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## Lessons learned from the study of human inborn errors of innate immunity

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### Abstract

Innate immunity contributes to host defense through all cell types and relies on their shared germline genetic background, whereas adaptive immunity operates via only three main cell types,  $\alpha\beta$  T cells,  $\gamma\delta$  T cells, and B cells, and relies on their somatic genetic diversification of antigen-specific responses. Human inborn errors of innate immunity often underlie infectious diseases. The range and nature of infections depend on the mutated gene, the deleteriousness of the mutation, and other ill-defined factors. Most known inborn errors of innate immunity to infection disrupt the development or function of leukocytes other than T and B cells, but a growing number of inborn errors affect cells other than circulating and tissue leukocytes. Here, we review inborn errors of innate immunity that have been recently discovered or clarified. We highlight the immunological implications of these errors.

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## INTRODUCTION

Innate immunity is a germline-encoded system that enables eukaryotes to defend themselves against infection (1, 2). It consists of three main components: 1) anatomical barriers, such as the physical barrier of intact skin and the chemical barrier of low gastric pH; 2) soluble proteins secreted onto mucosal surfaces or into the bloodstream, such as complement factors; 3) a cellular compartment composed of both hematopoietic and nonhematopoietic cells. Antigen presenting cells (APC), such as dendritic cells (DCs), phagocytes, such as neutrophils, cytotoxic/cytolytic cells, such as natural killer (NK) cells and other innate lymphoid cells (ILCs), together with non-hematopoietic cells, such as fibroblasts, keratinocytes, epithelial cells, and neurons, harbor pathways that allow an adequate response to infection. Pathogens are first detected via innate immune sensors or receptors. Several classes of microbial receptors have been described: Toll-like receptors (TLRs), retinoic-acid-inducible protein 1 (RIG-I)-like receptors (RLRs), Nod-like receptors (NLR), Ctype lectin receptors (CLRs), and DNA sensors (3–5). These receptors recognize microbial structures, such as lipoproteins, lipopolysaccharide (LPS), flagellin, peptidoglycan or microbial nucleic acids. Recognition activates downstream signaling cascades, leading to a rapid (occurring within hours) but short-lived immune response. This early immune response enables the host to survive until an adaptive response is generated, but its excessive activation can trigger auto-inflammation, which is defined as damage caused by dysregulated innate immune cells to host tissues (6, 7). Cell-intrinsic immunity is a branch of innate immunity in which a set of cellular antimicrobial defenses protects individual hematopoietic and non-hematopoietic cells against microbes, especially viruses, through autocrine pathways and intracellular mechanisms, such as the production of viral restriction factors (8, 9).

The study of inborn errors of immunity was long dominated by the concept of “conventional” primary immunodeficiencies (PIDs), in which rare Mendelian traits confer susceptibility to infection with a multitude of pathogens, in a completely penetrant manner and with a measurable effect on immune cells number or function. The prototype of such PIDs is X-linked (XL) agammaglobulinemia, which is caused by deleterious mutations in the Bruton tyrosine kinase gene (*BTK*). *BTK* is expressed in hematopoietic cells, and defects of this protein render the host susceptible, for life, to recurrent life-threatening infections with various microbes and result in a detectable immunological phenotype (little or absent immunoglobulin (Ig) production and few or absent B lymphocytes). In the 1910s, Nicolle described asymptomatic infections and documented the natural variability in host susceptibility to infection. In line with these observations, “monogenic infections” were described from the 1940s onward, and their molecular basis from the 1970s onward. Increased and selective susceptibility to infections with one or a narrow range of pathogens can be referred to as “non-conventional” PIDs and include many inborn errors of innate immunity (10). An example is the susceptibility to invasive *Neisseria* infections in patients

with late complement pathway defects (11–13). Over the last two decades, susceptibility to a narrow range of microbes, such as monogenic susceptibility to invasive pneumococcal disease (IPD), mycobacterial disease (MSMD), Herpes simplex virus 1 (HSV-1) encephalitis (HSE) and fungal disease, particularly chronic mucocutaneous candidiasis (CMC), have been ascribed to defects in single genes, often but not always encoding components of innate immunity (13, 14). However, dichotomous classifications making distinctions between adaptive and innate immunity, not to mention cell-intrinsic immunity, represent an oversimplification and prove difficult to apply to inborn errors of immunity. In fact, inborn errors of innate immunity may result in the absence or impaired production of cytokines essential for the development, survival, proliferation or function of B or T cells, and can lead to allergy and autoimmunity, indications of adaptive immune dysregulation. In this review, we therefore explore a set of inborn errors affecting “primarily” innate immunity, acknowledging their impact on the adaptive immune response. We focus on recently described gene defects in the cellular compartment of the innate immune response or on new insights into the pathogenesis of previously described defects (Table 1). So, although key to innate immunity against infections, the complement system (comprehensively reviewed elsewhere (15, 16)) will not be discussed here. For the recently described CD55 deficiency, we refer to the original publication (17).

## OVERVIEW OF NOVEL INBORN ERRORS ALONG MAJOR INNATE IMMUNE PATHWAYS

### A. Defects in the innate immune defense against commensal pyogenic bacteria and fungi

Pyogenic bacteria such as *Streptococcus pneumoniae* (*S. pneumoniae*) and *Staphylococcus aureus* (*S. aureus*) and fungi such as *Candida albicans* (*C. albicans*) are commensals of the human skin or mucosa and rarely cause severe disease. Detailed analysis of the immune system is therefore warranted in patients with invasive or recurrent pyogenic or fungal disease (18). The canonical nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) pathway is key in the innate immune response to this group of pathogens (Figure 1A) (19). Notably, proximal defects in the pattern recognition receptor signaling pathway underlie susceptibility to a narrow spectrum of pyogenic infections, while defects in more distal components of the NF- $\kappa$ B pathway result in broader phenotypes, including susceptibility to a range of infectious agents and developmental delay. Aside from NF- $\kappa$ B-related immune responses, important pathways in bacterial and fungal killing are phagocytosis and the filtration of encapsulated bacteria by the spleen.

### I. Defects in the NF- $\kappa$ B pathway

The NF- $\kappa$ B pathway consists of 1) a canonical pathway responsible for anti-microbial defense that relies on NF- $\kappa$ B essential modulator (NEMO)/ inhibitor of NF- $\kappa$ B kinase (IKK)  $\gamma$ -, IKK $\alpha$ - and IKK $\beta$ -mediated degradation of inhibitor of NF- $\kappa$ B (I $\kappa$ B)  $\alpha/\beta/\epsilon$  for the transfer of heterodimers formed by RelA or cRel and p50 to the nucleus, and 2) a non-canonical pathway that regulates lymphoid organogenesis, bone formation, B cell survival and function, and critically depends on NF- $\kappa$ B-inducing kinase (NIK) and IKK $\alpha$ -mediated processing of p100 into p52, to allow the formation of nuclear RelB:p52 dimers (figure 1).

NF- $\kappa$ B operates downstream from TLRs/interleukin (IL)-1 receptor (IL-1R), via a TLR-dependent adaptor, myeloid differentiation factor (MyD88), and the IL-1R-associated kinase (IRAK) complex, a dimer of two active kinases, IRAK-1 and IRAK-4. The canonical NF- $\kappa$ B pathway is also activated downstream from the B and T cell receptors (BCR, TCR), NK cell receptors (such as NKG2D), tumor necrosis factor (TNF) receptor superfamily, CLR (dectin-1, dectin-2, Mincle), and its effects are mediated by the CBM complex, consisting of caspase recruitment domain (CARD) molecules such as CARD9 and CARD11, B-cell lymphoma 10 (BCL10) and mucosa-associated-lymphoid tissue lymphoma-translocation gene 1 (MALT1). Additionally, linear ubiquitination, catalyzed by the linear ubiquitin assembly complex [LUBAC, formed by HOIL-1 (heme-oxidized IRP2 ligase 1L), HOIP (HOIL-1-interacting protein) and SHARPIN (Shank-associated RH domain-interacting protein)], plays a crucial role in NF- $\kappa$ B activation.

### 1. Upstream defects of the TLR and/or IL-1R signaling pathway

Biallelic loss-of-function mutations in *IRAK-4* and *MyD88* were identified in 2003 and 2008, respectively, in children with pyogenic bacterial infections (IPD, staphylococcal and *Pseudomonas aeruginosa* infections) and little clinical and biological inflammation (20, 21). Of note, the incidence of IPD typically decreases from adolescence onward Mendelian and the mortality of these two inborn errors of immunity declines with age (22, 23).

**IRAK1**—The role of IRAK-1 in the TLR/IL-1R signaling pathway was partially unveiled with the description of a boy who did not suffer from invasive pyogenic infections but who had weak inflammatory responses, like MyD88- and IRAK-4 deficient patients. He carried a *de novo* Xq28 microdeletion spanning Methyl CpG Binding Protein 2 (*MECP2*) and *IRAK1* (24). IRAK-1 is expressed in lymphocytes, granulocytes and monocytes, and any deficiency of this protein would therefore be likely to affect both innate and adaptive immunity. *In vitro* studies of the patient's cells showed IRAK-1 to be largely redundant for TLR/IL-1R signaling in peripheral mononuclear blood cells (PBMCs) and for the IL-1R response in fibroblasts, but essential for signaling downstream from TLR2/6, TLR4, TLR7, and TLR8 in the patient's fibroblasts and Epstein-Barr virus-immortalized (EBV-B) cells. However, as the patient died at seven months of age due to *MECP2* deficiency-related encephalopathy, it was not possible to determine the complete clinical and cellular phenotypes of IRAK-1 deficiency. The identification and study of additional patients with IRAK-1 deficiency are therefore required.

**TIRAP**—In a child presenting with *S. aureus* pneumonia and sepsis, a rare homozygous variant of TIR domain-containing adaptor protein (*TIRAP*), necessary for recruitment of MyD88 to TLR2 and TLR4, was found (25). The authors showed that the mutation was loss-of-function (LOF) and resulted in severely impaired responses to TLR1/2 and TLR4 stimulation, and completely abolished responses to TLR2/6 in various cell types (Simian-virus 40 (SV40)-fibroblasts, granulocytes, monocytes) *in vitro* (25). Intriguingly, seven healthy relatives were homozygous for the same variant but had never suffered from severe bacterial infections. Anti-staphylococcal lipoteichoic acid (LTA) antibodies (Ab) have been shown to enhance response to LTA (a ligand of TLR2), and could not be detected in the patient's plasma, yet were present in the healthy relatives. TLR2 activation in response to

LTA was rescued *in vitro* by addition of anti-LTA Ab-containing control plasma or anti-LTA monoclonal Ab to the patient's whole blood or PBMCs. Hence human AR TIRAP deficiency results in invasive staphylococcal disease only in the absence of anti-LTA Ab (25). This demonstrates the redundancy of TIRAP in the presence of anti-LTA Ab, underlying the interrelatedness of the innate and adaptive immune response: human adaptive immunity can in fact rescue an inborn error of innate immunity.

## 2. Inborn errors of NF- $\kappa$ B signaling

Defects in NF- $\kappa$ B activation lead to a broad range of developmental manifestations and infections due to impaired signaling pathways downstream of both innate and adaptive immune system receptors, as has recently comprehensively been reviewed by Zhang et al. (26). Autosomal dominant (AD) mutations in *NFKB1*, encoding p105/p50, and in *NFKB2*, encoding p100/p52, result in a common variable immunodeficiency (CVID) phenotype with recurrent infections and autoimmunity (27–32). Null mutations in *IKBK $\gamma$* , also known as NEMO, have been described in 2000 to cause incontinentia pigmenti in females and early fetal loss in males, while hypomorphic mutations classically cause XL recessive anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID) (33, 34). The first AD form of EDA-ID was identified in 2003, due to gain-of-function (GOF)/hypermorphic mutations in *NFKBIA*, encoding I $\kappa$ B $\alpha$ , in a patient with a phenotype similar to XL-EDA-ID. In these disorders, hematopoietic stem cell transplantation (HSCT) can only cure the hematopoietic defect but not the cell-intrinsic immunity of non-hematopoietic cells (35, 36). Biallelic mutations in *IKKB $\beta$* , encoding IKK $\beta$ , were identified as the cause of disrupted NF- $\kappa$ B signaling in patients with clinical characteristics of severe combined immunodeficiency (SCID), including early onset severe viral, bacterial, and fungal infections, despite normal B and T cell counts. The patients displayed impaired T and B cell activation and proliferation, particularly with a defect of TCR $\gamma\delta$  T cells, hypogammaglobulinemia, and NK cell deficiency (37, 38). Finally, homozygous LOF mutation in mitogen-activated protein kinase 14 (*MAP3K14*), encoding NIK, are responsible for the disruption of non-canonical NF- $\kappa$ B activation and a SCID phenotype with numeric and functional defects of B, T and NK cells (39).

## 3. Inborn errors of the CBM complex

CARD11, MALT1 and BCL10 deficiency all result in a similar phenotype of recurrent pyogenic and severe viral infections, yet an intestinal inflammatory phenotype predominates in MALT1 deficiency (40–43) and patients with CARD11 deficiency are typically highly susceptible to *Pneumocystis* infection (44, 45). Immunologically, patients present with a combined immunodeficiency with normal total numbers of T and B cells, mostly displaying a naïve phenotype, and impaired TCR and BCR responses (44–49). The underlying reason for these specific cellular phenotypes remains unclear, as BCL10 has been shown to be strongly expressed in bronchial and intestinal epithelial cells and, to a lesser extent, in lymphocytes and myeloid cells (47). MALT1 is expressed primarily in lymphocytes and myeloid cells and CARD11 in lymphocytes. Moreover, Perez-De Diego et al. reported a strong impairment of NF- $\kappa$ B mediated fibroblast function but normal monocyte-derived macrophage and dendritic cell responses to stimulation of TLR4, TLR2/6, and Dectin-1 in patients with BCL10 deficiency (47).

**CARD9**—First described by Glocker et al. in 2009, biallelic mutations in *CARD9* are deleterious for the innate immune defense against invasive fungal infections (50). Affected patients are particularly susceptible to superficial (CMC) or invasive (central nervous system) *Candida* infections, superficial or deep dermatophytosis, subcutaneous or invasive phaeohyphomycosis (caused by Dermatiaceous fungi), invasive *Exophiala* infections and extrapulmonary aspergillosis (50–54). Pro-inflammatory cytokine or chemokine responses to various fungal agonists were found impaired in patients' whole blood, monocyte-derived dendritic cells and macrophages (51, 53, 55, 56). Additionally, a defect of fungal killing by neutrophils and defective Th17 immunity were reported in some patients (55, 56). A recent study of two patients with invasive extra-pulmonary aspergillosis and null mutations of *CARD9* showed that *CARD9* -deficient neutrophils killed *Aspergillus* effectively but did not accumulate at sites of infection, an observation also made in *Candida* infection of the central nervous system (54, 56). However, the precise mechanism of susceptibility to invasive fungal infections in patients with *CARD9* deficiency remains to be defined.

#### 4. Inborn errors of LUBAC

**HOIL-1 and HOIP**—Three patients from two kindreds presenting with invasive pyogenic infections associated with autoinflammation and amylopectinosis-related myopathy and cardiomyopathy were found to have autosomal recessive (AR) HOIL-1 deficiency due to homozygous LOF mutations in *HOIL-1* (57). A patient with similar manifestations, together with viral infections, lymphangiectasia, lymphopenia, antibody deficiency and impaired T cell function harbored biallelic LOF mutations in *HOIP* (57, 58). Deficiencies of HOIL-1 or HOIP result in the destabilization of LUBAC, impaired linear ubiquitination of NEMO and, ultimately, weak NF- $\kappa$ B activation (57–60). Linear ubiquitination by LUBAC has recently been shown to restrict the growth of bacteria invading the cytosol by activating autophagy and NF- $\kappa$ B (61, 62). HOIP- and HOIL-1-deficient fibroblasts display impaired NF- $\kappa$ B activation in response to TNF and IL-1 $\beta$  (57, 58). By contrast, whole blood and monocytes from both HOIP- and HOIL-1-deficient patients responded strongly to IL-1 $\beta$  in terms of IL-6 production, which was significantly greater than the controls. The excessive monocyte response observed in these patients may account for their clinical autoinflammation (57, 58).

#### 11. Defects of phagocytes

Phagocyte defects comprise disorders in phagocytes number or function (adhesion, chemotaxis and/or killing) and were recently reviewed (63–65). Defects in the number of phagocytes such as congenital neutropenia present in infancy with severe and invasive pyogenic and fungal infections as well as mucosal inflammation, and are associated with an increased risk of myelodysplastic syndrome (MDS) or leukemia. Mutations in elastase neutrophil-expressed (*ELANE*) are responsible for around 50% of congenital neutropenia cases (65). A second set of defects results in impaired leukocyte adhesion, impaired phagocyte chemotaxis and/or motility, manifesting as delayed healing of the umbilical cord and omphalitis, bacterial/fungal infections and poor wound healing, but also with periodontitis and syndromic features (66). Finally, mutations in the genes encoding proteins responsible for superoxide production (gp91phox, p22phox, p47phox, p67phox and p40phox), and thus for bacterial and fungal killing, cause chronic granulomatous disease (CGD), manifesting with severe infections, especially in the form of abscesses, granulomata,



and an autoinflammatory phenotype (67, 68). We here discuss a number of newly described genes responsible for neutrophil defects.

### 1. Severe congenital neutropenia

**VPS45**—Vilboux et al. and Stepensky et al. independently investigated thirteen children with severe congenital neutropenia (SCN) who did not carry mutations in *ELANE* and who were resistant to granulocyte colony-stimulating factor (G-CSF) treatment (69, 70). The patients all presented before six months of age with severe to fatal pyogenic and fungal infections (mainly with *Pseudomonas*, *S. aureus* and other gram-positive bacteria, and *Aspergillus*), manifesting as omphalitis, superficial and deep abscesses, pneumonia, osteomyelitis and sepsis. Neurological involvement and myelofibrosis with extramedullary hematopoiesis, causing hepatosplenomegaly and/or nephromegaly, were also striking. Five of them succumbed to infection and six received HSCT, four of whom survived (69–73). These patients were found to carry homozygous mutations in *VPS45*, encoding vacuolar sorting-associated protein 45 (69, 70). *VPS45* is a regulator primarily associated with Golgi, transport vesicles and endosomal membranes. It is required for intracellular trafficking and recycling of proteins through the endocytic-lysosomal pathway. The described mutations lead to accelerated neutrophil and bone marrow myeloid cell apoptosis, as well as thrombocytopenia and thrombasthenia due to impaired granule metabolism (69, 70). Other lysosome-related proteins are responsible for neutropenia (e.g. in Chédiak-Higashi syndrome, Hermansky-Pudlak syndrome type 2 and Griscelli syndrome type 2), but the exact mechanism underlying the neutropenia in defects of endosomal-lysosomal proteins is unknown.

**JAGN1**—Another cause of SCN unresponsive to G-CSF was reported by Boztug et al. who identified homozygous mutations in the jagunal homolog 1 (*JAGN1*)-encoding gene *JAGN1* in fourteen patients with SCN (74). They manifested pyogenic bacterial infections, myeloid maturation arrest and bone and teeth abnormalities. Sixteen patients have been reported so far, one succumbed to sepsis and two were successfully treated with HSCT (74, 75). *JAGN1* is an endoplasmic reticulum (ER) protein involved in vesicular trafficking between the ER and the Golgi. It plays a crucial role in neutrophil differentiation and survival (74). *JAGN1* deficiency affects primarily neutrophils, which display scarce specific granules as well as aberrant ER structures and function, resulting in anomalous N-glycomic profiles and increased apoptosis (74). Furthermore, the defect of N-glycosylation also affects the G-CSF receptor, possibly explaining the common G-CSF resistance in these patients.

**CSF3R**—Biallelic defects of the G-CSF receptor-encoding gene *CSF3R* are responsible for another AR form of SCN, characterized by peripheral neutropenia without granulocyte maturation arrest and complete resistance to G-CSF treatment (76, 77). The expression of the mutant receptor on the cell membrane is severely reduced or completely abolished (76, 77) leading to absence of G-CSF response and neutropenia. Of note, mutations of *CSF3R* have been associated with acute myeloid leukemia in SCN. These acquired, somatic mutations affect the transmembrane or intracellular domain of the receptor, whereas the mutations underlying neutropenia are germline and affect the extracellular domain of the protein [reviewed in (78)].

**SMARCD2**—Witzel et al. recently reported four patients with delayed separation of umbilical cord, intractable diarrhea with failure to thrive, pneumonia, abscesses and recurrent sepsis, dysmorphic features and skeletal anomalies. Bone marrow analysis demonstrated scarcity of neutrophils with a granulocyte maturation arrest, neutrophil specific granule deficiency and a progression to MDS with blast excess in all patients; furthermore, one patient developed myelofibrosis (79). Two patients have undergone successful HSCT at 1 and 2 years of age respectively, and two succumbed to septic shock at one month and at five years of age (79). In these patients, homozygous mutations in SWI/SNF-related, matrix-associated, actindependent regulator of chromatin, subfamily D, member 2 (*SMARCD2*) were identified. SMARCD2 is part of a SWI/SNF (SWItch/Sucrose Non-Fermentable) complex, a family of chromatin-remodeling factors responsible for the unwrapping of nucleosomes, necessary for the regulation of differentiation in hematopoietic stem cells. Priam et al. have confirmed the essential role of SMARCD2 in granulopoiesis and granule production in neutrophils (80).

## 2. Defects in chemotaxis

**WDR1**—In the '70s, a defect of neutrophils actin polymerization and chemotaxis was described (the so-called “lazy leukocyte syndrome”), but no genetic cause could be determined (81, 82). Affected patients displayed mild neutropenia, abnormal neutrophil migration/mobilization and abnormal neutrophil morphology with nuclear lobe herniation and absence of cytosolic granules. In 2016, Kuhns et al. described five additional patients with lazy leukocyte syndrome that suffered from recurrent sinopulmonary and life-threatening systemic pyogenic infections, as well as severe chronic stomatitis, leading to oral stenosis (83). One patient succumbed to overwhelming infection and HSCT was life-saving in another patient. The group identified biallelic mutations in WD repeat-containing protein 1 (*WDR1*), the gene encoding actin-interacting protein 1 (Aip1), as a cause of this syndrome (83). Aip1 is required for adequate actin rearrangement and Aip1-deficient neutrophils display defects in polarization, chemotaxis and survival. Another homozygous mutation of *WDR1* was recently reported as the cause of severe autoinflammatory disease, periodic fever, severe stomatitis with oral stenosis and immunodeficiency with severe recurrent infections in two girls from a consanguineous family (84). They displayed increased inflammasome activation with high serum IL-18 levels and poor T cell proliferation *in vitro*, but no neutropenia. One patient succumbed to the disease and the other has been successfully treated with HSCT (84). These findings underline once again the key role of the actin cytoskeleton in human immune responses (85).

## III. Defect in a lymphoid organ: isolated congenital asplenia

The spleen is a secondary lymphoid organ, organized in white and red pulp separated by a marginal zone, serving critical functions both in innate and in adaptive immunity (86). Especially the marginal zone macrophages constitute the first defense against many viruses and bacteria that are filtered from the bloodstream. The adaptive immune response originating from the spleen is pivotal in the production of IgM-expressing memory B cells and their non-adherent reaction to polysaccharide antigens. Hence anatomic or functional asplenia, together with EDA-ID due to NEMO deficiency or *IKBKA* GOF mutations, and with IRAK4- and MyD88-deficiency, confers the highest risk to invasive infections with



pyogenic, encapsulated bacteria (*S. pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*) (87).

**RPSA**—Isolated congenital asplenia (ICA), the absence of a spleen at birth without associated congenital anomalies, such as cardiopathy as part of heterotaxy syndromes, had been described as a hereditary trait as early as in 1968 (88). However, the genetic cause of this inborn error of immunity remained enigmatic until Bolze et al. brought together a cohort of 33 patients with ICA presenting with fulminant bacterial infections in early childhood. Hypothesizing genetic homogeneity, they identified heterozygous mutations in ribosomal protein SA (RPSA) as underlying ICA in 18 patients from 8 kindreds (89). The described mutations resulted in haploinsufficiency of RPSA, with complete penetrance. The cohort of patients has now expanded to include 28 new kindreds. Nine new heterozygous protein-coding mutations are reported. Two mutations located in the 5'-UTR and five protein-coding mutations display incomplete penetrance (90). RPSA is part of the small subunit of the ribosome, is ubiquitously expressed, and is involved in pre-ribosomal RNA processing. The pathogenesis of ICA and the role of RPSA in this context are not yet understood. The phenotype associated with RPSA deficiency is striking, since haploinsufficiency in 15 other ribosomal proteins has been associated with Diamond-Blackfan anemia and not with splenic anomalies.

## B. Defects in the innate immune response to mycobacteria, *Salmonella* and *Candida*

The elucidation of the molecular mechanisms underlying MSMD has improved our understanding of the immune response to mycobacteria. All described diseases leading to MSMD affect the interferon (IFN)- $\gamma$ /IL-12 axis that, through secretion of IFN- $\gamma$ , IL-12 and IL-23, and induction of interferon stimulated genes (ISGs), forms a loop between APCs and T/NK cells. The IFN- $\gamma$ /IL-12 axis can be impaired by deleterious mutations in genes encoding pathway components, such as IFN- $\gamma$  receptor 1/2 (IFNGR1/2), signal transducer and activator of transcription 1 (STAT1), tyrosine kinase 2 (TYK2) and IL-12, but also other proteins, such as cytochrome B-245 beta chain (CYBB, or gp91phox), necessary for oxidative burst in macrophages, and NEMO, which regulates the CD40-dependent production of IL-12 (Figure 1-B). Some MSMD-causing defects are also responsible for susceptibility to infection with a narrow spectrum of other pathogens, such as *Salmonella*, viruses and *Candida*. Indeed, *C. albicans*-induced activation of the NF- $\kappa$ B pathway in phagocytes results in cytokine production, such as IL-12 and IL-23, which leads to activation of T helper (Th) cells (91). This results in retinoic acid-related orphan nuclear receptor  $\gamma$  T (ROR $\gamma$ T)-mediated cellular differentiation and IL-17 release by Th17 cells, connecting IL-23 function with *Candida* immunity (Figure 1-A). Knowledge on IL-17 immunity up to 2012 has been reviewed in Puel et al. (92). For a comprehensive review of MSMD-causing mutations published before 2013, we refer to Bustamante et al. (93).

### I. Inborn errors of interferon- $\gamma$ and IL-12 immunity

**TYK2**—Kreins et al. and Kilic et al. described a total of seven new patients from five families and four ethnicities with mycobacterial (Bacille Calmette-Guérin (BCG) and tuberculosis), intracellular bacterial (e.g. *Brucella*) and/or viral infections, harboring homozygous mutations in *TYK2* (94, 95). None of the patients displayed any of the signs of

hyper-IgE syndrome (HIES) as reported for the first patient described with AR TYK2 deficiency (96). TYK2 is expressed in T, B, and NK cells, myeloid cells and monocytes, and its scaffolding role contributes to the cell surface expression of type I IFN receptor 1 (IFNAR1), IL-12R $\beta$ 1 and IL10R2. As expected, the EBV-B cells of the TYK2-deficient patients did not express these receptors on the surface (94). The responses of both T cells and NK cells to IL-12 in these patients were impaired but not abolished, accounting for the MSMD. However, TYK2-deficient patients had normal *ex vivo* percentages of IL-17-producing T cells and did not present a CMC phenotype, despite an impaired response to IL-23 *in vitro*. Their response to IFN- $\alpha/\beta$  was completely abolished in Herpesvirus saimiri-immortalized (HVS)-T cells and impaired in EBV-B cells and Simian Virus 40 (SV-40)-immortalized fibroblasts, accounting for the viral phenotype. Finally, TYK2-deficient patients' EBV B cells showed very low basal expression of IFN- $\lambda$ -inducible genes, suggesting a role of TYK2 in their regulation.

**JAK1**—A young man suffering from recurrent non-tuberculous mycobacterial infection, warts, onychomycosis and scabies, was found to harbor two homozygous missense mutations in janus kinase 1 (*JAK1*) (97). The patient succumbed to early onset bladder carcinoma at 23 years of age. Many cytokines including IL-2, IL-4, IL-7, IL-9, IL-15, IL-21, IL-27, IL-6 family and IL-10 family cytokines signal through JAK1. Together with TYK2 and JAK2, JAK1 is a scaffolding protein for type I and II IFN receptors, and acts downstream by phosphorylating STAT proteins, such as STAT1 and STAT2. The authors showed impaired phosphorylation of JAK1 and of STAT1/2 upon stimulation of type I or II IFN receptors, and reduced ISGs transcription (97). Also, they showed reduced amounts of phosphorylated TYK2 and JAK2 upon stimulation with IFN- $\alpha$  or  $\gamma$  respectively. Together these broad signaling defects explain the observed susceptibility to non-tuberculous mycobacteria. Interestingly, they demonstrated that JAK1 kinase activity is needed to activate the signaling downstream from type I but not type II IFN, as IFN- $\gamma$  stimulation induced STAT1 phosphorylation also in the presence of a loss-of-kinase mutation in *JAK1*. The occurrence of carcinomas has been previously described in patients treated with JAK1 inhibitors for immunological disorders, in line with the presentation of this patient (97, 98).

**ISG15**—Bogunovic et al. studied three patients from two unrelated consanguineous families presenting with MSMD and asymptomatic intracranial calcifications and three Chinese siblings with seizures and intracranial calcifications reminiscent of Aicardi-Goutières syndrome, the prototypic type I interferonopathy (reviewed in (99)). All patients harbored homozygous LOF *ISG15* mutations (100, 101). The absence of BCG vaccination in some members of one family homozygous for the mutation accounted for the incomplete penetrance of the infectious phenotype (101). ISG15 is an ubiquitin-like molecule. It is induced by type I IFNs, and conversely it contributes to their downregulation. Primarily expressed by monocytes, myeloid cells, NK cells, T and B cells, it can covalently bind other proteins in a process called ISGylation. ISG15 also exists in a free form that can act intra- or extracellularly, exercising an immunomodulatory function on several immune cells, including neutrophils, NK cells, monocytes and lymphocytes, and promoting antimicrobial responses, for example by driving IFN- $\gamma$  production (102). Bogunovic et al. demonstrated

that granulocytes were the major source of extracellular ISG15 and that NK cells were the key ISG15-responsive leukocytes in terms of IFN- $\gamma$  secretion, accounting for the MSMD phenotype observed in vivo (100). This neutrophil/NK cell loop can be seen as the innate adjunct to the IL-12/IFN- $\gamma$  circuit of the adaptive immune system, which is also implicated in MSMD. The authors also showed that intracellular ISG15 deficiency prevented ubiquitin specific peptidase 18 (USP18) accumulation. USP18 inhibits IFN- $\alpha/\beta$  signaling, and its decrease is consistent with the higher levels of ISG expression in the patient's blood (103). The observed phenotypic dichotomy of this monogenic disease, with both MSMD and autoinflammation, reflects the different roles of extracellular (secreted) and intracellular ISG15. Unsurprisingly, AR human USP18 deficiency due to biallelic LOF mutations of *USP18* was recently described as a new type I interferonopathy presenting as pseudo-TORCH syndrome (neonatal neuroinflammation in the absence of typical TORCH infections) (104). Intriguingly, despite the demonstration of a role for ISG15 in antiviral defenses in mice, patients with ISG15 deficiency do not present a phenotype of susceptibility to viral infections (103).

**IRF8**—Hambleton et al. reported an infant presenting with disseminated BCG and CMC requiring HSCT, and two otherwise healthy subjects with a history of recurrent disseminated but curable BCG disease. All three subjects turned out to harbor mono- or biallelic mutations in IFN regulatory transcription factor 8 (*IRF8*) (105). IRF8 is a transcription factor expressed only in hematopoietic cells. It is a differentiation factor for granulocytes and macrophages, and is necessary for the development of dendritic cells. AR IRF8 deficiency was associated with the absence of conventional CD11c+ myeloid DCs, which secrete IL-12, and CD123+ plasmacytoid DCs (pDCs), the major producers of type I IFNs. This DC deficiency was accompanied by monocytopenia with granulocytic hyperplasia and high NK cell counts resembling hemophagocytic lymphohistiocytosis (HLH) (105, 106). T cells were normal in number, but displayed impaired IL-17 secretion in response to microbial or mitogen challenges. This finding suggests that T cells nurtured in the absence of an intact DC environment are functionally abnormal. AD IRF8 deficiency is associated with a DC deficiency limited to CD1c+CD11c+ cells (105). These findings demonstrate that the role of IRF8 in the human innate immune system extends beyond involvement in the transcriptional response of myeloid cells to IFNs and TLR agonists, to the control of DC development. Intriguingly, the reported patients did not have a phenotype of increased susceptibility to viral infections. Recently, AR IRF8 deficiency has been reported in a family with severe EBV infection and isolated NK cell deficiency of the CD56<sup>dim</sup> subset (107), and in a patient with a broad phenotype, including severe recurrent viral infections, DC and monocyte deficiency and T, B and NK cell dysfunction (108). The widespread immunological manifestations of different *IRF8* LOF mutations point to a broader role for this transcription factor than previously thought.

**IRF4**—Guérin et al. recently described a multiplex non-consanguineous family where four individuals affected by Whipple's disease (life-threatening intestinal and systemic infection by *Tropheryma whipplei*) were found to carry a heterozygous LOF mutation in *IRF4* (109). There was incomplete penetrance for Whipple's disease in the kindred. IRF4 is a lymphocyte-specific transcription factor with pleiotropic effects in T and B cells. In contrast

to other IRF proteins, its expression is not regulated by IFNs, but by pathways responsible for lymphocyte activation (110). IRF4 is required for the proliferation of CD4+ T cells in response to mitogens and for the production of IL-2, IL-4, and IFN- $\gamma$ , thus regulating both Th1 and Th2 responses. Moreover, it is essential to drive Th17 responses, partly through activation of ROR $\gamma$ T. Finally, it can bind IFN-stimulated response element (ISRE) promoters and either promote or repress the transcription of ISGs, while also exercising a negative regulation on TLR signaling (110, 111). Negishi et al. have in fact shown that IRF4 is induced upon TLR activation and exercises a negative-feedback regulation on the TLR signaling, possibly by competing with IRF5 for binding to MyD88 (111). *In vivo*, IRF4-knock-out mice show a more potent inflammatory response and succumb more rapidly than controls upon TLR stimulation (111). In the index family with IRF4 deficiency, the authors demonstrated loss of DNA binding ability to the ISRE promoters and of the induction of transcription by the mutated IRF4, resulting in impairment of multiple signaling pathways (for instance IFN $\gamma$ /STAT1, lymphotoxin-alpha (also known as TNF- $\beta$ ), IL-2RA). IRF4 haploinsufficiency is another example of how single-gene inborn errors of immunity can underlie life-threatening infectious disease during primary infection in otherwise healthy individuals.

**IL6ST**—Schwerd et al. studied a child with recurrent, early, severe bacterial respiratory and skin infections, bronchiectasis, skeletal anomalies including craniosynostosis, eczema and high IgE levels compatible with HIES, and found a homozygous LOF mutation in IL-6 signal transducer (*IL6ST*), encoding gp130 (112). Gp130 is a ubiquitously expressed cytokine receptor subunit involved in the recognition and signaling of multiple ligands, including IL-6, IL-11, IL-27 and oncostatin M (OSM). The authors showed that gp130 deficiency caused a complete loss of IL-6 signaling as measured by STAT3 phosphorylation in the patient's q LOF (112, 113). This highlights the essential contribution of the IL-21/STAT3 axis, but not gp130, to Th17 subset differentiation.

## II. Inborn errors of IL-17 immunity

The key role of the IL-17 pathway in the defense against *C. albicans* was demonstrated by the discovery of AD IL-17F and AR IL-17 receptor A (IL-17RA), IL-17RC and NF- $\kappa$ B activator 1 (ACT1) deficiencies underlying “isolated” CMC. Interestingly, the phenotype of IL-17RA deficiency was recently reported to be broader than initially thought (114). Indeed, Lévy et al. showed that 14 of 21 patients from 12 kindreds had staphylococcal skin disease, and that eight of these 21 patients had recurrent bacterial respiratory tract infections. These data suggest that IL-17RA is essential for mucocutaneous immunity to *C. albicans* in humans, and, to a lesser extent, for protection of the skin and mucosae against *Staphylococcus aureus*. Moreover, Conti et al (115). studied the mucosal function of the IL-17 pathway in a mouse model of oropharyngeal candidiasis and found neutrophil recruitment to the tongue of infected mice to be severely impaired in IL-23- and IL-17RA-deficient mice compared to wild type or IL-12-deficient mice (116). Therefore, despite belonging principally to the adaptive immunity, IL-17 pathway defects also affect the cell-intrinsic immunity of non-hematopoietic tissue, such as fibroblasts, keratinocytes or epithelial cells.

**STAT1**

AD *STAT1* GOF mutations were first described in 2011 (117). Recent advances in CMC genetics have shown that in over 50% of CMC cases a *STAT1* GOF mutation can be found, and more than 350 patients with *STAT1* GOF mutations have been described to date (117–119). The phenotype extends to bacterial, viral, mycobacterial, and invasive fungal infections (118). Forty percent of patients with *STAT1* GOF mutations have autoinflammatory (innate) and autoimmune (adaptive) manifestations, especially hypothyroidism (118). The stronger IFN signaling found in *STAT1* GOF mutations likely underlies these features. Other clinical features include aneurysms and increased risk of carcinoma, and recently a high prevalence of *STAT1* mutations has been described in patients suffering from JC virus-induced progressive multifocal leukoencephalopathy (PML) (120). Immunologically, patients with *STAT1* GOF mutations often have low proportions of circulating IL-17-producing T cells. A number of patients have also been found to have low memory B-cell and IgG2 and/or IgG4 levels (118). Based on the knowledge that janus kinase (JAK) 1 and 2 act upstream of *STAT1* dimers, the JAK1/2 inhibitors ruxolitinib and more recently baricitinib, have been successfully introduced into the treatment of patients with *STAT1* GOF mutations, to reverse autoimmunity and to treat CMC (121–125). However, major adverse effects, such as infection and a cytokine rebound effect, have been reported in patients treated with ruxolitinib for *STAT1* GOF mutations and other conditions (126–128). Recently, an international retrospective study on a cohort of 15 patients with *STAT1* GOF mutations who received HSCT showed poor overall survival (40%) and poor event-free survival (10%) (129).

**RORC**—Okada et al. studied seven patients from three unrelated kindreds presenting with mild CMC and severe mycobacterial infections (130). All patients developed disseminated mycobacterial infection and one died of BCG meningoencephalitis. Deleterious biallelic mutations of retinoic acid receptor-related orphan receptor C (*RORC*), encoding ROR $\gamma$  and ROR $\gamma$ T, were identified as the underlying genetic cause. The disease showed an AR transmission and was fully penetrant. ROR $\gamma$ T and ROR $\gamma$  are transcription factors, the first restricted to leukocytes and the second ubiquitously expressed. Consistent with the role of ROR $\gamma$ T as a master transcription factor for the production of IL-17, the patients had abnormally low frequencies of circulating IL-17A, IL-17F- and IL-22-producing T cells and ILC3, accounting for their CMC (131). On the other hand, impaired antigen-specific IFN- $\gamma$  production by  $\gamma\delta$ - and CD4<sup>+</sup>CCR6<sup>+</sup>  $\alpha\beta$  T cells probably accounted for their mycobacterial disease, to which their lack of mucosa-associated invariant T cells (MAIT) and NKT cells could contribute (130).

**POLA1**—XL reticulate pigmentary disorder (PDR) is a type I interferonopathy characterized by autoinflammation and immunodeficiency. An intronic mutation in DNA polymerase  $\alpha$  1 (*POLA1*), affecting splicing and reducing the expression of the protein, was recently found in 21 patients belonging to 12 kindreds (132). The hemizygous males manifest reticular pigmentation abnormalities with corneal inflammation and hypohydrosis, failure to thrive due to inflammatory bowel disease, characteristic facies and recurrent severe respiratory infections, mostly pyogenic but also mycobacterial (132). An augmented type I IFN response was demonstrated in *POLA1*-deficient fibroblasts, with enhanced expression

of IRF- and NF $\kappa$ B-induced genes, such as ISGs, accounting for the autoinflammatory features of the syndrome. Moreover, the authors proved that POLA-1 was involved in the generation of cytosolic RNA:DNA, which in turn is a downregulator of the IRF pathway: a deficient POLA-1 polymerase activity in the cytoplasm leads to reduced cytosolic RNA:DNA in the patients' cells and enhanced expression of IRF target genes. Finally, the patients showed low plasma levels of IFN- $\gamma$  and IL-17A, which could explain the infectious phenotype (132).

### C. Defects in the innate immune response against viruses

Host antiviral defense is based on the recognition of viral nucleic acid intermediates by membrane-bound TLRs or in the cytoplasm by intracellular viral sensors for DNA or RNA, such as RNA-sensing retinoic acid-inducible gene I (RIG-I), RIG-like receptors (RLRs), such as melanoma differentiation-associated protein 5 (MDA5), and DNA sensors. Recognition of the microbial ligand by these receptors induces the production of antiviral mediators, such as type I and III (IFN- $\lambda$ ) IFNs, via IRF3 and IRF7, through unique adaptors [TIR-domain-containing adaptor molecule 1 (TRIF), mitochondrial antiviral signaling protein (MAVS) and stimulator of IFN genes (STING)] (133, 134). Type I and III IFNs then activate innate cells such as NK and ILCs to eliminate virus-infected cells. The importance of the strict regulation of these pathways has been shown by the study of type I interferonopathies, a clinically heterogenic group of hereditary diseases with a constitutive activation of this pathway (Figure 2) (99).

#### I. Inborn errors of the TLR3 pathway

TLR3 binds double strand (ds) RNAs, leading to activation of a signaling cascade, in which the adapter molecule TRIF induces polyubiquitination of tumor necrosis factor receptor (TNFR)associated factor 3 (TRAF3) and the activation of IKK $\epsilon$  and TANK-binding kinase 1 (TBK1), resulting in IRF3 phosphorylation and the induction of a type I IFN response (Figure 2) (135). Human defects in several components of this pathway (TLR3, TRIF, TRAF3, TBK1 and UNC93B1 (115, 136–140)) have already been described as genetic etiologies of HSE, often displaying incomplete penetrance. HSE is a rare (1–2 cases/500,000/year) and devastating manifestation of primary HSV-1 infection that mostly affects children between the ages of six and 36 months (141). TLR3 has proved largely redundant for responses to dsRNA in various leukocytes, but not in neurons, accounting for the neuron-specific phenotype of TLR3 deficiency. Additionally, TBK1 has been implicated in autophagy, indicating a role in the cell-intrinsic immunity of neurons (142, 143).

**IRF3**—An additional important player in the TLR3 pathway was identified through the genetic study of patients with sporadic HSE (144, 145). Two patients were found to carry different heterozygous mutations in *IRF3*, resulting in an impaired type I and III IFN response to HSV-1, as demonstrated in PBMCs and fibroblasts *in vitro* (144, 145). Like *TRAF3* and *TBK1*, *IRF3* encodes a downstream component of the TLR3 pathway, but deficiencies of any one of these proteins result in a narrow phenotype, primarily affecting the central nervous system resident cells.



## II. Inborn errors of intracellular viral sensing

**DBR1**—Zhang et al. recently described an AR and fully penetrant genetic cause of brainstem viral encephalitis in five children from three kindreds (146). Four children presented with brainstem encephalitis from different viruses (HSV-1 and Influenza B) between the age of ten months and 12 years, and two died from the infection. A fifth child manifested brainstem encephalitis from Norovirus at the age of six months, but had a broader phenotype including growth and mental retardation, curly hair and congenital neutropenia. The authors identified biallelic LOF mutations in the gene encoding the only known human RNA lariat debranching enzyme (DBR1), resulting in severely impaired expression and enzymatic activity of DBR1. DBR1 acts by hydrolyzing 2'-to-5' branched phosphodiester bonds at the branch point of lariat intron RNA, and converting them into linear molecules and ensuring their rapid turnover. It is most represented in the peripheral and central nervous system, especially in the spinal cord and brainstem (147). In primary fibroblasts from the patients, the abundance of intronic lariat RNA was accordingly elevated, with a further marked increase after HSV-1 infection. Moreover, the authors showed impaired control of viral infections in patients' fibroblasts, despite intact TLR3- and IFN-responsive pathways. In fact, DBR1 deficiency did not disrupt the TLR3-IFN- $\alpha/\beta$  and IFN- $\alpha/\beta$ -STAT1 responses, implying a different, at present still elusive pathogenic mechanism than those underlying HSE of the forebrain.

**MDA5**—Rare heterozygous GOF mutations of IFN-induced helicase C domain-containing protein 1 (*IFIH1*), or melanoma differentiation-associated gene 5 (*MDA5*), cause AD Aicardi-Goutières syndrome (148, 149), a type I interferonopathy. A child suffering from severe, recurrent viral respiratory tract infections by human rhinovirus (HRV), influenza virus, and respiratory syncytial virus (RSV), and transiently low levels of Igs, T, B and NK cells, was shown to carry a homozygous LOF mutation in *MDA5* (150). The authors showed that MDA5 played a nonredundant protective role in the human airways, in sensing HRV and initiating innate immune responses against this virus, but not the other viruses, despite in vivo clinical susceptibility (150). High levels of HRV replication were observed in *MDA5*-silenced respiratory epithelial cells or fibroblasts and nasal epithelial cells from the *MDA5*-deficient patient, and the phenotype was rescued by transduction of fibroblast clones with wild-type MDA5. Additionally, Asgari et al. identified eight children carrying three putative LOF variants (homozygous in one) of *MDA5* in a group of 120 previously healthy children requiring intensive care support for severe illness caused by respiratory viruses (HRV and RSV) (151). These variants were found to have a high allele frequency in the general population (1.9%), and were proved to disrupt MDA5 signaling function, enzyme activity and protein stability *in vitro*. Moreover, mutant MDA5 protein interfered with the function and stability of the wild-type protein, suggesting a dominant-negative effect, possibly involving prevention of the formation of normal multimeric MDA5 filaments. The authors suggested that protective effect against type I diabetes and other autoimmune diseases might account for this high frequency (151). Zaki et al. described an additional patient (152). The broad spectrum of *MDA5* mutations again demonstrates the delicate balance between efficient host defense, inflammation and auto-immunity.

**POLR3A and POLR3C**—Ogunjimi et al. have recently identified four children, from a group of 21 patients affected by acute severe Varicella virus (VZV) infection (involving the lung or the central nervous system), harboring mutations in RNA polymerase III (*POLR3*) (153). Two patients displayed heterozygous mutations of either *POLR3A* or *POLR3C*, and the other two patients carried a heterozygous mutation in both genes. The penetrance of the disease is incomplete. The authors demonstrated that induction of IFN type I and III response by AT-rich DNA in human leukocytes is POL III–dependent, and that *in vitro* stimulation of patient-derived leukocytes with synthetic AT-rich DNA (poly(dA:dT)) or VZV genome elicits an impaired IFN response. However, the type I IFN response was normal in patients' PBMCs upon stimulation of the RIG-I/MAVS pathway with poly(I:C), downstream from POL III (153). Finally, they showed that patients' PBMCs were not able to restrict VZV virus replication *in vitro*, and that the transduction with wild type *POLR3C* or *POLR3A* rescued the control of viral replication in patients' deficient cells (153).

**SAMD9 and SAMD9L**—Very recently, sterile alpha motif domain-containing protein 9 (*SAMD9*) was shown to be a host innate antiviral factor against poxvirus (e.g. vaccinia and myxoma virus), Japanese encephalitis virus and low-risk Papillomavirus in humans (154–159). Mutations in *SAMD9* and its paralog SAMD9-like (*SAMD9L*) are associated with a heterogeneous clinical phenotype. *SAMD9* bears 59% amino acid similarity to *SAMD9L*. Both are located on 7q21 and are tumor suppressors, primarily expressed in hematopoietic cells and induced by TNF- $\alpha$ , IFN- $\alpha$  and IFN- $\gamma$ . Upon viral infection, *SAMD9* and *SAMD9L* downregulate IFN-driven hematopoiesis. Recently, two groups have identified heterozygous GOF mutations in *SAMD9* in children with growth failure, adrenal hypoplasia, genital anomalies, severe enteropathy, thrombocytopenia and anemia (160, 161). Most patients succumbed in infancy due to the hematological manifestations or due to infection with fungi (*Candida*) or bacteria (mostly *Staphylococcus*). Thymic size was small. Patients with *SAMD9L* GOF mutations instead develop ataxia-pancytopenia syndrome, with variable severity, and some experience viral infections, such as Cytomegalovirus (CMV) (162, 163). A subset of patients showed hematopoietic monosomy 7 (by uniparental disomy), deletion of 7q (so-called adaptation-by-aneuploidy) or neutralization of the GOF mutation by LOF mutations in *SAMD9* or *SAMD9L* (160–162, 164, 165). These adaptations were dynamic, progressive and often multiple and associated with increased survival. However, a subset of patients with monosomy 7 and 7q- developed MDS, probably due to haploinsufficiency of other 7q21 genes (162–165).

### III. Inborn errors of type I and III IFN amplification and responses

**IRF7**—In an otherwise healthy child suffering from life-threatening acute respiratory distress syndrome during primary Influenza A virus (IAV) infection at the age of 2.5 years, compound heterozygous null mutations of *IRF7* were identified (166). IRF7 is a transcription factor activated downstream of RIG-I, TLR3, TLR7, TLR9. It plays a crucial role in and amplifying IFN type I and III production upon detection of virus (167, 168). It is expressed in abundance by pDCs, the main producers of type I IFNs. The authors showed a complete lack of IFN- $\alpha$ 2b and decreased IFN- $\beta$  and IFN- $\lambda$ 1 production in the patient's pDCs and PBMCs upon exposure to different viruses or TLR stimulation. Moreover, IAV replication was significantly enhanced in the patient's inducible pluripotent stem cell-

derived pulmonary epithelial cells (PECs) and fibroblasts, and this phenotype was rescued by treatment with IFN- $\alpha$ 2b, IFN- $\beta$  or IFN- $\lambda$ 1. The absence of IRF7-dependent type I and III IFN amplification by pDCs, PECs, and possibly other cell types, probably accounts for the severe phenotype of this patient. By the time at which this case was reported, the child had not suffered from other severe infections, implying that human IRF7 is largely redundant in host defense against most common viruses (166).

**IFNAR2 and STAT2**—The key role of type I IFN in host antiviral defense is also highlighted by reports on human AR IFNAR2 and STAT2 deficiencies, displaying a similar phenotype and incomplete penetrance (169–172). These patients typically present with complicated vaccine-strain measles after immunization with the live vaccine, but can also suffer from life-threatening infections with other viruses. Duncan et al. identified a homozygous LOF mutation in *IFNAR2* in a previously healthy child, who died from encephalitis following the administration of live measles vaccine, and his newborn sister (170). The authors demonstrated that the mutation resulted in a loss of the IFN- $\alpha$  response in patient's fibroblasts *in vitro* (170). Nine patients with STAT2 deficiency have been described to date: two died of viral infections, six developed severe measles after vaccination, and excessive clinical inflammation has been reported in at least four patients (Kawasaki-like syndrome, HLH-like syndrome) (169, 171, 172). The recent finding that STAT2 is essential for the USP-18-mediated inhibition of type I IFN signaling, at least in the conditions studied *in vitro*, provides an illustration of the tight regulation embedded in the innate immune system (173).

**IRF9**—Downstream from IFNAR1/2, IRF9 combines with STAT1/STAT2 heterodimers to form the ISGF3 transcription factor. This translocates to the nucleus and initiates transcription after binding to an ISRE promoter. AR IRF9 deficiency was recently characterized in a child who presented with complications after measles-mumps-rubella vaccine, recurrent viral infections and severe IAV infection requiring intensive care treatment, a clinical picture overlapping with both IRF7 and STAT2 deficiency (174). The authors demonstrated absent activation of ISGF3, and absent transcription of factors driven by the ISRE promoter, which consequently impairs ISGs expression and anti-viral immunity in patient's fibroblasts. The impairment in transcriptional response to IFN stimulation was found to be as broad as that of STAT1- or STAT2-deficient patients.

**IFNAR1**—Hoyos-Bachiloglu et al. have reported a child, born from consanguineous parents, who at the age of 2 months suffered from *Streptococcus viridans* sepsis, severe CMV infection and mycobacteriosis, and went on to develop HLH. Of note, he later received attenuated measles, mumps and rubella virus vaccines without any adverse effect. The group identified homozygous mutations in both *IFNGR2* and *IFNAR1* (175). The mutation in *IFNGR2* is LOF and considered responsible for the mycobacterial susceptibility (175). The mutation in *IFNAR1* is a deletion replacing a stop codon with 46 new codons, resulting in a slightly longer protein. The effect is predicted to be deleterious based on decreased STAT1 and STAT2 phosphorylation, partial impairment of p-STAT1 nuclear translocation and failure to induce an appropriate antiviral response after IFN- $\alpha$  stimulation of the patient's fibroblasts, that was rescued by transduction with wild type *IFNAR1* (175).

However, the simultaneous presence of homozygous mutations in both type I and II IFN pathways renders difficult the attribution of the clinical infectious phenotype to one or the other gene defect.

#### IV. Inborn errors of NK cells and innate lymphoid cells

ILCs were recently described as a subfamily of lymphocytes differing from adaptive T cells in their absence of a clonotypic TCR and their independence of gene rearrangement (176). They are the “innate” counterparts of differentiated adaptive T cells and are able to respond to threats within hours of activation. ILCs are classified into three groups based on their phenotype and functional resemblance to T cytotoxic or helper cells: ILC1, ILC2 and ILC3 are driven by T-bet, GATA-3 and ROR $\gamma$ t, respectively, and secrete IFN- $\gamma$ , IL-5/IL-13 and IL-17/IL22, respectively (177). ILCs are abundant at mucosal surfaces, where they maintain the delicate balance between pathogen containment and avoidance of auto-inflammation, particularly in mice (176, 177). Research into human ILC development and function is in its infancy. Vély et al. showed that peripheral blood ILCs other than NK cells were more abundant in umbilical cord blood and in children than in adults (178). They also showed that T<sup>B</sup><sup>+</sup>NK<sup>-</sup> SCID patients with mutations in IL-2 receptor subunit gamma (*IL2RG*) or *JAK3* had no circulating ILCs, consistent with the dependence of these cells on IL-7 and IL-15 (178). Moreover, in the absence of myeloablative conditioning, ILC deficiency persists in blood and tissue after HSCT, with no major detectable clinical impact, even after long-term follow-up, at least in conditions in which functional T and B cells are present, suggesting that ILCs are redundant for host defense in humans. The ILC population is reconstituted after myeloablative HSCT, indicating that ILC precursors are present in human bone marrow and cord blood (178). Long-term observations in a larger number of patients are required to assess the potential increase in cancer risk and to determine whether the observed redundancy persists with aging. However, recent studies have shown that NK cells, ILC1, ILC2 and IL-22<sup>+</sup> ILC3 but not IL-17A<sup>+</sup> ILC3s can develop from ILC precursors in *RORC*-deficient patients (131). It is therefore possible that the lack of ILC3s in humans with biallelic LOF *RORC* mutations contributes to the susceptibility of these individuals to infection with *Candida* and mycobacteria. The role of NK cells in human immune defense remains a matter of debate and is accurately reviewed in several newly published papers (107, 179, 180). The patient described by Biron et al. in 1989 with severe varicella, recurrent viral infections, NK cell deficiency and lack of NK cytotoxic function was later found to harbor a mutation in *GATA2* (181, 182). Mace et al. went on to characterize the NK cell defect of *GATA2*-deficient patients (see paragraph on *GATA2*) (182). In another child with fatal varicella infection and NK cell deficiency with abolished NK cytotoxic function, Hanna et al. found a homozygous mutation in *RTEL1*, responsible for a form of dyskeratosis congenita with bone marrow failure (Hoyeraal-Hreidarsson syndrome) (183). These reports highlight how NK cells can be first affected in a variety of inborn errors, preceding the development of defects in other hematopoietic cell lines, and therefore deserve to be accurately studied. Novel findings in NK defects include the discovery of defects in mini-chromosome maintenance 4 (*MCM4*), Go-Ichi-Ni-San (*GINS*) complex subunit 1 gene (*GINS1*), *IRF8* and the extended phenotype of *GATA2* deficiency.

**MCM4**—Two independent groups recently identified a homozygous mutation in *MCM4* in 14 patients from five kindreds with NK cell deficiency, severe viral infection (EBV, CMV and other viruses), growth failure and adrenal failure (184, 185). These patients displayed a selective loss of mature CD56<sup>dim</sup> NK cells, due to blocking of the differentiation of CD56<sup>bright</sup> into CD56<sup>dim</sup>, lack of proliferation, and excess of spontaneous apoptosis of both CD56<sup>bright</sup> and CD56<sup>dim</sup> NK cells. Moreover, the patients showed signs of increased DNA breakage, highlighting the essential role of MCM4 in DNA replication during cell division.

**GIN51**—NK cell deficiency associated with neutropenia and intrauterine growth retardation has been reported in five patients from four kindreds displaying enhanced susceptibility to viral (CMV, VZV, RSV, Adenovirus), bacterial and fungal infections. All the affected patients had compound heterozygous mutations of *GIN51* (186). The GINS complex, like the MCM2–7 complex containing MCM4, is part of the CMG helicase (Cdc45, Mcm2–7, GINS) essential for eukaryotic DNA replication. Unlike patients lacking MCM4, patients with GINS1 deficiency have abnormally low numbers of both CD56<sup>bright</sup> and CD56<sup>dim</sup> NK cells. Finally, these patients have an excess of promyelocytes with reduced metamyelocyte and mature neutrophil levels, which can be corrected by G-CSF treatment.

**GATA2**—Heterozygous mutations in *GATA2*, resulting in haploinsufficiency of GATA2, are responsible for AD MonoMAC syndrome, Emberger syndrome and familial MDS/acute myeloid leukemia (AML) (187–190). The immunophenotype is characterized by monocytopenia, B and NK cell lymphopenia, clinically translating into mycobacterial, fungal and viral infections. The clinical spectrum has been extended in the last five years and involves susceptibility to disseminated nontuberculous mycobacterial infections, papillomavirus infections, opportunistic fungal infections, and pulmonary alveolar proteinosis; lymphedema, hearing loss and risk of miscarriage are also reported (191). In 2013, Mace et al. showed that the CD56<sup>bright</sup> NK cells of GATA2 deficient patients are absent or severely reduced in numbers, and that CD56<sup>dim</sup> cells are functionally impaired (182). Other characteristics are B cell, monocyte and DC deficiency, bone marrow hypocellularity and myeloid dysplasia, often with karyotypic abnormalities leading to MDS and leukemia (187, 191, 192). The only available treatment is HSCT, but the timing of this intervention is a matter of debate (193).

## FUTURE DIRECTIONS & CONCLUSION

We have reviewed here a set of recently described inborn errors of innate immunity conferring susceptibility to infection. The studies we described offer insights on the close interplay between innate and adaptive immunity and on the redundancy of some innate immune pathways and factors that can be traced back to the evolution of adaptive immunity. The innate immune system is more conserved through the species than the adaptive, nonetheless a great degree of variation has characterized the development of human innate immunity. Patin et al. have recently used flow cytometry and a genome-wide association approach to study 1000 healthy individuals, and have found that natural variation in the parameters of innate cells, such as the cell-surface expression of protein markers, is more strongly driven by genetic factors than in adaptive cells (194). In most of the inborn errors of innate immunity discussed here, adaptive immunity is also affected to some extent, and

conversely defects manifesting as T and B cell dysfunction often display some innate immunity involvement, as is the case in defects of NF- $\kappa$ B and the CBM complex. Some defects, such as those in the TLR3 pathway or in the type I/III IFN pathway, illustrate the redundancy of the pathway for host defense in general: the phenotype is in fact restricted to impaired cell-intrinsic immunity against one or a limited number of pathogens and in a single non-hematopoietic cell line. TIRAP deficiency, that only causes an infectious susceptibility in the absence of anti-LTA Ab, is a fine example of both the redundancy of an innate pathway and the mutual influence of innate and adaptive immunity. Finally, we illustrate that tight regulation of the immune pathways is crucial to confer protection from infections while avoiding auto-inflammation. In many conditions discussed here, the increased susceptibility to infection is associated with auto-inflammation, and defects in the same gene can cause either immunodeficiency or autoinflammation depending on their detrimental or enhancing effect on protein function, such as in *STAT1* and *MDA5* mutations. Infection and auto-inflammation can be allelic. From a clinical perspective, the inborn errors of innate immunity also teach us that the absence of a measurable immunological defect (e.g. hypogammaglobulinemia) does not exclude an immunodeficiency and should not result in a delay in treatment. Moreover, many of the described clinical entities present with hematological manifestations that can dominate the phenotype and result in fatal outcome (e.g. MDS/AML in *GATA2* deficiency and *SAMD9* GOF mutation). The intertwining of these manifestations also shows the importance of regulation of hematopoiesis upon infection. The genetic theory of infectious diseases (13) suggests that many inborn errors of immunity in general and of innate immunity in particular are yet to be characterized by the study of patients with severe infections. Explaining the underlying mechanisms of increased resistance to disease after infection with a pathogenic microbe is another challenge. Ultimately, these experiments of nature will improve our knowledge and understanding of human (innate) immunity to infection, and should enable us to provide better treatment to individual patients and entire populations.

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## ABBREVIATIONS

<b>Ab</b>	Antibody
<b>ACT1</b>	NF- $\kappa$ B activator 1
<b>AD</b>	Autosomal dominant



<b>Aip1</b>	Actin-interacting protein 1
<b>AML</b>	Acute myeloid leukemia
<b>APC</b>	Antigen presenting cell
<b>AR</b>	Autosomal recessive
<b>BAFFR</b>	B cell-activating factor receptor
<b>BCG</b>	Bacillus Calmette-Guérin
<b>BCL10</b>	B-cell lymphoma/leukemia 10
<b>BCR</b>	B cell receptor
<b>BTK</b>	Bruton tyrosine kinase
<b>CARD</b>	Caspase recruitment domain
<b>CBM complex</b>	CARD-BCL10-MALT1 complex
<b>CGD</b>	Chronic granulomatous disease
<b>CLR</b>	C-type lectin receptor
<b>CMC</b>	Chronic mucocutaneous candidiasis
<b>CMG</b>	CDC45, MCM2–7, GINS
<b>CMV</b>	Cytomegalovirus
<b>CSF3R</b>	G-CSF receptor
<b>CYBB</b>	Cytochrome B-245 beta chain
<b>DBR1</b>	Debranching enzyme 1
<b>DC</b>	Dendritic cell
<b>ds</b>	Double-stranded
<b>EBV</b>	Epstein-Barr virus
<b>EDA-ID</b>	Anhidrotic ectodermal dysplasia with immunodeficiency
<b>ELANE</b>	Elastase, neutrophil-expressed
<b>ER</b>	Endoplasmic reticulum
<b>GATA2</b>	GATA-binding protein 2
<b>G-CSF</b>	Granulocyte colony-stimulating factor
<b>GINS1</b>	Go-Ichi-Ni-San (GINS) complex subunit 1
<b>GOF</b>	Gain of function

<b>HIES</b>	Hyper-IgE syndrome
<b>HLH</b>	Hemophagocytic lymphohistiocytosis
<b>HOIL-1</b>	Heme-oxidized IRP2 ubiquitin ligase 1
<b>HOIP</b>	HOIL-1-interacting protein
<b>HSCT</b>	Hematopoietic stem cell transplantation
<b>HSE</b>	Herpes simplex virus 1 encephalitis
<b>HSV-1</b>	Herpes simplex virus-1
<b>HRV</b>	Human rhinovirus
<b>HVS-T cells</b>	Herpesvirus saimiri-immortalized T-cells
<b>IAV</b>	Influenza A virus
<b>ICA</b>	Isolated congenital asplenia
<b>IFIH1</b>	IFN-induced helicase C domain-containing protein 1
<b>IFN</b>	Interferon
<b>IFNAR</b>	Type I interferon receptor
<b>IFNGR</b>	Type II interferon receptor
<b>Ig</b>	Immunoglobulin
<b>I<math>\kappa</math>B</b>	inhibitor of NF- $\kappa$ B
<b>IKK</b>	I $\kappa$ B kinase
<b>IL</b>	Interleukin
<b>IL2RG</b>	IL-2 receptor subunit gamma
<b>IL6ST</b>	IL-6 signal transducer
<b>IL-1R</b>	Interleukin 1 receptor
<b>IL-17R</b>	Interleukin 17 receptor
<b>ILC</b>	Innate lymphoid cell
<b>IPD</b>	Invasive pneumococcal disease
<b>IRAK</b>	IL-1R-associated kinase
<b>IRF</b>	IFN regulatory transcription factor
<b>ISG</b>	IFN stimulated genes
<b>ISRE</b>	IFN-stimulated response element

<b>JAGN1</b>	jagunal homolog 1
<b>JAK</b>	Janus kinase
<b>LAD</b>	Leukocyte adhesion deficiency
<b>LOF</b>	Loss of function
<b>LPS</b>	Lipopolysaccharide
<b>LTA</b>	Lipoteichoic acid
<b>LT-<math>\beta</math>R</b>	receptor for lymphotoxin- $\beta$
<b>LUBAC</b>	Linear ubiquitination chain assembly complex
<b>MAIT</b>	Mucosa-associated invariant T cells
<b>MALT1</b>	Mucosa-associated lymphoid tissue lymphoma translocation protein 1
<b>MAP3K14</b>	Mitogen-activated protein kinase 14
<b>MAVS</b>	Mitochondrial antiviral signaling protein
<b>MCM2–7</b>	Mini-chromosome maintenance protein 2–7
<b>MCM4</b>	Mini-chromosome maintenance protein 4
<b>MDA5</b>	Melanoma differentiation associated gene 5
<b>MDS</b>	Myelodysplastic syndrome
<b>MECP2</b>	Methyl CpG-binding protein 2
<b>MonoMAC</b>	Monocytopenia and Mycobacterium Avium Complex/ Dendritic Cell, Monocyte
<b>B and NK</b>	Lymphocyte deficiency
<b>MSMD</b>	Mendelian susceptibility to mycobacterial disease
<b>MyD88</b>	Myeloid differentiation primary response gene 88
<b>NEMO</b>	NF-kappa-B essential modulator
<b>NF-<math>\kappa</math>B</b>	Nuclear factor kappa-light-chain-enhancer of activated B cells
<b>NIK</b>	NF- $\kappa$ B-inducing kinase
<b>NK</b>	Natural killer
<b>NLR</b>	Nod-like receptor OSM: oncostatin M pDC: Plasmacytoid DC

<b>PBMC</b>	Peripheral mononuclear blood cell
<b>PEC</b>	Pulmonary epithelial cells
<b>PID</b>	Primary immunodeficiency
<b>PML</b>	Progressive multifocal leukoencephalopathy
<b>POLA1</b>	DNA polymerase $\alpha$ 1
<b>POLR3</b>	RNA polymerase III
<b>RIG-I</b>	Retinoic-acid-inducible protein 1
<b>RLR</b>	RIG-I-like receptor
<b>RORC</b>	Retinoic acid receptor-related orphan receptor C
<b>RPSA</b>	Ribosomal protein SA
<b>RSV</b>	Respiratory syncytial virus
<b>SAMD9</b>	Sterile alpha motif domain-containing protein 9
<b>SAMD9L</b>	Sterile alpha motif domain-containing protein 9-like
<b>SCID</b>	Severe combined immunodeficiency
<b>SCN</b>	Severe congenital neutropenia
<b>SMARCD2</b>	SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily D, member 2
<b>SHARPIN</b>	Shank-associated RH domain-interacting protein ss: Single-stranded
<b>STAT</b>	Signal transducer and activator of transcription
<b>STING</b>	Stimulator of IFN genes
<b>SV40</b>	Simian virus 40
<b>TAK1</b>	Transforming growth factor beta-activated kinase 1
<b>TBK1</b>	TANK-binding kinase 1
<b>TCR</b>	T cell receptor
<b>Th</b>	T helper
<b>TIR</b>	Toll/IL-1 receptor
<b>TIRAP</b>	TIR domain-containing adaptor
<b>TLR</b>	Toll-like receptor
<b>TNF</b>	Tumor necrosis factor

<b>TNFR</b>	Tumor necrosis factor receptor
<b>TORCH</b>	Toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex
<b>TRAF</b>	TNF receptor-associated factor
<b>TRIF</b>	TIR domain-containing adaptor molecule 1
<b>TYK2</b>	Tyrosine kinase 2
<b>USP18</b>	Ubiquitin-specific peptidase 18
<b>VPS45</b>	vacuolar sorting-associated protein 45
<b>VARZ</b>	Varicella zoster virus
<b>WDR1</b>	WD repeat domain 1
<b>XL</b>	X-linked

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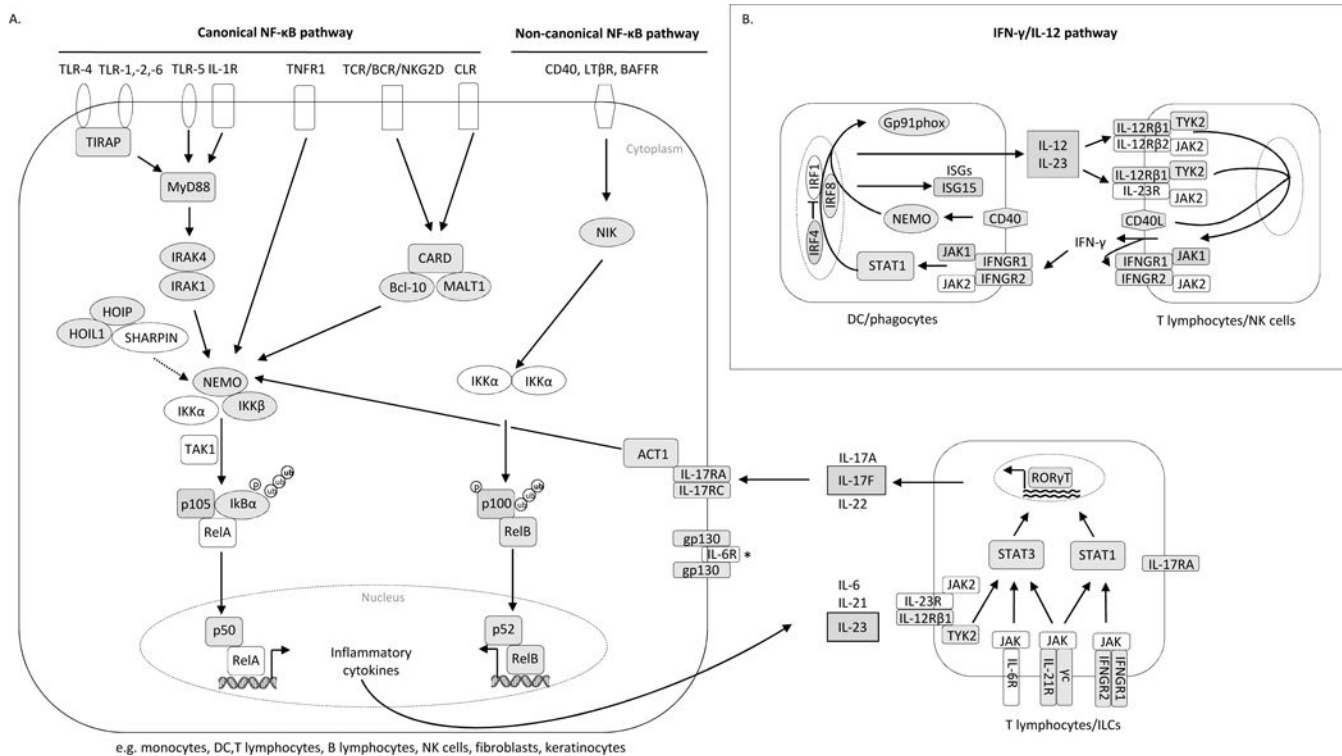
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**Figure 1: A). Recognition of conserved bacterial/fungal patterns by cell surface and endosomal TLRs and/or cell surface CLRs.** Bacterial components are recognized by TLR1/2, TLR2/6 and TLR4, triggering recruitment of the TIR domain-containing adapter molecules TIRAP and MyD88, while TLR5 and IL-1R directly activate MyD88, followed by recruitment of IRAK family members. Upon sensing of fungal infections, CLRs signal through the CARD9-BCL10-MALT1 complex. Both signaling pathways eventually lead to activation of the IKK complex (IKKα, IKKβ, and NEMO/IKKγ) and to the phosphorylation of IκBα via TAK1 (the classic MyD88-dependent pathway). After IκBα degradation, NF-κB heterodimers (p50:RelA or p50:cRel) translocate to the nucleus (canonical NF-κB pathway). By contrast, the noncanonical NF-κB pathway is induced upon activation of some TNF-R super-family members, such as CD40, BAFF-R or LT-β receptor, and involves the IKKα-mediated phosphorylation of p100 associated with RelB, leading to the generation of transcriptionally active p52:RelB complexes. IKKα activation and the phosphorylation of p100 depend on NIK activation. NFκB activation and translocation results in the induction of inflammatory cytokine genes (such as IL-21, IL-23 and IL-6). Upon binding to their receptors (expressed on T and innate lymphoid cells), the pro-inflammatory cytokines activate T cells via the transcription factor STAT3 and upregulate RORγT expression, resulting in the differentiation of these cells into IL17-producing T cells. \*gp130 is a ubiquitously expressed protein scaffolding many cytokine receptors, such as IL6R, IL-11R, IL-27R, oncostatin M and other. **B) IFN-γ/IL-12 response to mycobacterial infection and Salmonella.** Upon mycobacterial infection, the IFN-γ/IL-12 axis is induced in APCs and T/NK cells. IL-12, IL-23 and IFN-γ are secreted in a positive loop between them, and through their receptors (IL-12Rβ1/2, IL-12Rβ1/IL-23R and IFNGR1/2) activate downstream signaling via TYK2, JAK1–2 and STAT1, finally

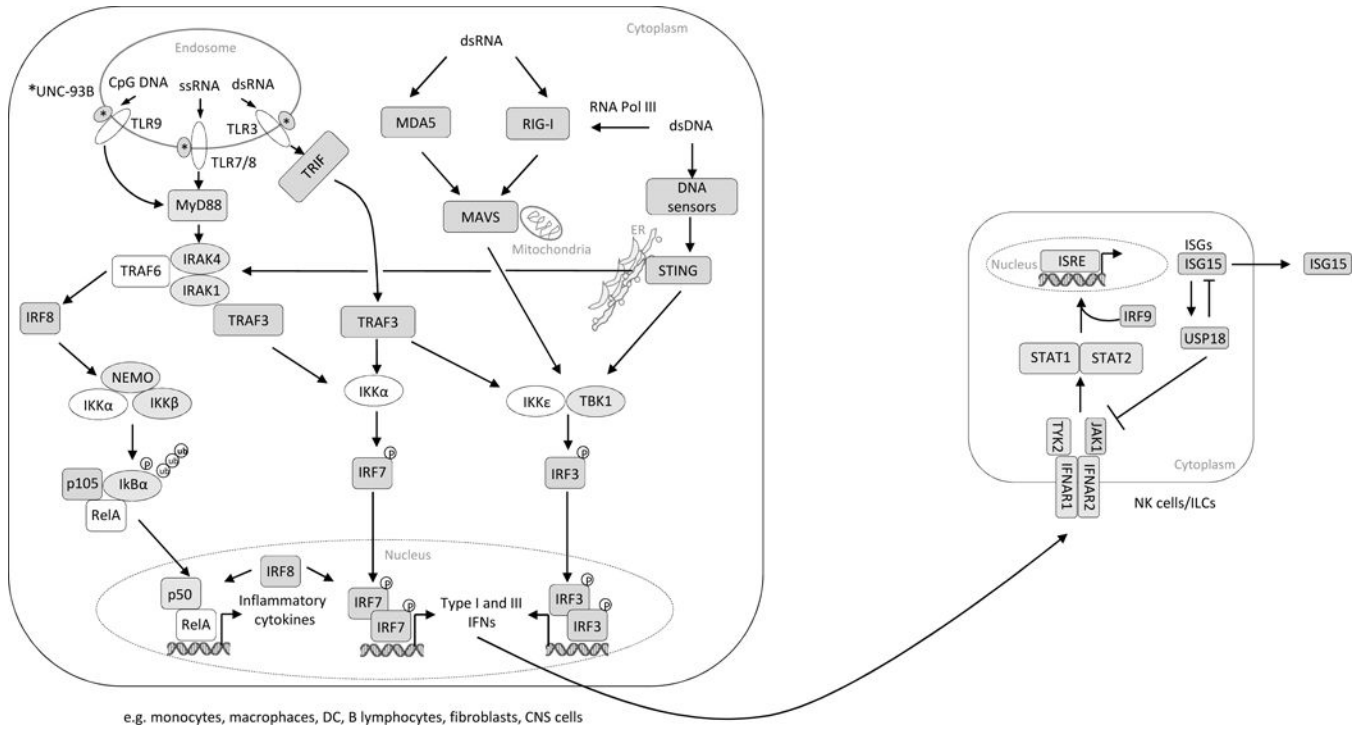
inducing the transcription of ISGs. For all proteins shadowed in grey mutations have been described.

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**Figure 2: Recognition of viral nucleic acids by endosomal TLRs, cytosolic RLRs and DNA sensors.**

The UNC-93B chaperone protein guides TLR7/8 and TLR9 trafficking from the ER to the endosome, where these receptors recognize viral ssRNA and CpG DNA, respectively. These TLRs recruit MyD88, IRAK4 and IRAK1, which activate TRAF3 and TRAF6. TRAF6, in turn, mediates the activation of NF-κB, leading to the induction of inflammatory cytokine genes, whereas TRAF3 activates IKKα, which catalyzes the phosphorylation of IRF7 and induces type I IFN genes (the classic MyD88-dependent pathway). After recognizing the viral dsRNA, UNC-93B-dependent endosomal TLR3 recruits the adapter molecule TRIF for the activation of TBK1 and IKKε, followed by the activation of IRF3 and upregulation of IFN production (the alternative TRIF-dependent pathway). IRF8 facilitates the activation of NF-κB and IRF7. RLRs, such as MDA5 and RIG-I recruit mitochondrial MAVS adapter molecules after the recognition of cytoplasmic viral dsRNA. Various cytoplasmic dsDNA sensors signal via the ER-located adapter molecule STING. The activation of these RNA and DNA signaling pathways results in the production of inflammatory cytokines via NF-κB activation, and IFN production via TBK1-IKKe-IRF activation. Secreted type I IFNs interact with their surface-expressed receptor IFNAR1/2, leading to the recruitment and activation of TYK2 and JAK1, which in turn phosphorylate and activate STAT1 and STAT2. STAT1/STAT2/IRF9 form complexes that interact with ISRE promoters for the induction of ISGs expression. Intracellular ISG15 is type I IFN-inducible and is involved in the USP18-dependent regulation of type I IFN and the prevention of type I IFN-dependent auto-inflammation. For all proteins 48 shadowed in grey mutations have been described.



**Table 1:**

Overview of recently described inborn errors of innate immunity to infections

Protein	Gene	OMIM n. gene / disease	Inheritance and penetrance	Cells where expressed (mRNA and/or protein)	Cells where tested	Results	Immunological phenotype	Infectious phenotype	Noninfectious phenotype	Autoinf ammation	N. of report patients	Therapy	Year of genetic report
<b>Upstream defects of the TLR and/or IL-1R signaling pathway</b>													
IRAK1	<i>IRAK1</i>	300283	XL	Ubiquitous	Fibroblasts PBMCs EBV-B cells	TLR responses: impaired responses in fibroblasts and EBV-B cells. Normal responses in PBMCs. Normal responses to IL-1 $\beta$ in fibroblasts and PBMCs	NA	NA	NA (MECP2 deletion sdr)	No	1	NA	2017 (24)
TIRAP	<i>TIRAP</i>	606252	AR - IP	Ubiquitous	Fibroblasts PBMCs Granulocytes	Impaired responses to TLR2 and TLR4 stimulation	NA	Severe suppylocecal infection	NA	No	8	NA	2017 (25)
<b>Inborn errors of the CBM complex</b>													
CARD9	<i>CARD9</i>	607212/ 212050	AR - CP	Granulocytes	PBMCs Monocyte-derived dendritic cells Macrophages	Impaired T cell dependent IL-17 production. Defective cytokine and chemokine production upon fungal stimulation. Impaired neutrophil killing. Impaired neutrophil recruitment to the site of infection.	Eosinophilia, high IgE	Superficial (e.g. chronic mucocutaneous candidiasis) and invasive (e.g. meningoenzephalitis) fungal infections	NA	No	58	HSCT GM-CSF G-CSF	2009 (50)
<b>Inborn errors of LUBAC</b>													
HOIL-1	<i>HOIL1 (RBCK1)</i>	610924	AR - CP	Ubiquitous	Fibroblasts EBV-B cells PBMCs	Impaired NF- $\kappa$ B responses in fibroblasts and EBV-B cells. Enhanced response to IL-1 $\beta$ in monocytes.	Impaired vaccine responses	Invasive bacterial infections.	Chronic autoinflammation, muscular amylopectinosis	Yes	3	NA	2012 (57)
HOIP	<i>HOIP (RNFS1)</i>	612487	AR - CP	Ubiquitous	Fibroblasts EBV-B cells PBMCs	Impaired linear ubiquitination and NF- $\kappa$ B activation in fibroblasts. Impaired NF- $\kappa$ B activation in B cells. Enhanced response to IL-1 $\beta$ in monocytes.	Lymphopenia, antibody deficiency and impaired distribution and function of T lymphocytes	Recurrent viral and bacterial infections.	Multisystem autoinflammation, chronic diarrhea, subclinical amylopectinosis, systemic lymphangiectasis,	Yes	1	NA	2015 (58)
<b>Defects of phagocytes</b>													
VPS35 (SCN5)	<i>VPS35</i>	610035/615285	AR - CP	Broadly expressed	Lymphoblasts Fibroblasts Platelets Neutrophils Bone marrow myeloid cells	Impaired cell migration, impaired phagocytosis, loss of lysosomes. Loss of $\alpha$ -granules in platelets	SCN, G-CSF treatment resistant. Platelet dysfunction, thrombocytopenia, progressive anemia	Invasive pyogenic bacterial and fungal infections of skin and urinary tract; sepsis	Extramedullary hematopoiesis, bone marrow fibrosis, nephromegaly, hepatosplenomegaly, neurological involvement	No	13	HSCT	2013 (69, 70)
JAGN1 (SCN6)	<i>JAGN1</i>	616012/ 616022	AR - CP	Ubiquitous	Neutrophils	Ultrastructural defects, few granules, aberrant glycosylation of GCSF-R, increased apoptosis	SCN, mostly G-CSF treatment resistant	Pyogenic bacterial infections of airways and skin; sepsis	Myeloid maturation arrest, osteopenia, teeth abnormalities, facial dysmorphism, short stature, pancreatic insufficiency	No	16	G-CSF HSCT	2014 (74)
G-CSF receptor (SCN7)	<i>CSF3R</i>	138971/ 617014	AR - CP	Granulocyte s, placenta and other tissues	PBMCs	Impaired glycosylation, expression at the cell surface and function	SCN, G-CSF treatment resistant	Pyogenic bacterial infections of airways, skin and urinary tract	NA	No	5	GM-CSF	2014 (76)

Protein	Gene	OMIM n. gene / disease	Inheritance and penetrance	Cells where expressed (mRNA and/or protein)	Cells where tested	Results	Immunological phenotype	Infectious phenotype	Noninfectious phenotype	Autoinf ammation	N. of reported patients	Therapy	Year of genetic report
SMARCD2 (SGD2)	<i>SMARCD2</i>	601736/617475	AR - CP	Hematopoietic progenitor cells	Hematopoietic c progenitor cells	Myeloid differentiation defects, defect of granulopoiesis and neutrophil granule scarcity	Neutropenia, neutrophil specific granule deficiency, granulocyte maturation arrest	Severe recurrent bacterial infections, sepsis and parasitic infections	Developmental delay, skeletal anomalies, dysmorphic features, delayed separation of umbilical cord, progressive myeloid dysplasia and MDS, chronic diarrhea	No	4	H SCT	2017 (79)
Alp1	<i>WDR1</i>	604734	AR - CP	Ubiquitous	Neutrophils	Impaired neutrophil adhesion, impaired chemotaxis and survival due to impaired actin rearrangement	Mild neutropenia, hypoplasia of neutrophil nuclear lobes, absence of neutrophil granules	Progenia bacterial infections of skin and oral tract, sepsis, disseminated lethal Varicella Zoster infection	Impaired wound healing, recurrent oral candidiasis with oral steatorrhea	Yes	6	H SCT	2016 (83)
<b>Defect in a lymphoid organ: Isolated congenital asplenia</b>													
Riboso mal protein SA	<i>RPSA</i>	150370/271400	AD - IP	Ubiquitous	PBMCs	Haploinsufficiency	Asplenia	Invasive bacterial infections	Isolated congenital asplenia	No	>30	NA, penicillin prophylaxis	2013 (89)
<b>Inborn errors of interferon-γ and IL-12 immunity</b>													
TYK2	<i>TYK2</i>	176941/611521	AR - CP	Broadly expressed	EBV-B cells, SV40 fibroblasts, HV5-T cells, PBMCs, Fibroblasts	Impaired responses to type I IFN, IL-12/IL-23 and IL-10	NA	Mendelian susceptibility to mycobacterial disease and other infections with intracellular organisms and viruses	Hyper-IgE syndrome reported in only one patient	No	8	NA	2006 (96), 2012 (95), 2015 (94)
JAK1	<i>JAK1</i>	147795	AR - CP	Broadly expressed	PBMCs, Fibroblasts	Impaired responses to type I and II IFN, IL-2, IL-4, IL-10, IL-27	Progressive T lymphopenia, increased IgG and IgA	Mendelian susceptibility to mycobacterial disease, warts, superficial parasitic and fungal infections	Early onset bladder carcinoma	No	1	NA	2016 (97)
ISG15	<i>ISG15</i>	147571/616126	AR - CP	Broadly expressed	PBMCs, Granulocytes, SV-40 fibroblasts, EBV-B cells	Enhanced type I IFN response, impaired IFN-γ production by NK and T cells	NA	Mendelian susceptibility to mycobacterial disease	Intraocular calcifications	Yes	6	NA	2012 (100)
USP18	<i>USP18</i>	607057/617397	AR - CP	Broadly expressed	Brain tissue, Fibroblasts	Enhanced STAT1 and STAT2 phosphorylation and transcription of ISGs upon type I IFN stimulation	Thrombocytopenia	NA	PseudoTORCH syndrome	Yes	5	NA	2016 (104)
IRF8	<i>IRF8</i>	601565/614894	AR - CP	Hematopoietic cells	PBMCs, Dermal APCs	Impaired IL-12/IFN-γ response, tissue macrophages and DC deficiency, impaired NK cytotoxic function and differentiation	Monocyte and DC deficiency, NK cell deficiency with decreased CD56dim NK cells	Severe opportunistic infections, mycobacterial infections, candidiasis. Severe EBV, viral and bacterial infections	Myeloprolifer ation, lymphadenopathy, bronchiectasis	No	4	H SCT	2011 (105, 107)
IRF8	<i>IRF8</i>	601565/614893	AD - CP	Hematopoietic cells	PBMCs, EBV-B cells	Reduced IL-12 response	Deficiency of CD11c +CD1c+ DCs	Mendelian susceptibility to mycobacterial disease	NA	No	2	NA	2011 (105)
IRF4	<i>IRF4</i>	601900	AD - IP	Bone marrow, lymphoid tissues and gastrointestinal mucosa	EBV-B cells, PBMCs	Impaired Th cell responses	NA	Whipple's disease ( <i>Tropheryma whippelii</i> infection)	NA	No	4	NA	2018 (109)
gp130	<i>IL6ST</i>	600694	AR - CP	Ubiquitous	PBMCs, EBV-B cells, T lymphoblasts	Suppressed STAT1 and STAT3 activation and signaling upon IL-6 or IL-11 stimulation, impaired upon IL-27 or OSY-72 stimulation. Absent acute phase response after stimulation with IL6.	Increased naive B cells, reduced nonswitched memory B cells, eosinophilia, high IgE	Recurrent severe bacterial respiratory infections with bronchiectasis,	Skeletal anomalies, craniosynostosis, absent acute phase response	No	1	NA	2017 (112)
<b>Inborn errors of IL-17 immunity</b>													
STAT1	<i>STAT1</i>	600555/614162	AD - *CP GOF *almost CP	Broadly expressed	PBMCs, EBV-B cells, Fibroblasts	Increased responses to type I and II IFNs, IL-6 and IL-21,	Low Th17 proportions +/- low memory B cells	Chronic mucocutaneous candidiasis, bacterial and viral infections, invasive fungal	Intraocular aneurysms, autoimmunity, enteropathy, bronchiectasis	Yes	>350	JAK inhibitor (ruxolitinib) H SCT	2011 (119, 196)

Protein	Gene	OMIM n. gene / disease	Inheritance and penetrance	Cells where expressed (mRNA and/or protein)	Cells where tested	Results	Immunological phenotype	Infectious phenotype	Noninfectious phenotype	Autoinf ammation	N. of report ed patients	Therapy	Year of genetic report
								infections, mycobacterial disease					
RORY $\gamma$ T	<i>RORC</i>	602943/ 616622	AR – CP	RORY broadly expressed RORY $\gamma$ T lymphocytes and fetal lymphocytes	PBMCs	Almost absent Th17 cells. Impaired IFN- $\gamma$ production by $\gamma\delta$ T cells and CD4+CCR6+CXCR3+ $\alpha\beta$ T cells.	Modest T lymphopenia low IL23, absence of NKT and MAIT cells	Disseminated mycobacterial infections and CMC	NA	No	7	NA	2015 (197)
DNA polymerase $\alpha$ -1 (PDR)	<i>POLA1</i>	312040/ 301220	XL – CP	Ubiquitous	Fibroblasts	Constitutive activation of type I IFN response and pro-inflammatory genes	NA	Recurrent pulmonary infections with bronchiectasis	Type I interferonopathy with chronic diarrhea, failure to thrive, IBD, urethral strictures, diffuse reticulate skin hyperpigmentation, hypohidrosis, corneal scarring, characteristic faces	Yes	21	NA	2016 (198)
<b>Inborn errors of the TLR3 pathway</b>													
IRF3	<i>IRF3</i>	603734	AD - IP	Broadly expressed – relevant for CNS cells	PBMCs Fibroblasts	Impaired IFN response to AT-rich DNA, dsDNA and HSV-1 infection	NA	Herpes simplex encephalitis	NA	No	2	NA	2015 (144, 145)
<b>Inborn errors of intracellular viral sensing</b>													
DBR1	<i>DBR1</i>	607024	AR – CP	Ubiquitous, but strongest in the spinal cord and brainstem	Fibroblasts	Deficient larit processing and impaired control of viral infections	Congenital neutropenia (not fully penetrant)	Viral brainstem encephalitis	Growth retardation, mental retardation, curly hair	No	5	NA	2018 (146)
MDA5	<i>MDA5 (IFIH1)</i>	606951	AR – CP AD – IP LOF	Broadly expressed	Respiratory epithelial cells Fibroblasts	Impaired MDA5 enzymatic and IFN-inducing function. Impaired response to HRV and RSV infection.	NA	HRV and other respiratory viral infections	NA	No	10	NA	2017 (150-152)
RNA polymerase III	<i>POLR3A POLR3C</i>	614258 617454	AD – IP Digenic or monogenic	Ubiquitous	PBMCs Monocytes/macrophages Fibroblasts Keratinocytes	Impaired IFN response to AT-rich DNA and VZV infection	NA	Acute severe VZV infection with lung and CNS involvement	NA	No	4	NA	2017 (153)
SAMD9	<i>SAMD9</i>	610456/617053	AD - IP GOF	Broadly expressed	Bone marrow cells Adrenal cortex cells Fibroblasts	Structural and functional alterations of the endosome system, inhibition of cell proliferation	Variable mild lymphopenia	Severe invasive fungal and bacterial infections	MIRAGE syndrome, MDS, infection, growth failure, adrenal hypoplasia, genital anomalies, enteropathy, developmental delay, thrombocytopenia and anemia	Yes	19	HSCT	2016 (161)
SAMD9L	<i>SAMD9L</i>	611170	AD - IP GOF	Broadly expressed	EBV-B cells PBMCs Bone marrow cells	Inhibition of cell proliferation	Pancytopenia	Bacterial and viral infections	Alopecia/cerebellar atrophy, pancytopenia, MDS	No	25	HSCT	2016 (163)
<b>Inborn errors of type I and III IFN amplification and responses</b>													
IRF7	<i>IRF7</i>	605047/ 616345	AR – CP		Fibroblasts PBMCs pDCs PECs	Impaired responses to type I and III IFNs	NA	Influenza virus life-threatening infection	NA	No	1	NA, influenza a vaccination	2015 (199)
STAT2	<i>STAT2</i>	600556/ 616636	AR – IP	Broadly expressed	Fibroblasts PBMCs	Impaired type I IFN response to viral infections	NA	Severe viral infections (disseminated vaccine-strain measles)	Mitochondrial anomalies, Kawasaki-like syndrome, HLH-like syndrome.	Yes	9	NA, avoid MMR live vaccination	2013 (169)
IFNAR2	<i>IFNAR2</i>	602376/ 616669	AR – IP	Broadly expressed	Fibroblasts	Impaired type I IFN responses to viral infections	NA	Disseminated vaccine-strain measles and mumps	NA	No	2	NA, avoid MMR live vaccination	2015 (170)
IRF9	<i>IRF9</i>	147574	AR – CP	Broadly expressed	EBV-B cells SV40-fibroblasts	Impaired type I IFN response to viral infections	NA	Severe viral infections (Influenza virus life-threatening infection).	NA	No	1	NA	2018 (175)

Protein	Gene	OMIM n. gene / disease	Inheritance and penetrance	Cells where expressed (mRNA and/or protein)	Cells where tested	Results	Immunological phenotype	Infectious phenotype	Noninfectious phenotype	Autoinf ammation	N. of report ed patients	Therapy	Year of genetic report
IFNAR1	<i>IFNAR1</i>	107450	AR Digenic with <i>IFNGR2</i> mutation	Broadly expressed	Fibroblasts	Impaired type I IFN responses to viral infections	NA	Disseminated CMV, <i>Streptococcus viridans</i> sepsis, mycobacterial disease	HLH	No	1	HSCT	2017 (176)
<b>Inborn errors of NK cells / with NK cells affected</b>													
MCM4	<i>MCM4</i>	602638/609981	AR - CP	Ubiquitous	Fibroblasts EBV-B cells PBMCs	DNA replication defect	NK cell deficiency (reduction of CD56dim NK cells, reduced proliferation and excess spontaneous apoptosis of NK cells)	Recurrent viral infections, especially herpesviruses; viral pulmonary infections leading to respiratory failure	Adrenal insufficiency, severe intra- and extracrine growth retardation, microcephaly, DNA repair disorder and susceptibility to cancer	No	24	Corticoid replace ment therapy	2012 (185, 186, 200)
GINS1	<i>GINS1</i>	610608	AR - CP	Ubiquitous	PBMCs Fibroblasts	DNA replication defect	NK cell deficiency neutropenia, autoimmune cytopenia, lymphopenia	Bacterial/viral respiratory and GI infections, herpesviruses infections	Intra- and extracrine growth retardation, facial dysmorphism, eczema, hypothyroidism, cancer, enteropathy, glaucoma	No	5	G-CSF	2017 (187)
GATA2	<i>GATA2</i>	137295/614172	AD - CP	Hematopoietic progenitors, nonhematopoietic embryonic stem cells, lymphatic cells	PBMCs Bone marrow cells	Absent or severely deficient CD56bright NK cells. Functionally impaired CD56dim NK cells.	Deficiency of monocytes, DCs, NK cells and B lymphocytes	Susceptibility to viral infections, mycobacteria, HPV, histoplasmosis	Alveolar proteinosis, MDS/AML, lymphedema, hearing loss, miscarriage	No	>400	HSCT	2011 (188-191)

Legend: AML: acute myeloid leukemia; APC: antigen presenting cell; AR: autosomal recessive; AD: autosomal dominant; CBM: CARD-BCL1054 MALT1 complex; CMV: Cytomegalovirus; CNS: central nervous system; CP: complete penetrance; DC: dendritic cell; EBV-B: EBV-immortalized B cell; G-CSF: granulocyte colony-stimulating factor; GI: gastrointestinal; GM-CSF: granulocyte-macrophage colony-stimulating factor; GOF: gain of function; HLH: hemophagocytic lymphohistiocytosis; HPV: Human papillomavirus; HRV: Human rhinovirus; HSCT: hematopoietic stem cell transplantation; HVS-T: herpesvirus saimiri-immortalized T-cell; IBD: inflammatory bowel disease; IFN: interferon; Ig: immunoglobulin; IL: interleukin; ILC: innate lymphoid cell; IP: incomplete penetrance; ISG: IFN-stimulated gene; LOF: loss of function; LUBAC: Linear ubiquitination chain assembly complex; MAIT: mucosa-associated invariant T cells; MDS: myelodysplastic syndrome; MMR: measles-numps-rubella; n: 60 number; NA: not applicable; OMIM: Online Mendelian Inheritance in Man; PBMC: peripheral blood mononuclear cell; pDC: plasmacytoid DC; PDR: reticulate pigmentary disorder; PEC: pulmonary epithelial cells ref: reference; RSV: Respiratory syncytial virus; SCN: severe congenital neutropenia; SGD: specific granule deficiency; SV40-fibroblast: simian virus 40-immortalized fibroblast; Th: T helper; TLR: Toll-like receptors; 93 TORCH: toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex; VZV: Varicella zoster virus; XL: X-linked.