



## Full length article

## Pattern recognitions receptors in immunodeficiency disorders



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## ABSTRACT

Pattern recognition receptors (PRRs) recognize common microbial or host-derived macromolecules and have important roles in early activation and response of the immune system. Initiation of the innate immune response starts with the recognition of microbial structures called pathogen associated molecular patterns (PAMPs). Recognition of PAMPs is performed by germline-encoded receptors expressed mainly on immune cells termed pattern recognition receptors (PRRs). Several classes of pattern recognition receptors (PRRs) are involved in the pathogenesis of diseases, including Toll-like receptors (TLRs), C-type lectin receptors (CLRs), and Nod-like receptors (NLRs). Patients with primary immune deficiencies (PIDs) affecting TLR signaling can elucidate the importance of these proteins in the human immune system. Defects in interleukin-1 receptor-associated kinase-4 and myeloid differentiation factor 88 (MyD88) lead to susceptibility to infections with bacteria, while mutations in nuclear factor- $\kappa$ B essential modulator (NEMO) and other downstream mediators generally induce broader susceptibility to bacteria, viruses, and fungi. In contrast, TLR3 signaling defects are associated with susceptibility to herpes simplex virus type 1 encephalitis. Other PIDs induce functional alterations of TLR signaling pathways, such as common variable immunodeficiency in which plasmacytoid dendritic cell defects enhance defective responses of B cells to shared TLR agonists. Altered TLR responses to TLR2 and 4 agonists are seen in chronic granulomatous disease (CGD) and X-linked agammaglobulinemia (XLA). Enhanced TLR responses, meanwhile, are seen for TLRs 5 and 9 in CGD, TLRs 4, 7/8, and 9 in XLA, TLRs 2 and 4 in hyper IgE syndrome (HIES), and for most TLRs in adenosine deaminase deficiency. In this review we provide the reader with an update on the role of TLRs and downstream signaling pathways in PID disorders.

## 1. Introduction

Toll-like receptors (TLRs) are an important family of pattern recognition receptors (PRRs) which are expressed broadly by immune and non-immune cells such as epithelial cells, neutrophils, macrophages and dendritic cells (DCs). They recognize both microbial and host-derived macromolecules and enable the early detection of infection and other potential threats such as viruses (Kawai and Akira,

2010). Moreover, TLRs play a critical role in the initiation of the long-lived adaptive immune responses by promoting antigen presentation (Uehara et al., 2007; Pegu et al., 2008; Schenten and Medzhitov, 2011).

There are 13 TLRs known across species. TLRs1-9 are conserved in both mice and humans, whereas mouse TLR10 is nonfunctional and TLR11, TLR12 and TLR13 are absent from the human genome (Kawai and Akira, 2010). TLRs receptors act to detect diverse pathogen-associated molecular patterns (PAMPs) and endogenous danger

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associated molecular patterns (DAMPs) (Kono and Rock, 2008; Medzhitov, 2009) which are generally microbial and endogenous molecules identified as TLR ligands (Jin et al., 2007; Shimizu, Kida and Kuwano, 2005). TLR1 and TLR6 work in concert with TLR2 to detect di- and triacylated lipoproteins from Mycoplasma and other bacteria (Jin et al., 2007; Shimizu, Kida and Kuwano, 2005). Numerous agonists for TLR2 have been reported, including lipoteichoic acid (Gram-positive bacteria), lipoarabinomannan (Mycobacteria), zymosan (fungi) as well as a number of envelop antigens from viruses (Lien, 1999; Drage et al., 2009; Ozinsky et al., 2000; Bieback et al., 2002). TLR4 is a sensor of LPS from Gram-negative bacteria; it has also been shown to bind the heat-shock proteins (HSP) 60 and 70, the fusion protein of respiratory syncytial virus and fungal mannan (Medzhitov et al., 1997; Bulut et al., 2002; Kurt-Jones et al., 2000; Tada et al., 2002).

A major agonist for TLR5 is flagellin, which is conserved among many microbial species. The intracellular TLRs 3, 7/8, and 9 sense double-stranded RNA, single stranded RNA, and unmethylated (microbial) DNA oligonucleotides, respectively (Alexopoulou et al., 2001; Diebold et al., 2004; Heil et al., 2004; Hemmi et al., 2000). The ligand for TLR10 has not yet been identified, though roles for this receptor in the recognition of viral infection and in inflammatory regulation recently, has been documented (Lee et al., 2014; Oosting et al., 2014). TLR11, like TLR5, recognizes flagellin, but it is localized in endolysosomes. TLR12 is mainly expressed in myeloid cells and can recognize *T. gondii* and can function either as a heterodimer with TLR11 or alone (Broz and Monack, 2013). Recent studies have reported that TLR13 can recognize a conserved CGGAAAGACC in *Staphylococcus aureus* and *E. coli* 23 S rRNA that can induce a TLR13-dependent transcriptional response resulting in pro-IL-1 $\beta$  induction (Kawai and Akira, 2006) (Fig. 1). However, as these TLRs do not exist in man the relevance to human disease is limited.

### 1.1. TLR signaling

TLRs and members of the IL-1R family contain an intracellular domain, the Toll–IL-1R (TIR) domain (Kawai et al., 2010). TIR-containing TLRs and IL-1Rs recruit cytosolic adaptors such as MyD88, TRIF, TIRAP (Kenny and O'Neill, 2008; O'Neill and Bowie, 2007; Medzhitov et al., 2010). The TIR pathway depends on MyD88 activation, which is used by all TLRs except for TLR3 and by at least three IL-1Rs: IL-1R, IL-18R, and IL-33R (Fig. 1).

Two pathways have been described in TLRs stimulation: a) The classical pathway activates of both nuclear factor  $\kappa$ B (NF- $\kappa$ B) and mitogen-activated protein kinases (MAPKs) via the IRAK complex. This complex consists of two active kinases (IRAK-1 and IRAK-4) and two noncatalytic subunits (IRAK-2 and IRAK-3/M).

The classical proinflammatory TLR signaling pathway activates the synthesis and release of inflammatory cytokines and chemokines such as IL-1 $\beta$ , -6, -8, and -12 and TNF- $\alpha$  via and NF- $\kappa$ B-mediated process. b) The alternative activation pathway in TLR signaling is controlled by another key adaptor, TRIF. This is the only adaptor used by TLR3 although TLR4 may also use TRIF in addition to MyD88 (Fig. 1). The other TIR adaptor molecules serve as co-adaptors or negative regulators. The sorting adaptor TIRAP could able to recruits MyD88 to TLR2 and TLR4, whereas TRAM recruits TRIF to TLR4 (Fig. 1) (Kenny and O'Neill, 2008; O'Neill and Bowie, 2007). Stimulation of these pathways via TLRs can also lead to the production of mediators such as interferon following activation of interferon regulatory factors (IRFs) (Fig. 1).

Four primary immunodeficiencies (PIDs) disease are linked to signaling defects within the TLR canonical pathway due to mutations in MyD88, IRAK4, NF- $\kappa$ B essential modulator (NEMO) and the NF- $\kappa$ B inhibitor IKB- $\alpha$  (Courtois et al., 2003; Doffinger, 2001; Picard et al., 2003; von Bernuth et al., 2008). Defects in NEMO and IKB- $\alpha$  also impair the alternative TRIF-dependent activation pathway. The critical

infectious phenotype of patients with any of these four PIDs defects is the occurrence of pyogenic bacterial infections.

Moreover, three other genetic defects caused by mutations in TLR3, UNC93B and TRAF3 have been reported which principally affect the alternative TRIF-dependent signaling pathway (Casrouge, 2006; Perez de Diego et al., 2010; Zhang et al., 2007a, 2007b). Furthermore, mutations in UNC93B and TRAF3 pathways also impair the TLR7 and TLR9 pathways. The important infectious in the patients with TLR3, UNC93B, or TRAF3 deficiency is herpes simplex encephalitis (Casanova and Abel, 2005).

In this view the details of the infections striking patients with mutations in the alternative pathway have been described (Perez de Diego et al., 2010; Zhang et al., 2007a, 2007b).

### 1.2. Defects in TLR signaling in primary immunodeficiency disorders

Defects in TLRs and their downstream signaling pathways as seen in various diseases including primary immunodeficiency disorders (PIDs) has been described. These are a broad spectrum of genetically determined diseases which result in impaired immunity and increased susceptibility to infection (Hampson et al., 2012). The field has advanced greatly over the past two decades with identification of the gene mutations that encode components of the immune system particularly in TLR signaling. This has enabled the development of insightful models to test TLR function and may provide experimental systems to test gene therapy approaches (Qasim et al., 2009).

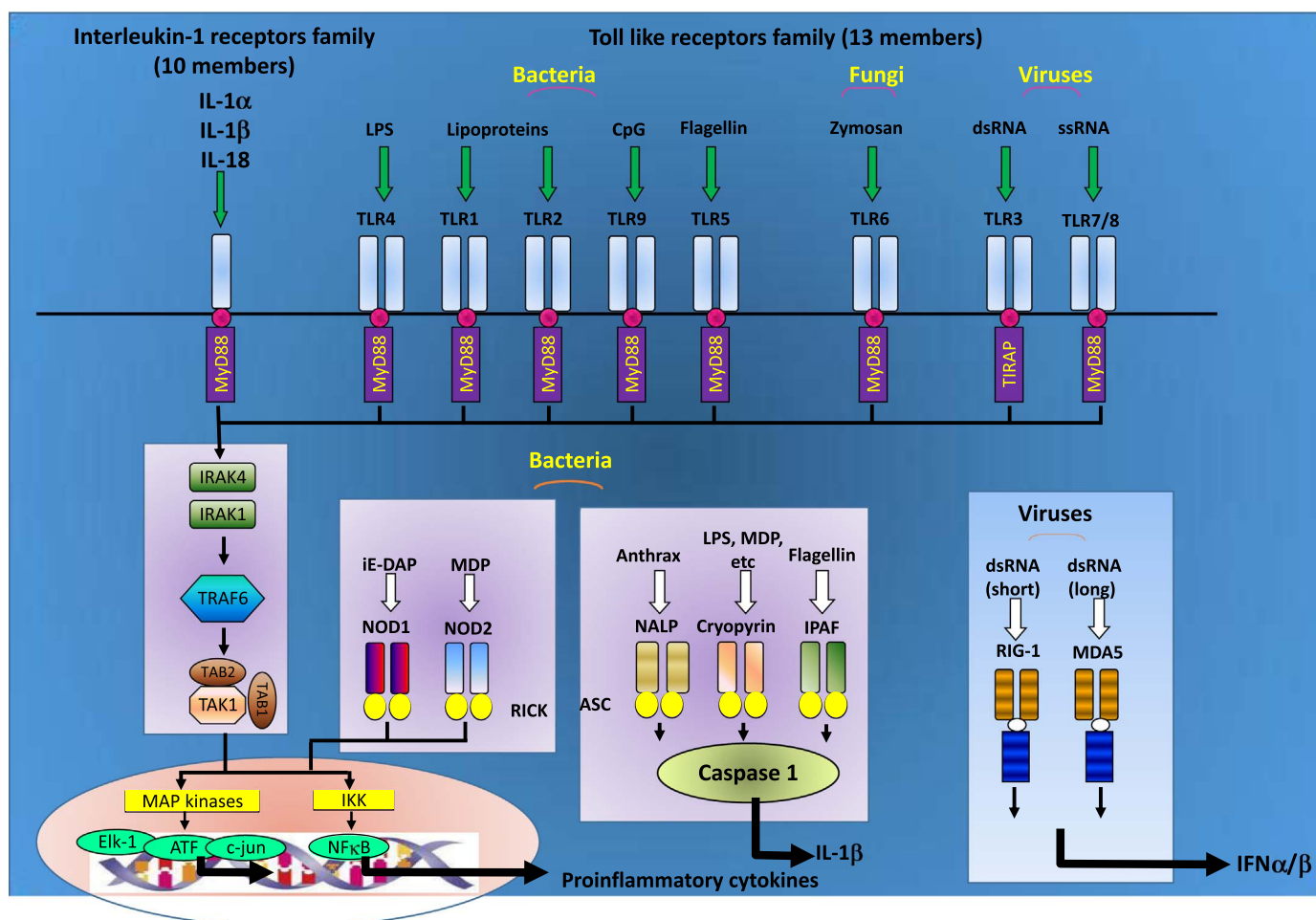
These mutations result in more than 90 known defects in PIDs with an overall prevalence of 1:10,000. Nevertheless, despite increased understanding of the molecular pathogenesis of PID and improved genetic testing, many cases remain undiagnosed (Cunningham-Rundles et al., 2004). Some of the mutations are identified in genes that control the development of cell lineages as a whole, explaining the classical forms of PIDs, whereas others have identified specific defects in well-defined pathways of immune activation (Rosen et al., 1995; Buckley, 2000; Notarangelo et al., 2009; Casanova et al., 2008; Bustamante et al., 2008; Botto et al., 2009). Defects in interleukin (IL)-12 or interferon (IFN)-gamma receptor have been shown to result in defective cellular immunity and an increased susceptibility to infections by intracellular pathogens such as *Mycobacteria* and *Salmonella* (Al-Muhsen and Casanova, 2008; van de Vosse et al., 2009) and defects in the IFN signaling pathway lead to increased susceptibility to viruses (Sancho-Shimizu et al., 2011). In addition, recent studies have identified genetic defects that impair pathogen recognition by the innate immune system, leading to an increased susceptibility to specific classes of microorganisms (Netea and van der Meer, 2011) such as the interaction of PRRs with *Mycobacterium tuberculosis* (Mortaz et al., 2015).

This review focusses on the defects and malfunction of TLRs and their downstream signaling which occur in PID patients particularly in relation to respiratory disease. In addition, other diseases are discussed where appropriate.

## 2. Hyper-IgE syndromes

Hyper-IgE syndrome (HIES) is considered as a PID marked by abnormalities in the coordination of cell-cell signaling which affects Th17 cells, B cells and neutrophil responses. Clinical manifestations include recurrent skin and lung infections, serum IgE elevation, connective tissue repair and development alterations, and the propensity for vascular abnormalities and tumor development (Rael, 2012; Freeman and Holland, 2010). STAT3 signaling, DOCK8 signaling, and TYK2 signaling alterations have been implicated in 3 forms of HIES (Rael et al., 2012).

Originally, dominant negative mutations in STAT3 were thought to be responsible for most cases of sporadic and autosomal dominant HIES/Job's syndrome (Holland et al., 2007; Minegishi et al., 2007)



**Fig. 1. Schematic of cell surface and intracellular localization of bacteria-recognizing TLRs.** All TLRs that recognize bacteria apart from TLR3, which engages TIRAP and signals through TRIF, acts through MyD88. Activation of MyD88 leads to stimulation of a downstream phosphorylation cascade involving IRAK4/TRAF6 and TAK culminating in activation of inflammatory pathways such as NF-κB and MAPK leading to enhanced inflammatory and immune gene expression. TRIF is used in conjunction with TRAM in the TLR4-MyD88-independent pathway. Dashed arrows indicate translocation into the nucleus. Abbreviations: LPS: lipopolysaccharide, dsRNA: double-strand RNA, ssRNA: single-strand RNA, MAPK: mitogen-activated protein kinases, NF-κB: nuclear factor-κB, IRF3: interferon regulatory factor 3, TRIF: TIR-domain-containing adaptor protein inducing IFNβ, TRAF3: TNF receptor-associated factor 3, TBK1: TANK-binding kinase 1, TLRs: Toll-like receptors TYK2, Tyrosine kinase 2; UNC93B1: Unc-93 homolog B1.

although a case of TYK2 deficiency with elevated IgE levels had been described (Minegishi et al., 2006). In 2009, mutations in the DOCK8 (OMIM\*611432) were found to cause a rare, novel autosomal recessive PID syndrome characterized by decreased numbers of T and B cells, elevated IgE levels, and eosinophilia (Zhang et al., 2009). It is now established that mutations in DOCK8 account for nearly all cases of the autosomal recessive form of HIES. Dominant negative mutations in this gene lead to the AD-HIES and a marked reduction in Th17 cells (Woellner et al., 2010). Additional innate immune response deficiencies in AD-HIES patients have been described such as altered TLR2 responses in the absence of Th17 (Minegishi et al., 2009). Other PRR-associated molecules including DOCK8, Dectin-1 and Dectin-2 have also been implicated as being defective in these patients (Griggs et al., 2008) (Fig. 1).

In DOCK8 patients, a deficiency in IL-17, may deviate the adaptive and innate immune system communication responses to *Candida*. This process may involve the Th17 cytokines, IL-17 and IL-22, which regulate the expression of antimicrobial peptides such as histatins and β-defensin-2 (Conti et al., 2011). The host defense against *Candida* infections in human subjects relies on innate as well as adaptive immune mechanisms. Recognition of *Candida* is triggered through lectins including Dectin-1 and Dectin-2. Experimental evidence from in vitro and in vivo studies in mice suggests that Dectin-1 signals via the tyrosine kinase Syk and via a downstream complex of the cytosolic

proteins CARD9, Bcl-10, and MALT1 to the transcription factor nuclear factor-κB (NF-κB), which acts as a central regulator in the production of inflammatory cytokines (Geijtenbeek and Gringhuis, 2009).

The responses mediated by the IL-17-producing Th17 subset of T lymphocytes play an essential role in the host immunity against *Candida* infections (Cua and Tato, 2010). Th17 cells play a critical role in the recruitment and activation of neutrophil granulocytes, both directly through CXCL8 production (Pelletier et al., 2010), and indirectly, by inducing the production of CSF and CXCL8 (Ouyang et al., 2008) in tissue-resident cells. In patients with Th17 immunity defects, neutrophils are functional and can prevent invasive fungal infections, but because of the lack of Th17 cell-produced cytokines, trafficking to sites of infection is impaired, leading to local candidiasis. Systemic fungal infections occur in neutropenia or diseases with neutrophil dysfunction, such as chronic granulomatous disease with defective oxidative burst (Antachopoulos et al., 2007; Pappas et al., 2009). Thus, Th17 cells play a central role in defense against fungi in human subjects and therefore it is not surprising that defects in Th17 immunity can result in enhanced susceptibility to fungal infections (Conti and Gaffen, 2010; Scully et al., 1994).

Host immune pathways against *Candida* sp. in humans have been implied in the clearance of these fungal infections. This is illustrated by the prevalence of invasive *Candida* spp infections in chronic granulo-

matous disease (CGD), which is caused by defects in the reduced NADPH oxidase enzyme complex required for microbial killing (van den Berg et al., 2009; Kuhns et al., 2010; Beut'e et al., 2011) and also by the improved survival upon granulocyte transfusion in case of disseminated candidiasis during chemotherapy-related conditions of prolonged neutropenia (Safdar et al., 2004).

In patients with AD-HIES, impaired neutrophil trafficking and signaling occur (Minegishi et al., 2009). This is exemplified by an inability of induce skin keratinocytes and bronchial epithelial cells to recruit neutrophils in response to anti-staphylococcal molecules such as CXCL8. Finally, neutrophil defects such as those seen in patients with severe congenital neutropenia, result in chronic mucocutaneous candidiasis (CMC) (Rezaei et al., 2005, 2007).

### 3. Microbial infection

#### 3.1. Legionnaires' disease

*Legionella pneumophila* is a motile gram-negative bacterium and cause of a severe form of pneumonia called Legionnaires' disease (Fields et al., 2002). *Legionella pneumophila* is the sixth leading cause of death in the United States; it infects alveolar macrophages and is recognized by several TLRs (Hawn et al., 2006). Hawn et al. examined the role of TLR5 during the murine response to aerosolized *Legionella pneumophila* infection and found that TLR5 recognizes *Legionella pneumophila* in alveolar macrophages and performs a distinct role during in vivo pulmonary immune response through regulation of early neutrophil recruitment and subsequent later development of pneumonia (Hawn et al., 2007) (Fig. 2). As stated above, TLR5 recognizes bacterial flagellin and 10% of affected individuals have a point mutation that introduces a stop codon within the TLR5 ligand binding domain (TLR5392STOP) (Hayashi et al., 2001). TLR5 recognition of flagellin regulates early neutrophil recruitment to the lung and influences persistence of airspace inflammation up to 6 days after infection (Hawn et al., 2007). The TLR5392STOP mutation functions as a dominant negative receptor that severely impairs signaling and this mutation is associated with susceptibility to pneumonia caused by *Legionella pneumophila* (Hawn et al., 2003). These data emphasize the important role for TLR5 in the innate immune response of the lung epithelium.

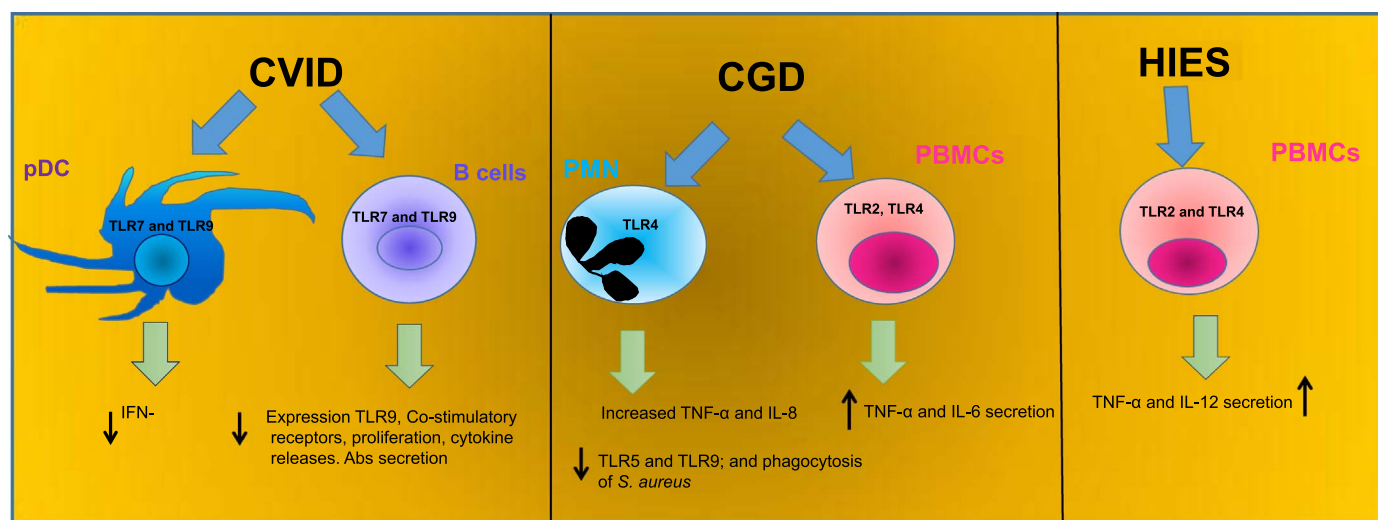
#### 3.2. Mycobacterial infection

##### 3.2.1. Mendelian susceptibility to mycobacterial diseases (MSMD)

MSMD is a rare syndrome caused by weakly virulent mycobacteria, such as *Mycobacterium bovis* BCG vaccines and non-tuberculous environmental mycobacteria (OMIM 209950) (Hamosh et al., 2005; Casanova and Abel, 2002; Filipe-Santos, 2006). Defects in the IL-12/IFN $\gamma$  receptors and their signaling have an important role in the pathogenesis of the MSMD due to reduced expression and/or function of these mediators which play an important role in intracellular *Mycobacterium* killing. Mutations in two genes, NEMO/IKK $\gamma$  and CYBB (which encodes for gp91phox – an essential component of the NADPH oxidase in phagocytes), have long been known to cause other human diseases such as incontinentia pigmenti and anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID). EDA-ID is a complex developmental and immunological syndrome caused by hypomorphic mutations in NEMO/IKK $\gamma$  which encodes a regulatory component of the IKK complex (Zonana et al., 2000; Jain et al., 2001; Doffinger et al., 2001).

Recently, mutations in both these genes have been shown to cause X-linked (XR)-MSMD. The MSMD-causing mutations in NEMO/IKK $\gamma$  selectively affect the CD40-dependent induction of IL-12 in mononuclear cells whereas the MSMD-causing mutation in CYBB selectively affects the respiratory burst in macrophages. Mutations in NEMO/IKK $\gamma$  and CYBB may therefore cause MSMD by selectively exerting their deleterious impact on a single signaling pathway (CD40–IL-12, NEMO) or a single cell type (macrophages, CYBB) (Jouanguy et al., 2007; Zhang et al., 2008). On the other hand, mutations in five autosomal genes involved in IL-12–dependent, IFN $\gamma$ –mediated immunity cause MSMD (Filipe-Santos, 2006) and NEMO/IKK $\gamma$  is clearly connected with the IL-12–IFN $\gamma$  circuit and MSMD may therefore be described as a disorder of IL-12–IFN $\gamma$  signaling. The connection of the CYBB mutation with the previously identified mutations in autosomal genes controlling IL-12–IFN $\gamma$  signaling is less clear. Thus, both NEMO/IKK $\gamma$  and CYBB may be considered as MSMD-causing genes and MSMD is therefore allelic with two other XR PIDs: EDA-ID (NEMO) and CGD (CYBB).

In contrast, as STAT1 is a key signaling component of IFN response (Chapigier et al., 2009) and a deficiency in STAT1-dependent cellular responses to both IFN $\alpha/\beta$  and IFN $\gamma$  caused by autosomal recessive



**Fig. 2. Possible role of TLRs in pathogenesis of CGD, CVID and hyper IgE syndrome.** Cell type specific functional defects of TLR signaling in CVID, CGD and hyper IgE syndrome. While the normal pDC response to stimulation with TLR7 and TLR9 agonists is secretion of high levels of IFN- $\alpha$ , pDCs of subjects with CVID show defective responses. Similarly, while normal B cells are sensitive to stimulation with TLR7 and TLR9 agonists, B cells from patients with CVID are less responsive. Neutrophils from CGD subjects express and release greater amounts of inflammatory cytokines in response to TLR4 but have a reduced response, particularly phagocytosis of *S. aureus*, in response to TLR5 and TLR9 activation. PBMCs from these subjects have a greater inflammatory response (TNF- $\alpha$  and IL-6) to TLR2 and TLR4 stimulation. A similar heightened cytokine secretory response (TNF- $\alpha$  and IL-12) to TLR2 and TLR4 stimulation is seen in PBMCs from patients with hyper IgE syndrome. Abbreviations CVID, common variable immunodeficiency; CGD, chronic granulomatous disease; pDC, plasmacytoid dendritic cell; TLR, Toll-like receptor.



complete STAT1 deficiency and partially recessive STAT1 mutations have been described in MSMD (Kong et al., 2010; Chapgier et al., 2009; Vairo et al., 2011; Dupuis et al., 2003; Chapgier et al., 2006). In STAT1 deficient patients, responses to both IFN $\alpha$  and IFN $\gamma$  are impaired (Chapgier et al., 2009) resulting in downstream effects on IL-27 and IFN  $\gamma$ 1 signaling pathways and thereby potentially contributing to the predisposition to bacterial and viral infections respectively (Chapgier et al., 2009).

In addition, active phosphorylated STAT1/STAT2 heterodimers are released into the cytosol, where they combine with IFN-stimulated gene factor 3 $\gamma$  (ISGF3 $\gamma$ ), also known as p48 or IRF9, to form ISGF3 (Chapgier et al., 2009). ISG15 is an intracellular ubiquitin-like molecule involved in ISGylation (Farrell et al., 1979), is IFN $\alpha$ / $\beta$ -inducible and when secreted acts on T-cells and NK cells to induce IFN $\gamma$  production (Bogunovic et al., 2012).

ISG15 is released by human neutrophils, monocytes and lymphocytes and is present in the secretory granules of granulocytes (Bogunovic et al., 2013). The lack of mycobacterium-induced ISG15 secretion by granulocytes reduces IFN $\gamma$  production by NK cells. Thus, ISG15 plays an essential role as an IFN $\gamma$ -induced secreted molecule for optimal anti-mycobacterial immunity (Bogunovic et al., 2012) (Fig. 2).

### 3.2.2. TLRs in mycobacterial infection

Mycobacterial infection affects PIDs such as severe combined immunodeficiency (SCID) and chronic granulomatous diseases (CGD, gp91phox, gp22phox, gp47phox, gp67phox) (Casanova, 2002; Dorman, 2000; Alinejad Dizaj et al., 2016; Casanova et al., 1995; Bustamante, 2007; Bustamante, 2011). Recent evidence suggests that there is an altered TLR agonist response in CGD patients which is cell-type dependent. For example Rahman and colleagues reported that CGD peripheral blood-derived macrophages released significantly lower levels of pro-inflammatory cytokines after 24 h stimulation with TLR2 and TLR4 agonists (Rahman et al., 2009). However, earlier studies reported increased inflammatory cytokine release following stimulation of peripheral blood leukocytes with TLR2 and TLR4 agonists (Bylund et al., 2007).

There are no reports of TLR abnormalities in severe combined immunodeficiency (SCID). However, TLR2 and TLR4 play a major role in the enhanced inflammation seen in SCID mice (Mutoh et al., 2009). In addition, PID patients with IRAK4 deficiency have recurrent severe infections (cellulitis, arthritis, meningitis, osteomyelitis, organ abscesses and sepsis) mainly caused by *S. aureus*, *S. pneumoniae* (*pneumococcus*) and *Pseudomonas aeruginosa* (Picard et al., 2011). Similar to patients with MyD88 defects, the clinical status of these patients with IRAK-4 deficiency improves with age, regardless of therapy.

## 4. Herpes simplex encephalitis (HSE)

Herpes simplex encephalitis, was first described in 1941 (Smith et al., 1941) and is the most common sporadic viral encephalitis in the Worldwide (Whitley and Kimberlin, 2005). Pattern recognition of viruses is mediated by TLR3, TLR7/8 and TLR9 and members of Rig1 helicase family. Although no defects in the Rig1 helicase family have been reported, increased susceptibility to HSV encephalitis has been described in patients with heterozygous mutations of a TLR3 pathway gene such as TLR3, UNC93B1, TRIF, TRAF3, and TBK1 (Zhang et al., 2013). TLR3 is one of the most highly conserved TLRs in humans and recognizes dsRNA, a by-product produced during viral replication of most viruses including HSV-1 (Jacobs and Langland, 1996). TLR3 is expressed on CNS-resident cells that are permissive for HSV-1 infection (Lafaille et al., 2012). High susceptibility to HSV-1 infection in patient-specific induced pluripotent stem cells (iPSC) derived from UNC-93B1 and TLR3-deficient neurons and oligodendrocytes has been demonstrated recently (Lafaille et al., 2012). Impaired CNS-intrinsic TLR3-dependent IFN $\alpha$ / $\beta$  and IFN $\gamma$  immunity to HSV-1 may therefore underlie HSE in children at

the age of 3 month to 6 years with TLR3 pathway deficiencies (Lafaille et al., 2012) (Fig. 2).

## 5. Role of TLRs in chronic granulomatous disease

Chronic granulomatous disease (CGD) is caused by genetic mutations in components of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase signaling which induces reactive oxygen species required for the respiratory burst which is used by phagocytes to kill bacteria (Segal et al., 2000; Bylund et al., 2005; Rosenzweig, 2008; Gardiner et al., 2013). In the absence of a functional NADPH oxidase system, neutrophils are incapable of killing phagocytosed bacteria and fungi, leaving patients at increased risk of recurrent pyogenic infections (Al-Herz et al., 2014). Other immune defects in CGD patients include inflammatory disorders, which are restricted to the gastro-intestinal tract, that are thought to be independent of infection (Al-Herz et al., 2014; Alimchandani et al., 2013).

Furthermore, a usual form of CGD is caused by mutations in the X-chromosome located CYBB gene, which affects males but importantly spares the carrier mothers (Al-Herz et al., 2014).

NADPH oxidase activation and reactive oxygen species generation in murine macrophages and neutrophils is dependent on the TLR signaling components MyD88 and phospho-p38 MAPK pathways (Laroux et al., 2005). Moreover, dendritic cells that have matured in response to exposure to TLR2 or TLR4 agonists express higher levels of p47phox and gp91 phox in the cells (Vulcano et al., 2004). However, most observations regarding the role of the TLRs system in CGD is based on studies in primary human cells from patients with CGD.

For example, peripheral blood mononuclear cells secrete increased levels of TNF- $\alpha$  and CXCL8/IL-8 following LPS stimulation (Hatanaka et al., 2004). Later studies also reported that CGD PBMCs treated with TLR2 and TLR4 agonists secreted higher levels of TNF- $\alpha$  and IL-6 (Bylund et al., 2007). These studies also demonstrated that TLR-induced activation of NF- $\kappa$ B was independent of reactive oxygen species production. These authors proposed that reactive oxygen species are needed for the appropriate dampening of responses to TLRs signaling. This was further supported by the observation that a lack of a ROS response to TLR stimulation is correlated with greatly enhanced cytokine release from CGD monocytes stimulated by LPS (Brown et al., 2008).

Further investigation of TLRs in CGD patients demonstrated that the expression of TLR5 and TLR9, but not of TLRs 1, 2, or 4, were lower in neutrophils of CGD patients (Hartl et al., 2008). In contrast, B lymphocytes derived from patients with CGD produced elevated levels of pro-inflammatory and anti-inflammatory cytokines upon TLR7 or TLR9 stimulation (McLetchie et al., 2015). This hyper-response to TLR ligands was explained, in part, by the up-regulation of TLR7 and TLR9 mRNA and protein expression in the oxidase-deficient human B cells. Furthermore, B cells with defects in NADPH oxidase function had a greater phosphorylation of the downstream p38 MAPK compared with oxidase-sufficient B cells (McLetchie et al., 2015).

## 6. Role of TLRs in common variable immunodeficiency disease

Common variable immunodeficiency (CVID), the most common symptomatic PID, is a diagnosis by hypogammaglobulinemia and recurrent sinupulmonary recurrent infections from inadequate quantity and quality of protective antibodies (Chapel and Cunningham-Rundles, 2009; Al-Herz et al., 2014). CVID patients are at increased risk of autoimmune, inflammatory, and malignant complications (Mortaz et al., 2016; Cunningham-Rundles and Bodian, 1999). CVID encompasses a heterogeneous group of patients, the large majority having no known underlying genetic cause (Al-Herz et al., 2014).

Given the hallmark of hypogammaglobulinemia, B cells have been heavily studied in this disorder, with defects reported in proliferation,

class switch recombination, differentiation, and immunoglobulin (Ig) secretion. In addition, T cell cytopenia and defects in TLR-independent cytokine production (Giovannetti et al., 2007) and reduced numbers of dendritic cells (Viallard et al., 2005; Taraldsrud et al., 2014) have been described in CVID patients. In addition, there is evidence for increased monocyte activation *in vivo* in these patients (Barbosa et al., 2012).

B cells and plasmacytoid dendritic cells (pDCs) from CVID patients have defective TLR7 and TLR9 signaling associated with deficient IFN- $\alpha$  secretion, impaired B cell function alter innate immune responses. These defects may account for the increased susceptibility to the enteroviral and rhinoviral infections seen in these patients (Yu et al., 2009; Dropulic and Cohen, 2011). In addition, activation of Th22/Tc22 cells with TLR2 and TLR7/8 agonists induced a polyfunctional response only in CD4<sup>+</sup> CD38<sup>+</sup> T cells with no effect in CD8<sup>+</sup> cells (de Lollo et al., 2016). Overall, these data may suggest a potential role for TLR ligands as adjuvants to stimulate adaptive T cell responses and provide evidence for a CD8<sup>+</sup> T cell population that is unresponsive to innate stimuli in CVID patients.

## 7. Summary

In summary, we have highlighted here that defects in TLRs and downstream signaling pathways have been detected in many patients with PIDs. Further delineation of these defects may not only provide greater insight into disease mechanisms but may result in novel therapeutic opportunities including gene therapy for these patients.

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