European Journal of Pharmacology 808 (2017) 49–56

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Full length article

Pattern recognitions receptors in immunodeficiency disorders

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ARTICLE INFO

Keywords:
Primary immune deficiencies
IgE syndrome
TLRs
Chronic granulomatous disease

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-κB 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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http://dx.doi.org/10.1016/j.ejphar.2017.01.014
Received 18 October 2015; Received in revised form 4 January 2017; Accepted 13 January 2017
Available online 14 January 2017

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 *Staphylicoccus aureus* and *E. coli* 23 S rRNA that can induce a TLR13-dependent transcriptional response resulting in pro-IL-1β 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 κB (NF-κB) 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-1β, −6, −8, and −12 and TNF-α via and NF-κB-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-κB essential modulator (NEMO) and the NF-κB inhibitor IKB-α (Courtois et al., 2003; Doffinger, 2001; Picard et al., 2003; von Bernuth et al., 2008). Defects in NEMO and IKB-α 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)