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REVIEW

The roles of toll like receptor 3, 7 and 8 in allergic rhinitis pathogenesis

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Abstract Allergic rhinitis, as an allergic and nasal hypersensitivity disease, is associated with the inflammation of nasal mucosa. It appears that innate immune receptors are the important risk factors in the pathogenesis of the inflammatory disease. Toll-like receptors (TLRs) are the most important receptors of innate immunity; their crucial roles in the recognition of allergens and subsequently pathogenesis of allergic diseases have been evaluated recently. TLR3, 7 and 8 are the intracellular members of the innate immune receptors and recognize intracellular single and double strand RNAs. This review article collected the investigations regarding the roles of TLR3, 7 and 8 in the allergic rhinitis pathogenesis.

Abbreviations: AP-1, activator protein 1; DAMP, damage associated molecular patterns; IRAK1, interleukin-1 receptor associated kinase-1; LBP, LPS binding protein; LPS, lipopolysaccharide; 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 receptors; 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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Introduction

Innate immunity is a main full consideration target for involvement in human pro-inflammatory diseases including allergic diseases.[1] Innate immunity contains several receptors which have common features regarding ligand recognition.[2,3] Innate immune receptors recognize ligands with similar features entitled pathogen associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs).[4] Toll-like receptors (TLRs), as the most known innate immune receptors, express either on the cell membrane or in the cytoplasmic vesicles.[5,6] These molecules recognize a wide range of PAMPs/DAMPs and subsequently can participate in the recognition of several pathogens/allergens and also may participate in the induction of the immune related diseases.[7] TLR3, 7 and 8 are the most important receptors which recognize single and double strand RNAs and subsequently activate pro-inflammatory transcription factors through two distinct intracellular signaling pathways.[6,8] Accordingly, it has been hypothesized that the TLRs may participate in human pro-inflammatory based diseases.

Allergic rhinitis is a pro-inflammatory based disorder which is categorized as an allergic disease.[1] The disease is associated with nasal airways damages and is prevalent in both developed and developing countries.[9] Based on the crucial roles of innate immunity responses in human pro-inflammatory based diseases, it may be hypothesized that TLR3, 7 and 8 may play significant roles in the induction and progression of allergic rhinitis. This review article has aimed to describe the roles of TLR3, 7 and 8 in the pathogenesis of allergic rhinitis.

Description of allergic rhinitis

Allergic rhinitis is associated with an inflammation in the nasal membrane[10] in which eyes, ears, sinuses and oropharynx may be involved.[9] After exposure to a specific allergen, IgE will be produced and binds to mast cells to produce sensitive mast cells which respond to re-entered allergens and accordingly some mediators will be released from mast cells.[11] These mediators like histamine, tryptase, chymase, kinins, and heparin can lead to the symptoms like rhinorrhea, sneezing, itching, nasal congestion, redness, tearing, swelling, ear pressure and post nasal drip.[12] Approximately 30–60 million people (10–30 present of adults and 40 present of children) are affected by allergic rhinitis in each year.[13] However, mortality is rare but some morbidities like otitis media, eustachian tube dysfunction, sinusitis, nasal polyps, atopic dermatitis and allergic conjunctivitis are associated with allergic rhinitis.[14] Treatment of allergic rhinitis according to treatment of allergic rhinitis by American family physicians is dependent on the severity of symptoms. The first line is second-generation oral or intra nasal antihistamine. Decongestants or nasal irrigation for nasal congestion, intranasal antihistamines or ipratropium for rhinorrhea, corticosteroids for mild to moderate symptoms intranasal and intranasal cromolyn and corticosteroids can be administrated in severe cases.[15,16] Oral leukotriene receptor antagonist with oral or nasal antihistamine is considered and if the symptoms persist we can choose immunotherapy.[17] Based on the effects of the anti-inflammatory effects of the chemotherapies on the expression and functions of TLRs, it has been hypothesized that TLRs may participate in the pathophysiology of allergic rhinitis. Additionally, based on the fact that the most current therapies can be associated with various side effects, thus, novel molecular therapies need to be explored for the treatment of this disease.[17] Therefore, if TLR3, TLR7 and TLR8 participate in the pathophysiology of allergic rhinitis, hence, they may be considered as future targets for molecular therapies.

Introducing of TLR3, TLR7 and TLR8

TLRs have a similar structure including, three well known domains, leucine-rich repeats (LRRs), transmembrane and Toll/interleukin-1 receptor (TIR). The LRRs domain is the section responsible for recognition of appropriate ligands, while TIR domain participate in activation of intracellular signaling pathways. TLRs recognize their ligand in both homodimeric and heterodimeric forms. TLR3, 7 and 8 recognize their ligand in homodimeric forms only in the intracellular cytoplasmic vesicles. TLR3 recognizes double-strand RNAs (dsRNAs), while TLR7 and TLR8 target double-strand RNAs (dsRNAs). TLR3/ligand interaction leads to activation of intracellular signaling in TIR-domain-containing adapter-inducing interferon-β (TRIF) dependent pathway, while, TLR7 and TLR8/ligands interactions result in activation of the intracellular signaling in myeloid differentiation primary response (MYD88) dependent pathway.

TLR3, 7 and 8 and their roles in allergic rhinitis

Although an in vitro study by Globinska et al. revealed that innate immune responses to TLR3, TLR7 and TLR8 agonists were similar in nasal epithelial cells obtained from both patients with allergic rhinitis and healthy controls,[18] based on the important roles of TLR3, TLR7 and TLR8 in recognition of ds/ss-RNAs, it has been hypothesized that expression and functions of the intracellular receptors may be complicated during allergic rhinitis. Interestingly, previous and recent investigations demonstrated that associations of TLR3, TLR7 and TLR8 with allergic rhinitis are different.

Accordingly one study demonstrated that mesenchymal stem cells derived from the patients suffering from allergic rhinitis express TLR3 more than other TLRs such as TLR5 and TLR2.[19] Although mesenchymal stem cells play key roles in regulation of immune responses in the human tissues,[20,21] they play controversial roles during allergic rhinitis and induce a significant increased activation of allergen-challenged lymphocytes from allergic rhinitis subjects and consequently increased expressions of inflammatory cytokines, major histocompatibility complex (MHC)-II and ligands for co-stimulatory factors, CD86.[22] Increased expression of TLR3 on the mesenchymal stem cells in patients suffering from allergic rhinitis[19] may propose that TLR3 may participate in the different functions of the cells during allergic rhinitis. In other words, it appears that TLR3 is a key molecule to induce pro-inflammatory properties of mesenchymal stem cells during allergic rhinitis. In addition

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