytial virus (RSV) [24] and with intracellular bacteria, mainly low-virulence mycobacteria such as BCG vaccine and *Mycobacterium kansasii* [8, 24]. Some infections are similar to those detected in patients with combined T-cell immunodeficiencies but with normal lymphocyte numbers and function of T-cells [24].

A milder form of partial AR STAT1 deficiency has been described in some patients [8], whose cells produce residual quantities of functional STAT1 corresponding to approximately 10–25% of the normal levels, depending on the mutation. The clinical signs and symptoms of these patients are less severe compared to the complete form, with lighter infections with intracellular bacteria such as *Salmonella*, *Mycobacterium avium*, and BCG and with viruses such as CMV, VSR, and HSV-1 [24].

AR STAT2 deficiency is associated with impaired type I IFN signaling and shows incomplete penetrance for various viral infections with diverse signs and symptoms. Severe pneumonitis caused by the measles vaccine strain has been described.

The impaired response to IFNα and infections with more aggressive viruses in patients with AR STAT2 deficiency is part of the phenotype of patients with complete AR STAT1 deficiency, although with a less severe clinical presentation [25].

6.8 Warts, Hypogammaglobulinemia, Infections, Myelokathexis (WHIM Syndrome)

WHIM syndrome is a rare immunodeficiency characterized by warts, hypogammaglobulinemia, infections, and myelokathexis (retention of mature neutrophils in the bone marrow).

Most patients carry heterozygous gain-of-function mutations in the *CXCR4* gene.

The disease should be suspected in any patient with warts, leukopenia, and severe neutropenia. Examination of the bone marrow shows myeloid hypercellularity and morphologic abnormalities consistent with apoptosis (hypersegmented nuclei with long filaments connecting nuclear lobes). Patients can also have variable hypogammaglobulinemia that may affect all isotypes, marked reduction of CD27+ memory B-cells, reduction of T lymphocyte subsets and a proliferative response to mitogens (in some patients only), and reduction in the number and function of dendritic cells contributing to the high susceptibility to specific viral infections [26].

The clinical manifestations usually start in childhood, and in general bacterial infections (especially those due to encapsulated germs) are more frequent than viral ones [27].

Although it has been proposed that infection by human papilloma virus (HPV) is the only one to which patients with WHIM syndrome are susceptible, lymphoproliferative disorders associated with Epstein-Barr virus (EBV), as well as herpes zoster and recurrent serious oral and genital herpes simplex infections, have been reported, demonstrating that these patients have a greater generalized susceptibility to viruses of the herpes family.

Bacterial infections are recurrent, mainly involving the respiratory, gastrointestinal, and cutaneous systems [26]. The respiratory infections mainly manifest as pneumonias and sinusitis due to pathogens such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Proteus mirabilis*. In some cases, recurrent pneumonias may lead to severe bronchiectasis with the possible occurrence of chronic *Pseudomonas aeruginosa* or *Burkholderia cepacia* [27] infection.

6.9 Epidermodysplasia Verruciformis (EV)

Epidermodysplasia verruciformis (EV) is a rare disorder of genetic heterogeneity characterized by abnormal susceptibility to skin infections caused by HPV, whose serotypes are not pathogenic for the healthy population. There is a specific susceptibility to HPV 3 and 10 in plane warts and to HPV 5 and 8 in skin carcinomas. UV light is likely to be involved in the progression from benign warts to malignancy. However, cancers develop slowly, but progressive lesions and metastases have been observed in some patients.

The lesions usually arise in childhood or at the beginning of adolescence and are highly resistant to treatment.

The main manifestations of EV are hypo- and hyperpigmented reddish squamous maculae, wart-like papillomatous lesions, seborrheic keratosis lesions, and versicolor pityriasis lesions. Skin lesions tend to disseminate throughout the body, although the mucosal membranes are spared.

The *EVER1* (*TMC6*) and *EVER2* (*TMC8*) genes are involved in resistance against skin infections caused by HPV mostly by regulating the distribution of intracellular zinc and by inducing TNF-α, which is important for the prevention of HPV persistence inside the cells.

Most patients present mutations in the *EVER1* and *EVER2* genes. Both mutations code for proteins that inhibit essential transcription factors and that negatively regulate cell-mediated immunity.

EV-like disease has been described in some T-cell deficiencies such as SCID and mutations in the *RHOH*, *MST1*, *CORO1A*, and *IL-7* genes.

Patients with mutations in *RHOH* suffer bronchopulmonary diseases, patients with mutations in *CORO1A* have a high risk of bronchiectasis, and a patient with mutation in *MST1* has been reported to suffer recurrent chronic pulmonary infections [28].

6.10 Chronic Mucocutaneous Candidiasis (IL-17RA Deficiency, IL-17F Deficiency, ACT1 Deficiency, STAT1 Gain of Function)

Chronic mucocutaneous candidiasis (CMC) is a term that describes a group of clinical phenotype presenting as recurring or persistent infections of the skin, nails, and mucous membranes caused by yeast *Candida*, mostly *albicans*, but alternatively by other strains (*C. glabrata*, *C. krusei*, *C. dubliniensis*).

Resistance and tolerance mechanisms participate to the interplay between host and pathogens. IL-17- mediated response has been shown to be crucial for host resistance to respiratory infections, whereas its role in host tolerance during chronic airway colonization is still unclear.

Evidence suggests that CMC can be present in patients with primary defects affecting both the adaptive and innate immunities that activate Th17 pathway. IL-17-mediated immunity plays a double-edged activity during chronic airway infection: on one side, it contributes to the control of *Pseudomonas aeruginosa* burden, modulating host resistance, while, on the other, it alters host tolerance, propagating exacerbated pulmonary neutrophilia and tissue remodeling [29].

6.10.1 *IL-17RA and IL17F Deficiency*

Studies of Th17 cells and IL-17A have revealed important roles for IL-17A in the development of allergic and autoimmune diseases as well as in protective mechanisms against bacterial and fungal infections, functions that were previously believed to be mediated by Th1 or Th2 cells [30].

Th17 cytokines protect hosts from pathogens at epithelial and mucosal tissues including the skin, lungs, and intestine. Both IL-17A and IL-17F enhance protective immune responses by inducing the production of CXC chemokines, G-CSF, and antimicrobial peptides in epithelial cells and keratinocytes. Indeed, studies using cytokine- and receptor-deficient mice showed that IL-17A and IL-17F were required for responses to *Klebsiella pneumoniae* in the lungs [31].

6.10.2 **ACT1** *Deficiency*

ACT1 is an adaptor protein acting downstream from IL-17RA, IL-17RC, and IL-17RB in humans [32]. Mouse fibroblasts lacking ACT1 display low levels of KC/CXCL1 and IL-6 expression in response to stimulation with IL-17A and IL-17F [33]. In addition, abolition of the IL-25-/IL-17E-induced expression of IL-4, IL-5, IL-13, eotaxin-1 (CCL11), and pulmonary eosinophilia has also been observed in the lung tissues of ACT1-deficient mice [34].

6.10.3 **STAT1** *Gain-of-Function (GOF) Mutation*

GOF mutation reduces the dephosphorylation of activated STAT1 protein, leading to accumulation of phosphorylated STAT1 in the nucleus. Persistently activated STAT1 may shift the immune response toward STAT1-dependent interleukin-17 inhibitors and away from STAT3-mediated induction of IL-17 T-cell generation [35]. GOF mutations affecting STAT1 lead to defective IL-17 T-cell development, characterized by reduced production of IL- 17 and IL-22; these cytokines are essential for the antifungal defense of the skin and mucosa. Patients with AD GOF *STAT1* mutations present with CMC [35]. Clinical manifestations include chronic oropharyngeal candidiasis, cutaneous dermatophytosis, and autoimmune phenomena, such as hypothyroidism and autoimmune hepatitis [36].

Respiratory viral infections have been reported like respiratory syncytial virus (RSV) bronchiolitis and influenza infections [37, 38]. Bacterial infections, mostly caused by *S. aureus*, have also frequently been reported [37].

6.11 CARD9 Deficiency

Human CARD9 deficiency is an AR PID caused by biallelic mutations in the gene *CARD9*, which encodes a signaling protein that was found downstream of many C-type lectin receptors (CLRs). CLRs encompass a large family of innate recognition receptors, expressed predominantly by myeloid and epithelial cells, which bind fungal carbohydrates and initiate antifungal immune responses. Although other receptor families are involved in innate antifungal recognition, only mutations in the CLR pathway have thus far been associated with the spontaneous development of fungal infections in humans. CARD9 deficiency is associated with the spontaneous development of persistent and severe fungal infections that primarily localize to the skin and subcutaneous tissue, mucosal surface, and/or central nervous system (CNS) [39].

The first manifestation associated with CARD9 deficiency affects the skin and subcutaneous tissues. Patients in this category present with severe persistent fungal infections of the skin, nails, and scalp, with occasional contiguous dissemination to the subcutaneous layers, lymph nodes, and bones [40].

The second predominant manifestation of human CARD9 deficiency is systemic fungal disease, which primarily manifests as fungal meningoencephalitis caused by *Candida* species. Some patients have also developed bone infection of the vertebra [41]. Less often, CARD9-deficient patients develop phaeohyphomycosis caused by *Exophiala* species that targets the CNS and/or other deep tissues including the liver, bones, and lungs [42].

In relation to the role of CARD9 in neutrophil accumulation during fungal disease, it was demonstrated a neutrophil recruitment defect to the *Aspergillus fumigatus*-infected lung in CARD9−/− mice, which was also linked to poor CXC chemokine production in the lungs [43]. However, in that model, CARD9 was only partially required in the later stages of infection for neutrophil accumulation in the infected lung.

Thus, the collective dependence on CARD9 for neutrophil recruitment during pulmonary mold infections appears relatively mild compared to the universal reliance required for neutrophil accumulation and protection against *Candida* infection in the CNS [44]. This dichotomy observed in mice between the CARD9 dependence for protection against molds and yeasts may help justify why human CARD9 deficiency does not appear to associate with pulmonary fungal infections, despite the continuous environmental exposure to fungal spores.

6.12 Autoimmune Polyendocrinopathy with Candidiasis and Ectodermal Dystrophy (APECED)

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is a rare disorder caused by mutations in the autoimmune regulator (*AIRE*) gene.

Patients with APECED progressively develop multiple organ-specific autoimmunity of endocrine and nonendocrine tissues. Loss of function of the AIRE protein results in decreased expression of self-antigens in medullary thymic epithelial cells and in failure to establish central tolerance to a range of different autoantigens [45].

Although the underlying mechanism is not well understood, some APECED patients have significant pulmonary disease. Recently, in several APECED patients with autoimmune pulmonary disease, a potassium channel regulating protein (KCNRG) preferentially expressed in the epithelial cells of terminal bronchioles was identified as the putative target antigen [46].

Lung disease was described in two Sicilian brothers with APECED. They were compound heterozygotes with R203X/R257X. The elder brother had experienced recurrent lower respiratory infections since 5 years of age and over the years developed severe obstructive lung disease resulting in bronchiectasis, *cor pulmonale*, and terminal respiratory failure, which led to death at 18 years of age. Both brothers had circulating autoantibodies against tryptophan hydroxylase, and serotonin-producing cells were absent in the duodenal mucosa [46].

An obliterating bronchiolitis has been described also in a Hispanic child [47], and another severe fatal chest disease was observed in an adult woman [48].

Finally, in two short reports, other respiratory illnesses were described. Asthma and chronic hypersensitivity pneumonitis were described in a young girl [19, 49] and autoimmune bronchiolitis in four French children and adolescents [9, 50]. In this last report, the authors concluded that autoimmune bronchiolitis is a very rare but potentially life-threatening component of APECED, emphasizing the diversity of autoimmune targets in this disorder.

6.13 Monocyte Deficiencies (GATA2 Deficiency, IRF8 Deficiency)

6.13.1 GATA2 Deficiency

GATA2 is a zinc finger transcription factor essential for differentiation of immature hematopoietic cells. Among many other functions, GATA2 regulates the phagocytosis of alveolar macrophages [51].

GATA2 deficiency is a recently described disorder of hematopoiesis, lymphatics, and immunity, caused by heterozygous mutations leading to haplo-insufficiency of the transcription factor GATA2. The deficiency presents with a complex array of diagnoses and symptoms of varying extent including myelodysplastic syndrome; acute myelomonocytic leukemia; chronic myelomonocytic leukemia; severe viral, disseminated mycobacterial and invasive fungal infections; pulmonary arterial hypertension; warts; panniculitis; human papillomavirus (HPV)-positive tumors; Epstein-Barr virus (EBV)-positive tumors; venous thrombosis; lymphedema; sensorineural hearing loss; miscarriage; and hypothyroidism. Lymphopenia, monocytopenia, and

primary lymphedema also must be considered as part of the disease [52]. Most patients have unremarkable childhood vaccination and infection histories. In relation to infections, nontuberculous mycobacterial infections and general warts are the most common manifestations.

However, *Pneumocystis jiroveci* is not a part of the spectrum of the pathogens that affect these patients; *Pneumocystis jiroveci* pneumonia (PCP) must be considered in patients with profound CD4 dysfunction or lymphopenia. A woman with GATA2 deficiency, lymphedema, lymphopenia, and monocytopenia was described with recurrent PCP, complicated by severe acute respiratory distress syndrome in the setting of influenza A H1N1 coinfection [53]. Experimental mouse models have found a relationship between GATA2 expression and *Pneumocystis jiroveci* infection. Loss of GATA2 production reduces alveolar macrophage phagocytic activity in response to *Pneumocystis jiroveci* infection in mice [52].

Pulmonary alveolar proteinosis is a characteristic feature of *GATA2* mutation that could be reported in about 18% of all subjects with GATA2 deficiency [52].

6.13.2 IRF8 Deficiency

IRF8 is a member of the interferon regulatory factor family that is expressed in myeloid cells such as macrophages and dendritic cells and that activates or represses gene transcription upon stimulation with IFNγ, lipopolysaccharide, and other microbial stimuli. IRF8 plays an important role in several aspects of myeloid cells, including differentiation and maturation of early progenitor cells, expression of intrinsic antimicrobial defenses, and production of the IL-12 cytokine, which is essential for priming of early T-cell-mediated immune response. IRF8 mutant mice are susceptible to a number of intracellular infections including pulmonary tuberculosis [54].

Two types of IRF8 deficiency have been reported. The AR form (due to homozygous K108E mutations) leads to a complete absence of circulating monocytes and dendritic cells. One patient identified with this genotype presented in early infancy with severe disseminated BCG infection, oral candidiasis, severe respiratory viral infection, and striking myeloproliferation [55].

The milder AD form (due to heterozygous T80A mutation) causes selective depletion of circulating dendritic cells. Two patients with this genotype had disseminated BCG disease in early childhood [55].

6.14 NK Cell Deficiencies (MCM4 Deficiency)

Human NK cells play critical role in human innate immune response, particularly the control of viral infection and antitumor surveillance functions. Differing to B and T lymphocytes, NK cells do not possess antigen-receptor rearrangement and do not require pre-activation in order to recognize and lyse target cells.

Patients with genetic defects of human NK cells present a primary immunodeficiency affecting NK cell development (number), function, or both [56]. An impor-

tant tool in the understanding of human NK cells and NK cell subsets has been the discovery of PIDs that affect the generation or homeostasis of NK cells or specific NK cell subsets as well as those that affect NK cell function. There are over 300 genetic deficiencies of human immunity, and nearly 50 are known to have at least some impact on NK cells [57].

Human NK cell deficiencies can be divided into two categories. Those in the first category are characterized by effects on the number of NK cells in the peripheral blood, while effects on the function of NK cells characterize those in the second one. NK cell deficiencies in the first category have been labeled "classical NK cell deficiencies," and those in the second category have been labeled "functional NK cell deficiencies" [58, 59].

The first example of a classical NK cell deficiency was reported in 1989 in a girl with severe varicella and other complicated herpes virus infections [60]. She was determined to stably lack both NK cells in peripheral blood and peripheral blood NK cell cytotoxic activity against the prototypical human NK cell target cell, the K562 erythroleukemia cell line. The first example of a functional NK cell deficiency was described in 1982 in three siblings with severe Epstein-Barr virus infection [61]. All three individuals in this family presented deficient K562 target cell killing activity, and the surviving affected individual has had persistently deficient function over a 30-year period.

6.14.1 MCM4 Deficiency

MCM4 is a highly conserved DNA helicase that is recruited to origins of replication to promote the unwinding and polymerization of chromosomal DNA and cell proliferation [62]. Patients with AR MCM4 deficiency presented with a developmental syndrome including NK cell deficiency. The analyzed patients shared the same spliced defect [63].

The NK cell pattern in the patients is especially unusual. There is a development defect in transition of $CD56^{bright}$ (immature cells) to $CD56^{dim}$ (mature) NK cells, as evidenced by the lack of $CD56^{dim}$ NK cells in the peripheral blood and the preservation of the small $CD56^{bright}$ NK cells[63,64]. This observation suggests that MCM4 is required for terminal NK cell maturation.

Clinically, patients usually present growth retardation, adrenal insufficiency, and lymphoma. From an infectious standpoint, patients can experience complications from EBV, unusual susceptibility to herpes viruses, and presumed complications of viral illness symptoms clinically consistent with an NK cell deficiency [63, 64].

6.15 Pulmonary Alveolar Proteinosis

Pulmonary alveolar proteinosis (PAP) is a rare syndrome characterized by the accumulation of surfactant in alveolar macrophages and alveoli resulting in hypoxemic respiratory failure. These disorders are defined in the context of abnormalities of

surfactant clearance and are caused by disruption of granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling (primary or idiopathic PAP) or by an underlying disease that impairs alveolar macrophage number or functions including surfactant catabolism (secondary PAP) [65].

The primary and the most common clinical form of PAP, which accounts for 90% of cases, is caused by anti-GM-CSF autoantibodies and is considered a primary immunodeficiency [66]. The other form of PAP is often secondary to hematologic diseases (myelodysplastic syndrome, acute myelogenous leukemia, acute lymphoblastic leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia, aplastic anemia, multiple myeloma, lymphoma, and Waldenstrom macroglobulinemia), nonhematologic malignancies (lung adenocarcinoma, glioblastoma, melanoma), infectious diseases (CMV, *Mycobacterium tuberculosis*, *Nocardia*, *Pneumocystis jirovecii*), and immunosuppressive drugs or encountered in the setting of defined primary immunodeficiency, such as ADA deficiency, GATA2 deficiency, and lysinuric protein intolerance [65].

Usually the onset of clinical manifestations is insidious, and the most important symptom is progressive dyspnea [67]. Patients are also susceptible to pulmonary and extrapulmonary infections frequently caused by opportunistic pathogens [68].

6.16 Trypanosomiasis

The trypanosomiases consist of a group of important animal and human diseases caused by parasitic protozoa of the genera *Trypanosoma* and *Leishmania*. In South and Central America, Chagas's disease (American trypanosomiasis) remains one of the most prevalent infectious diseases.

Chagas's disease is caused by the protozoan *Trypanosoma cruzi* and is endemic in Latin America. This protozoan is most commonly transmitted through the feces of an infected triatomine but can also be congenital, via contaminated blood transfusion or through direct oral contact. In the acute phase, the disease can cause cardiac derangements like myocarditis, conduction system abnormalities, and/or pericarditis. Untreated patients can advance to the chronic phase. Up to one-half of these patients will develop a cardiomyopathy, which can lead to cardiac failure and/or ventricular arrhythmias, both of which are major causes of mortality.

The parasite's ability to escape and/or modulate both innate and adaptive immune responses is crucial for their survival.

Leishmania can escape complement-mediated lysis by targeting host cells through complement activation. Expression of a modified surface lipophosphoglycan (LPG) [69] was found to enhance the synthesis of surface proteinase gp63 [70] and PSA-2 [71] preventing insertion or deposition of the lytic C5b-C9 complex, thereby enhancing tolerance of complement-mediated lysis (CML). *Trypanosoma cruzi* blood forms can also survive complement activation as they express glycoproteins such as gp160, gp58/68, and T-DAF. These proteins can bind to C3b and C4b, which allow evasion of complement [72, 73].

Leishmania sp. and *T. cruzi* are able to resist the antimicrobial mechanisms induced in phagocytic and even in non-phagocytic cells. During the acute phase of infection, *T. cruzi* replicates extensively and releases immunomodulatory molecules (GPI-mucins, trans-sialidase, glycoinositolphospholipids (GPILs), the cysteine proteinase cruzipain), which play an important role in subverting the host's innate immunity. GPI-mucins are responsible for parasite surface variability, leading to differential tissue adherence and evasion of host innate immune responses. Moreover, they render DCs dysfunctional for protective responses [74]. Persistence of *Leishmania* and infection progression are caused by the inability of phagocytes to elicit both effective innate and adaptative responses [75]. *Leishmania* alters some biological functions (retention of intracellular iron, alteration of the DNA methylation status of many host genes with antimicrobial functions, and disruption of cholesterol dynamics) to promote parasite growth.

Ten patients with congenital Chagas's disease were reported with pneumonitis. Amastigotes were found in the lungs in seven of these cases, and in two of these patients, parasitized cells were seen in the alveolar lumen. Parasites were found both in the lungs and in the amniotic epithelium of the extraplacental membranes and umbilical cord in five patients. Probably the infection of the amniotic epithelium in the lungs was carried by the amniotic fluid [76].

6.17 Isolated Congenital Asplenia (ICA)

The spleen represents the largest accumulation of lymphoid tissue in the human body. It also filters the blood; splenic red pulp is primarily dedicated to picking up foreign particles, in addition to worn-out, damaged, or otherwise altered erythrocytes. Meanwhile, the white pulp activates the immune response when antigens and their antibodies are present in the blood [77].

Splenic phagocytes play a crucial role in removal of complement-opsonized pneumococci from the blood, a process that is enhanced by the presence of specific antibody against the polysaccharide capsule of the organism. These immunological observations are supported by clinical experience in which deficiency of specific antibody or hyposplenism led to an increase in the risk of pneumococcal disease [78, 79].

Congenital asplenia often occurs in the context of a recognized malformation syndrome and is associated with complex visceral defects as part of heterotaxy syndromes with bilateral right sidedness [80, 81].

In contrast, isolated congenital asplenia (ICA) is characterized by the absence of heterotaxy or cardiac defects and was first thought to be very rare and sporadic [82]. Studies of case reports suggested probably autosomal dominant inheritance pattern.

Clinical presentation of ICA can be varied based on the age of presentation with increased severity in infants and decreasing severity with age likely due to maturation of cell-mediated immunity beyond 2 years of age [83]. The most frequent pathogens are encapsulated bacteria, especially *Streptococcus pneumonia*.

Infants and young children with ICA presenting with overwhelming sepsis have a high mortality, and the diagnosis is made after autopsy [84]. The Howell-Jolly bodies are intraerythrocytic remnants of an immature erythrocyte, which is normally removed in the spleen. Their presence is considered to signify a high likelihood of splenic dysfunction [85]. The presence of Howell-Jolly bodies in the peripheral blood smear may provide a clue for early diagnosis in patient presenting with sepsis or recurrent febrile illness and trigger an evaluation of splenic function [86].

References

1. Hambleton S, Goodbourn S, Young DF, Dickinson P, Mohamad SM, Valappil M, et al. STAT2 deficiency and susceptibility to viral illness in humans. Proc Natl Acad Sci. 2013;110(8):3053–8.
2. Turvey SE, Broide DH. Innate immunity. J Allergy Clin Immunol. 2010;125(2):S24–32.
3. Courtois G, Smahi A, Reichenbach J, Döffinger R, Cancrini C, Bonnet M, et al. A hypermorphic IκBα mutation is associated with autosomal dominant anhidrotic ectodermal dysplasia and T cell immunodeficiency. J Clin Invest. 2003;112(7):1108–15.
4. Ghosh S, May MJ, Kopp EB. NF-kappa B and Rel proteins: evolutionarily conserved mediators of immune responses. Annu Rev Immunol. 1998;16:225–60.
5. Picard C, Casanova J-L, Puel A. Infectious diseases in patients with IRAK-4, MyD88, NEMO, or IκBα deficiency. Clin Microbiol Rev. 2011;24(3):490–7.
6. Abinun M, Flood T, Cant A, Spickett G, Appleton A. Anhidrotic ectodermal dysplasia associated with specific antibody deficiency. Eur J Pediatr. 1996;155(2):146–7.
7. Boisson B, Puel A, Picard C, Casanova J-L. Human IκBα gain of function: a severe and syndromic immunodeficiency. J Clin Immunol. 2017;37(5):397–412.
8. Sancho-Shimizu V, de Diego RP, Jouanguy E, Zhang S-Y, Casanova J-L. Inborn errors of antiviral interferon immunity in humans. Curr Opin Virol. 2011;1(6):487–96.
9. Zinngrebe J, Rieser E, Taraborrelli L, Peltzer N, Hartwig T, Ren H, et al. LUBAC deficiency perturbs TLR3 signaling to cause immunodeficiency and autoinflammation. J Exp Med. 2016;213(12):2671–89.
10. Tokunaga F. Linear ubiquitination-mediated NF-κB regulation and its related disorders. J Biochem. 2013;154(4):313–23.
11. Aksentijevich I, Zhou Q. NF-κB Pathway in autoinflammatory diseases: dysregulation of protein modifications by ubiquitin defines a new category of autoinflammatory diseases. Front Immunol. 2017;8:399.
12. Boisson B, Laplantine E, Prando C, Giliani S, Israelsson E, Xu Z, et al. Immunodeficiency, autoinflammation and amylopectinosis in humans with inherited HOIL-1 and LUBAC deficiency. Nat Immunol. 2012;13(12):1178.
13. Sancho-Shimizu V, de Diego RP, Lorenzo L, Halwani R, Alangari A, Israelsson E, et al. Herpes simplex encephalitis in children with autosomal recessive and dominant TRIF deficiency. J Clin Invest. 2011;121(12):4889–902.
14. Herman M, Ciancanelli M, Ou Y-H, Lorenzo L, Klaudel-Dreszler M, Pauwels E, et al. Heterozygous TBK1 mutations impair TLR3 immunity and underlie herpes simplex encephalitis of childhood. J Exp Med. 2012;209(9):1567–82.
15. Andersen LL, Mørk N, Reinert LS, Kofod-Olsen E, Narita R, Jørgensen SE, et al. Functional IRF3 deficiency in a patient with herpes simplex encephalitis. J Exp Med. 2015;212(9):1371–9.
16. Casrouge A, Zhang S-Y, Eidenschenk C, Jouanguy E, Puel A, Yang K, et al. Herpes simplex virus encephalitis in human UNC-93B deficiency. Science. 2006;314(5797):308–12.
17. Al-Muhsen S, Casanova J-L. The genetic heterogeneity of mendelian susceptibility to mycobacterial diseases. J Allergy Clin Immunol. 2008;122(6):1043–51.

18. Galal N, Boutros J, Marsafy A, Kong XF, Feinberg J, Casanova JL, et al. Mendelian susceptibility to mycobacterial disease in Egyptian children. Mediterr J Hematol Infect Dis. 2012;4(1):e2012033.
19. Fieschi C, Bosticardo M, De Beaucoudrey L, Boisson-Dupuis S, Feinberg J, Santos OF, et al. A novel form of complete IL-12/IL-23 receptor β1 deficiency with cell surface-expressed nonfunctional receptors. Blood. 2004;104(7):2095–101.
20. Bustamante J, Picard C, Boisson-Dupuis S, Abel L, Casanova JL. Genetic lessons learned from X-linked Mendelian susceptibility to mycobacterial diseases. Ann N Y Acad Sci. 2011;1246(1):92–101.
21. Lee W-I, Huang J-L, Yeh K-W, Jaing T-H, Lin T-Y, Huang Y-C, et al. Immune defects in active mycobacterial diseases in patients with primary immunodeficiency diseases (PIDs). J Formos Med Assoc. 2011;110(12):750–8.
22. Rocca S, Schiavoni G, Sali M, Anfossi AG, Abalsamo L, Palucci I, et al. Interferon regulatory factor 8-deficiency determines massive neutrophil recruitment but T cell defect in fast growing granulomas during tuberculosis. PLoS One. 2013;8(5):e62751.
23. Bogunovic D, Byun M, Durfee LA, Abhyankar A, Sanal O, Mansouri D, et al. Mycobacterial disease and impaired IFN-γ immunity in humans with inherited ISG15 deficiency. Science. 2012;337(6102):1684–8.
24. Boisson-Dupuis S, Kong X-F, Okada S, Cypowyj S, Puel A, Abel L, et al. Inborn errors of human STAT1: allelic heterogeneity governs the diversity of immunological and infectious phenotypes. Curr Opin Immunol. 2012;24(4):364–78.
25. Moens L, Van Eyck L, Jochmans D, Mitera T, Frans G, Bossuyt X, et al. A novel kindred with inherited STAT2 deficiency and severe viral illness. J Allergy Clin Immunol. 2017;139(6):1995–7.e9.
26. Rezaei N, Hedayat M, Aghamohammadi A, Nichols KE. Primary immunodeficiency diseases associated with increased susceptibility to viral infections and malignancies. J Allergy Clin Immunol. 2011;127(6):1329–41.e2.
27. Kawai T, Malech HL. WHIM syndrome: congenital immune deficiency disease. Curr Opin Hematol. 2009;16(1):20.
28. Przybyszewska J, Zlotogorski A, Ramot Y. Re-evaluation of epidermodysplasia verruciformis: reconciling more than 90 years of debate. J Am Acad Dermatol. 2017;76(6):1161–75.
29. Lorè NI, Cigana C, Riva C, De Fino I, Nonis A, Spagnuolo L, et al. IL-17A impairs host tolerance during airway chronic infection by Pseudomonas aeruginosa. Sci Rep. 2016;6:25937.
30. Iwakura Y, Ishigame H, Saijo S, Nakae S. Functional specialization of interleukin-17 family members. Immunity. 2011;34(2):149–62.
31. Aujla SJ, Chan YR, Zheng M, Fei M, Askew DJ, Pociask DA, et al. IL-22 mediates mucosal host defense against Gram-negative bacterial pneumonia. Nat Med. 2008;14(3):275.
32. Boisson B, Wang C, Pedergnana V, Wu L, Cypowyj S, Rybojad M, et al. An ACT1 mutation selectively abolishes interleukin-17 responses in humans with chronic mucocutaneous candidiasis. Immunity. 2013;39(4):676–86.
33. Swaidani S, Bulek K, Kang Z, Liu C, Lu Y, Yin W, et al. The critical role of epithelial-derived Act1 in IL-17-and IL-25-mediated pulmonary inflammation. J Immunol. 2009;182(3):1631–40.
34. Claudio E, Sønder SU, Saret S, Carvalho G, Ramalingam TR, Wynn TA, et al. The adaptor protein CIKS/Act1 is essential for IL-25-mediated allergic airway inflammation. J Immunol. 2009;182(3):1617–30.
35. Liu L, Okada S, Kong X-F, Kreins AY, Cypowyj S, Abhyankar A, et al. Gain-of-function human STAT1 mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. J Exp Med. 2011;208(8):1635–48.
36. Engelhardt KR, Grimbacher B. Mendelian traits causing susceptibility to mucocutaneous fungal infections in human subjects. J Allergy Clin Immunol. 2012;129(2):294–305.
37. Uzel G, Sampaio EP, Lawrence MG, Hsu AP, Hackett M, Dorsey MJ, et al. Dominant gain-of-function STAT1 mutations in FOXP3 wild-type immune dysregulation–polyendocrinopathy–enteropathy–X-linked–like syndrome. J Allergy Clin Immunol. 2013;131(6):1611–23.e3.

38. Lee PP, Mao H, Yang W, Chan K-W, Ho MH, Lee T-L, et al. Penicillium marneffei infection and impaired IFN-γ immunity in humans with autosomal-dominant gain-of-phosphorylation STAT1 mutations. J Allergy Clin Immunol. 2014;133(3):894–6.e5.
39. Drummond RA, Lionakis MS. Mechanistic insights into the role of C-type lectin receptor/CARD9 signaling in human antifungal immunity. Front Cell Infect Microbiol. 2016;6:39.
40. Lanternier F, Pathan S, Vincent QB, Liu L, Cypowyj S, Prando C, et al. Deep dermatophytosis and inherited CARD9 deficiency. N Engl J Med. 2013;369(18):1704–14.
41. Gavino C, Cotter A, Lichtenstein D, Lejtenyi D, Fortin C, Legault C, et al. CARD9 deficiency and spontaneous central nervous system candidiasis: complete clinical remission with GM-CSF therapy. Clin Infect Dis. 2014;59(1):81–4.
42. Lanternier F, Barbati E, Meinzer U, Liu L, Pedergnana V, Migaud M, et al. Inherited CARD9 deficiency in 2 unrelated patients with invasive Exophiala infection. J Infect Dis. 2014;211(8):1241–50.
43. Jhingran A, Kasahara S, Shepardson KM, Junecko BAF, Heung LJ, Kumasaka DK, et al. Compartment-specific and sequential role of MyD88 and CARD9 in chemokine induction and innate defense during respiratory fungal infection. PLoS Pathog. 2015;11(1):e1004589.
44. Whibley N, Jaycox JR, Reid D, Garg AV, Taylor JA, Clancy CJ, et al. Delinking CARD9 and IL-17: CARD9 protects against Candida tropicalis infection through a TNF-α–dependent, IL-17–independent mechanism. J Immunol. 2015; https://doi.org/10.4049/jimmunol.1500870.
45. Anderson MS, Venanzi ES, Klein L, Chen Z, Berzins SP, Turley SJ, et al. Projection of an immunological self shadow within the thymus by the aire protein. Science. 2002;298(5597):1395–401.
46. Popler J, Alimohammadi M, Kämpe O, Dalin F, Dishop MK, Barker JM, et al. Autoimmune polyendocrine syndrome type 1: utility of KCNRG autoantibodies as a marker of active pulmonary disease and successful treatment with rituximab. Pediatr Pulmonol. 2012;47(1):84–7.
47. Martinez Lopez MM, Gonzales Casado I, Alvarez Doforno R, et al. AIRE gene mutation in polyglandular syndrome type 1. An Pediatr (Barc). 2006;64(6):583–7.
48. Korniszewski L, Kurzyna M, Stolarski B, Torbicki A, Smerdel A, Ploski R. Fatal primary pulmonary hypertension in a 30-yr-old female with APECED syndrome. Eur Respir J. 2003;22(4):709–11.
49. Milenkovic T, Zdravkovic D, Djordjevic M, Podkrajsek K, Minic P, Battelino T. A novel AIRE gene mutation in an APS1 patient with adrenal failure, hypoparathyroidism, ovarian failure, growth hormone deficiency, asthma and chronic otitis with effusion (abstract). Horm Res. 2007;68(1):61.
50. Dubois N, Tardivel I, Kajosaari M, Vialettes B, Carel J. Autoimmune bronchiolitis is a life threatening component of autoimmune polyendocrine syndrome type 1 (APS-1). Horm Res. 2007;68(1):61.
51. Tang X, Lasbury ME, Davidson DD, Bartlett MS, Smith JW, Lee C-H. Down-regulation of GATA-2 transcription during Pneumocystis carinii infection. Infect Immun. 2000;68(8):4720–4.
52. Lasbury ME, Tang X, Durant PJ, Lee C-H. Effect of transcription factor GATA-2 on phagocytic activity of alveolar macrophages from Pneumocystis carinii-infected hosts. Infect Immun. 2003;71(9):4943–52.
53. González-Lara MF, Wisniowski-Yáñez A, Pérez-Patrigeon S, Hsu AP, Holland SM, Cuellar-Rodríguez JM. Pneumocystis jiroveci pneumonia and GATA2 deficiency: expanding the spectrum of the disease. J Infect. 2017;74(4):425–7.
54. Marquis J-F, Kapoustina O, Langlais D, Ruddy R, Dufour CR, Kim B-H, et al. Interferon regulatory factor 8 regulates pathways for antigen presentation in myeloid cells and during tuberculosis. PLoS Genet. 2011;7(6):e1002097.
55. Hambleton S, Salem S, Bustamante J, Bigley V, Boisson-Dupuis S, Azevedo J, et al. IRF8 mutations and human dendritic-cell immunodeficiency. N Engl J Med. 2011;365(2):127–38.
56. Jouanguy E, Gineau L, Cottineau J, Béziat V, Vivier E, Casanova J-L. Inborn errors of the development of human natural killer cells. Curr Opin Allergy Clin Immunol. 2013;13(6):589.

57. Mace EM, Orange JS. Genetic causes of human NK cell deficiency and their effect on NK cell subsets. Front Immunol. 2016;7:545.
58. Orange JS. Human natural killer cell deficiencies and susceptibility to infection. Microbes Infect. 2002;4(15):1545–58.
59. Orange JS. Human natural killer cell deficiencies. Curr Opin Allergy Clin Immunol. 2006;6(6):399–409.
60. Biron CA, Byron KS, Sullivan JL. Severe herpesvirus infections in an adolescent without natural killer cells. N Engl J Med. 1989;320(26):1731–5.
61. Fleisher G, Starr S, Koven N, Kamiya H, Douglas SD, Henle W. A non-X-linked syndrome with susceptibility to severe Epstein-Barr virus infections. J Pediatr. 1982;100(5):727–30.
62. Bochman ML, Schwacha A. The Mcm complex: unwinding the mechanism of a replicative helicase. Microbiol Mol Biol Rev. 2009;73(4):652–83.
63. Gineau L, Cognet C, Kara N, Lach FP, Dunne J, Veturi U, et al. Partial MCM4 deficiency in patients with growth retardation, adrenal insufficiency, and natural killer cell deficiency. J Clin Invest. 2012;122(3):821–32.
64. Orange JS. Unraveling human natural killer cell deficiency. J Clin Invest. 2012;122(3):798–801.
65. Borie R, Danel C, Debray M, Taille C, Dombret M, Aubier M, et al. Pulmonary alveolar proteinosis. Eur Respir Rev. 2011;20(120):98–107.
66. Browne SK, Holland SM. Immunodeficiency secondary to anti-cytokine autoantibodies. Curr Opin Allergy Clin Immunol. 2010;10(6):534.
67. Suzuki T, Sakagami T, Young LR, Carey BC, Wood RE, Luisetti M, et al. Hereditary pulmonary alveolar proteinosis: pathogenesis, presentation, diagnosis, and therapy. Am J Respir Crit Care Med. 2010;182(10):1292–304.
68. Seymour JF, Presneill JJ. Pulmonary alveolar proteinosis: progress in the first 44 years. Am J Respir Crit Care Med. 2002;166(2):215–35.
69. McConville M, Ralton J. Developmentally regulated changes in the cell surface architecture of Leishmania parasites. Behring Inst Mitt. 1997;99:34–43.
70. Brittingham A, Morrison CJ, McMaster WR, McGwire BS, Chang K-P, Mosser DM. Role of the Leishmania surface protease gp63 in complement fixation, cell adhesion, and resistance to complement-mediated lysis. J Immunol. 1995;155(6):3102–11.
71. Lincoln LM, Ozaki M, Donelson JE, Beetham JK. Genetic complementation of Leishmania deficient in PSA (GP46) restores their resistance to lysis by complement. Mol Biochem Parasitol. 2004;1(137):185–9.
72. Zambrano-Villa S, Rosales-Borjas D, Carrero JC, Ortiz-Ortiz L. How protozoan parasites evade the immune response. Trends Parasitol. 2002;18(6):272–8.
73. Cestari I, Evans-Osses I, Schlapbach LJ, de Messias-Reason I, Ramirez MI. Mechanisms of complement lectin pathway activation and resistance by trypanosomatid parasites. Mol Immunol. 2013;53(4):328–34.
74. Chaussabel D, Pajak B, Vercruysse V, Bisseyé C, Garzé V, Habib M, et al. Alteration of migration and maturation of dendritic cells and T-cell depletion in the course of experimental Trypanosoma cruzi infection. Lab Investig. 2003;83(9):1373.
75. Freitas-Teixeira P, Silveira-Lemos D, Giunchetti R, Baratta-Masini A, Mayrink W, Peruhype-Magalhães V, et al. Distinct pattern of immunophenotypic features of innate and adaptive immunity as a putative signature of clinical and laboratorial status of patients with localized cutaneous leishmaniasis. Scand J Immunol. 2012;76(4):421–32.
76. Bittencourt AL, de Freitas LAR, de Araujo MOG, Jácomo K. Pneumonitis in congenital Chagas' disease. Am J Trop Med Hyg. 1981;30(1):38–42.
77. Cesta MF. Normal structure, function, and histology of the spleen. Toxicol Pathol. 2006;34(5):455–65.
78. Bisno AL, Freeman JC. The syndrome of asplenia, pneumococcal sepsis, and disseminated intravascular coagulation. Ann Intern Med. 1970;72(3):389–93.
79. Ellis EF, Smith RT. The role of the spleen in immunity: with special reference to the post-splenectomy problem in infants. Pediatrics. 1966;37(1):111–9.

80. Freedom RM. The asplenia syndrome: a review of significant extracardiac structural abnormalities in 29 necropsied patients. J Pediatr. 1972;81(6):1130–3.
81. Ivemark B. Implications of agenesis of the spleen on the pathogenesis of conotruncus anomalies in childhood. Acta Paediatr. 1955;44(6):590–2.
82. Myerson RM, Koelle WA. Congenital absence of the spleen in an adult: report of a case associated with recurrent Waterhouse-Friderichsen syndrome. N Engl J Med. 1956;254(24):1131–2.
83. Maddux AB, Douglas IS. Is the developmentally immature immune response in paediatric sepsis a recapitulation of immune tolerance? Immunology. 2015;145(1):1–10.
84. Mahlaoui N, Minard-Colin V, Picard C, Bolze A, Ku C-L, Tournilhac O, et al. Isolated congenital asplenia: a French nationwide retrospective survey of 20 cases. J Pediatr. 2011;158(1):142–8. e1.
85. William BM, Corazza GR. Hyposplenism: a comprehensive review. Part I: basic concepts and causes. Hematology. 2007;12(1):1–13.
86. Mathew H, Dittus C, Malek A, Negroiu A. Howell-Jolly bodies on peripheral smear leading to the diagnosis of congenital hyposplenism in a patient with septic shock. Clin Case Rep. 2015;3(8):714–7.