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Immunobiology of toll-like receptors in allergic disease

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Abstract

Allergic diseases prevalence rates have increased dramatically over the last 50 years in developed countries and one explanation might be that modern practices in public health lead to a decreased exposure towards pathogens resulting in a misguided immune response.

Recently, it has become evident that immune responses against pathogens are initiated by Toll-like receptors (TLRs) that recognize a variety of structures derived from viruses, bacteria, fungi or protozoa. In this review we will discuss TLR ligands, TLR signaling in regard to Th1 and Th2 immune responses, their involvement in the development and their therapeutic potential in treatment of allergic disease.
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Keywords: Toll-like receptors; Allergy

Abbreviations: CMV, cytomegalovirus; GPI, glycosylphosphatidylinositol; HSV, herpes-simplex virus; IC, immune complex; IRAK-1, IL-1 receptor associated kinase 1; IRAK-4, IL-1 receptor associated kinase 4; IRF, interferon regulatory factor; ISRE, interferon stimulated response element; JNK, jun amino-terminal kinase; LBP, LPS binding protein; LCMV, lymphochoriomeningitis virus; LPS, lipopolysaccharide; LTA, lipoteichoic acid; MAL, MyD88-adaptor like; MCMV, murine cytomegalovirus; MMTV, mouse mammary tumor virus; MyD88, myeloid differentiation protein 88; NDV, newcastle disease virus; NF-κB, nuclear factor κB; NIPCs, natural interferon-α producing cells; PAMP, pathogen associated molecular pattern; PDC, plasmacytoid dendritic cell; PG, peptidoglycan; RIP1, receptor-interacting protein-1; RSV, respiratory syncytial virus; TBK1, TANK binding kinase 1; TICAM1, TIR domain containing molecule 1; TIRAP, TIR-associated protein; TLR, toll-like receptor; TRAF-6, TNF receptor associated factor-6; TRAM, TRIF-related adaptor molecule; TRIF, TIR-domain containing adaptor protein-inducing IFNß; VSV, vesicular stomatitis virus; WNV, West Nile virus

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Toll-like receptors and their ligands

Toll receptors are type I transmembrane proteins that are evolutionarily conserved between insects and vertebrates (Rock et al., 1998). In Drosophila, Toll was first identified as an essential molecule for dorsal-ventral patterning of the embryo and subsequently as a key molecule for the antifungal immune response in the adult animal (Anderson et al., 1985; Lemaitre et al., 1996). A homologous family of toll receptors, termed toll-like receptors (TLRs) exists in vertebrates (Rock et al., 1998). So far, 13 members (TLR1-13) have been reported which are fundamental in recognition of pathogen associated molecular patterns (PAMPs) (Tabeta et al., 2004; Takeda and Akira, 2005). The family of TLRs recognizes various PAMPs from different pathogenic origins such as bacteria, viruses, fungi or protozoan parasites (Table 1) (Tabeta et al.,

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Table 1. Pathogen derived ligands for TLRs

Receptor	Ligand
TLR1/TLR2	Triacyl lipopeptide
TLR2	Lipoprotein/lipopeptide, Lipoteichoic acid, Glycoinositol-phospholipids, Hemagglutinin, Structural viral proteins, Glycoinositolphospholipid *Endogenous ligands: Gp96,Hsp60, Hsp70, Hyaluronic acid, HMGB1*
TLR3	Double-stranded RNA
TLR4	Lipopolysaccharide, RSV fusion protein, MMTV envelope protein *Endogenous ligands: Gp96, Hsp60, Hsp70, Hyaluronic acid, Heparan sulphate, Fibronectin, Fibrinogen, Surfactant-protein A, HMGB1, β-defensin*
TLR5	Flagellin
TLR6/TLR2	Diacyl lipopetides
TLR7	Imidazoquinoline, loxoribine,
TLR8	Imidazoquinoline, ss RNA
TLR9	CpG-containing DNA
TLR10	?
TLR11	Profilin
TLR12, 13	?

2004). One subfamily of TLRs that consists of TLR1, 2, 4, 5, 6 and 11 is expressed on the surface of cells, recognizes a plurality of different structures and can be phagocytosed. In contrast, the other subfamily is formed by TLR3, 7, 8 and 9 that are localized inside the cell in the endoplasmic reticulum and endosomes or lysosomes where these receptors recognize nucleic acid (see below).

TLR4

The endotoxin lipopolysaccharide (LPS), a compound of the outer cell membrane of gram negative bacteria is a very potent PAMP among the cell wall components. The lipid portion of the LPS, termed Lipid A, is responsible for the immune stimulating activity (Alexander and Rietschel, 2001). TLR4 is the key molecule of LPS induced signaling (Poltorak et al., 1998) and utilizes several cofactors for efficient recognition. LPS associates first with LPS binding protein (LBP) and then with CD14, a glycosylphosphatidylinositol (GPI) anchored protein (Heumann et al., 2003). This complex binds to MD2 and associates with TLR4 which leads to its aggregation and subsequent signaling (Poltorak et al., 1998; Shimazu et al., 1999). Some viral-envelope proteins such as the fusion protein F from respiratory syncytial virus (RSV) and the envelope protein of mouse mammary tumor virus (MMTV) also activate TLR4 and induce cytokine production (Kurt-Jones et al., 2000; Haynes et al., 2001; Rassa et al., 2002; Jude et al., 2003). In addition, MMTV activates B cells via TLR4 and induces maturation of bone marrow-derived dendritic cells that up-regulate expression of the MMTV entry receptor (CD71) and therefore facilitate infection and may attenuate the antiviral response (Rassa et al., 2002; Burzyn et al., 2004).

TLR2, TLR1 and TLR6

Apart from LPS other components of the cell wall found in gram positive and gram negative bacteria can stimulate innate immune cells. For example, lipoteichoic acid (LTA), an amphiphilic negatively charged glycolipid and lipoproteins are potent immune stimulators and activate TLR2 (Schwandner et al., 1999; Takeuchi et al., 1999). TLR2 associates with TLR1 and TLR6 and this interaction allows discrimination of differences within the lipid part of lipoproteins. Accordingly the TLR2/TLR1 heterodimer recognizes triacylated lipopeptides, whereas the complex consisting of TLR2 and TLR6 is activated by diacylated lipopeptides (Alexopoulou et al., 2002; Ozinsky et al., 2000; Takeuchi et al., 2001; Takeuchi et al., 2002). Furthermore, LPS from certain bacterial strains such as *Legionella pneumophila*, *Leptospira interrogans* and *Porphyromonas gingivalis* has been described to act as a ligand for TLR2 and not for TLR4 (Werts et al., 2001; Girard et al., 2003; Akamine et al., 2005). However, these results must be viewed with caution since impurities in the LPS preparation could account for a LPS independent TLR2 activation (Asai et al., 2005). The recognition of peptidoglycan (PG), a large molecular structure composed of alternating *N*-acetyl glucosamine (GlcNac) and *N*-acetyl muramic acid (MurNac) sugar chains that are interlinked by peptide bridges has also been attributed to TLR2, but this observation is still controversial (Schwandner et al., 1999; Michelsen et al., 2001). Again the contribution of TLR2 in the recognition of PG must be viewed with caution since impurities in the biochemically purified PG such as lipoproteins or LTA could account for TLR2 activation (Travassos et al., 2004). In addition, TLR2 is activated by viral proteins such as the hemagglutinin from measles virus and structural proteins from cytomegalovirus (CMV) and herpes-simplex virus-1 (HSV-1) (Bieback et al., 2002; Compton et al., 2003; Kurt-Jones et al., 2004; Aravalli et al., 2005). The protozoan parasites *Trypanosoma cruzi*, *Toxoplasma gondii*, *Leishmania major* and *Plasmodium falciparum* contain further TLR2 ligands such as GPI anchors (Mun et al., 2003; de Veer et al., 2003).

TLR5

Many pathogens are motile and use a flagellum as the motility apparatus. The major component of the flagellum

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