Allergol Immunopathol (Madr). 2015;43(4):416–420

Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica

www.elsevier.es/ai

REVIEW

Toll-like receptor 4 plays significant roles during allergic rhinitis

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Received 2 January 2014; accepted 2 April 2014
Available online 3 August 2014

KEYWORDS
Allergic rhinitis;
TLR4;
Inflammation

Abstract Allergic rhinitis is a nasal hypersensitivity and allergic disease which leads to inflammation of nasal mucosa. Previous investigations revealed that innate immune receptors play a key role in the pathogenesis of inflammatory diseases including allergic diseases. Toll-like receptors (TLRs), which are important innate immune receptors, play crucial roles in the recognition of foreign antigens, including allergens, and subsequently for the induction of immune responses such as inflammation. There are several controversial reports regarding the roles of TLR4 in the pathogenesis of allergic rhinitis. This review presents current information regarding the roles of TLR4 in the pathogenesis of allergic rhinitis and the plausible mechanisms which lead to the expression and function of TLR4 in this disease.

Abbreviations: AP-1, activator protein 1; DAMP, damage associated molecular patterns; IRAK1, interleukin-1 receptor associated kinase-1; LBP, LPS binding protein; LPS, lipopolysacharide; MAPK, mitogen-activated protein kinase; MD2, myeloid differentiation factor 2; MHC, major histocompatibility complex; MYD88, myeloid differentiation primary response; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PAMP, pathogen associated molecular patterns; PRR, pathogen recognition receptor; TAK1, transforming growth factor b-activated kinase 1; TIRAP, TIR domain-containing adaptor protein; TLR, Toll-like receptor; TRAF6, TNF receptor associated factor; TRAM, TRIF-related adaptor molecule; TRIF, TIR-domain-containing adapter-inducing interferon-β.

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http://dx.doi.org/10.1016/j.aller.2014.04.006
0301-0546/

Introduction

Toll-like receptors (TLRs) are the main intra/extra-cellular immune cell receptors which belong to the pathogen recognition receptor (PRR) family. These molecules play crucial roles in the recognition of pathogen associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs) and subsequently facilitate the induction of immune responses such as inflammation.[1]

TLR/PAMP or DAMP interactions result in various alterations in immune cell function and surface molecules including expression of homing molecules,[2] NADPH oxidase activation[3] and inflammatory cytokine secretion.[4] Like other TLRs, TLR4 acts via interaction with its corresponding ligands (see following sections) in both MYD88 and TRIF dependent manners.[5]

Allergic rhinitis is an allergic disease of nasal airways which is associated with inflammatory conditions and it may be hypothesised that TLR4 may play critical roles in the pathogenesis of allergic diseases such as allergic rhinitis. Therefore, the aim of this study was to review recent information regarding the relationship between TLR4 and allergic rhinitis. This study also presents recent information regarding the possible mechanisms leading to alterations in the expression of TLR4 and its signalling molecules in these patients.

Allergic rhinitis: an inflammatory disease

Allergic rhinitis, which is also known as nasal allergy and nasal hypersensitivity, is defined as an allergic condition of the nasal airways.[6,7] It can be induced in individuals with a sensitised immune system via inhalation of an allergen, including pollen and dust or particles of shed skin and hair of animals (animal dander).[8] In sensitive individuals, the allergen stimulates the production of IgE which binds to FCεRI on mast cells and basophiles and induces secretion of several mediators including histamine, leukotrienes, prostaglandins and associated enzymes including tryptase.[8] These mediators cause nasal passages swelling, paroxysmal repetitive sneezing, itchy and watery eyes and elevation in mucus production, via stimulation of the mucous glands and vascular permeability (known as primary phase) and activation and perpetuation of inflammatory cells (late phase).[9] The severity of symptoms varies among individuals. Pollinosis and hay fever are two forms of allergic rhinitis caused by pollens of any plants and grass pollens, respectively.[10,11] It has been documented that genetic, immunological and environmental parameters play important roles in the pathogenesis of allergic rhinitis.[12] Allergic rhinitis is prevalent worldwide and investigators estimate that 30% of people experience this disease at least once in their lives.[13] Depending on the causative antigens, period of exposure, severity of symptoms and disease types, allergic rhinitis is classified to several clinical manifestations. The most commonly used classification uses perennial and seasonal occurrence to define the disorder.[14] There are various forms of therapies for allergic rhinitis as follows: (1) oral antihistamines, (2) topical antihistamines, (3) decongestants (via activating alpha-adrenergic receptors), (4) intranasal glucocorticoids, (5) leukotriene receptor antagonists and (6) intranasal cromolyns (by stabilisation and inhibition of the degranulation of mast cells).[15,16] The current therapies are associated with several side effects and in some cases patients present drug resistance; hence, novel therapies must be explored for the treatment of this disease.[17] In order to design a successful therapy, it is important to understand the roles played by immune-related molecules.

TLR4: structure, genomic location and agonists

TLR4, which is also known as CD284 or ARMD10, is the receptor for several microbial PAMPs, which will be discussed below. The TLR4 protein consists of three complex domains including extracellular leucine-rich repeats (LRRs), a hydrophobic transmembrane and an intracytoplasmic Toll/interleukin-1 receptor (TIR) domain. TLR4 recognises several microbial and non-microbial molecules as a homodimer which leads to the activation of various intracellular signalling pathways (see following sections).

Various molecules have been identified as agonists for TLR4.[18] LPS is the most important agonist of TLR4 and is recognised by a TLR4/CD14/MD2 complex.[19] LPS binding protein (LBP) is responsible for binding LPS to a glycosylphosphatidylinositol-anchored protein called CD14 which subsequently delivers the LPS to a soluble protein, MD2 (also known as lymphocyte antigen 96).[19] MD2 binds non-covalently to the extracellular domain of TLR4 inducing a conformational change in the MD-2 structure which results in binding of the MD-2-TLR4 complex to a second TLR4 molecule.[19] Following TLR4 homo-dimerisation, TRIF and MYD88 dependent intracellular signalling pathways will be activated (see next section). Short ragweed (SRW) pollen, high-mobility group box-1, hyaluronan, heat shock protein 60, free fatty acids, allergenic nickel and the adjuvant monophosphoryl lipid A (MPLA) are agonists for TLR4 which are used as adjuvants for the induction of immune responses against vaccination.[20–22] Interestingly, high-mobility group box-1, hyaluronan, heat shock protein 60 and free fatty acids, which are endogenous TLR4 ligands, not only activate TLR4 directly, but can also bind and transport LPS to TLR4 which increases cell sensitivity to LPS suggesting that endogenous TLR4 ligands can be considered as PAMP binding/sensitising molecules.[23]

TLR4 signalling

Interactions of TLR4 and its corresponding ligands lead to the recruitment of TIRAP/MYD88 and TRAM/TRIF, TIR-containing adaptor molecules, which participate in stimulation MYD88 and TRIF-dependent signalling pathways, respectively.[24] Previous in vitro and in vivo studies demonstrated that TLR4/ligands interaction at the plasma membrane leads to recruitment of TIRAP which allows binding of the adaptor protein, MyD88. Following recruitment of MYD88 several intracellular signalling molecules such as IRAK4, IRAK1, TRAF6, TAK1, NF-κB, AP-1 and IRF5 are activated.[18] NF-κB, AP-1 and IRF5 are transcription factors that induce transcription of several pro-inflammatory cytokines.[25] Additionally, upon internalisation of TLR4 to the endosomes and interactions with its agonists, another signalling pathway, the