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Critical role of Toll-like receptors in pathophysiology of allergic asthma

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ABSTRACT

Allergic asthma is an airway disease, characterized by reversible bronchoconstriction, chronic inflammation of the airway, and thickness of smooth muscle in the respiratory tract. Asthma is orchestrated by an excessive Th2-adaptive immune response, in which innate immunity plays a key role. Recently TLRs have received more and more attention as they are central to orchestrate the innate immune responses. TLRs are localized as integral membrane or intracellular glycoproteins with those on the cell surface sensing microbial antigens and the ones, localized in intracellular vesicles, sensing microbial nucleic acid species. Having recognized microbial antigens, TLRs conduct the immune response towards a pro- or anti-allergy response. As a double-edged sword, they could initiate either harmful or helpful responses by the immune system in case of allergic asthma. In the current review, we will describe the role of TLRs and their signaling pathways in allergic asthma.

1. Introduction

Allergic asthma is a complicated chronic airway inflammatory disorder with a globally increasing rate of prevalence and occurrence over the past decades (Lambrecht and Hammad, 2012; Wu et al., 2014). Asthma is characterized by reversible bronchoconstriction, chronic inflammation of the airway, infiltration of eosinophils, hyper-responsiveness, and thickness of smooth muscle cell layer in the airway. The chronic inflammation in asthma is usually eosinophilic and is orchestrated by a complex network of different inflammatory cytokines with positive or negative feedback on each other. It leads to hypertrophy of smooth muscle cells, hyperplasia of mucus-secreting goblet cells, angiogenesis, and fibrosis (Athari and Athari, 2014; Lambrecht and Hammad, 2012; Wu et al., 2014).

Th2 response plays a key role in asthmatic patients as it both causes the immune cells increase and releases inflammatory mediators within the respiratory tract. IgE-producing B cells are the main cells responsible for pathophysiology of asthma (Lambrecht and Hammad, 2015; Wu et al., 2014). Asthma is handled by complex mechanisms. Although innate immunity plays a key role in asthma, excessive amount of Th2-adaptive immune responses lead to a subsequent development of pathogenesis in the disease (Hilvering et al., 2015; Lambrecht and Hammad, 2015; Szefler, 2013).

Thanks to specific Pattern-Recognition Receptors (PRRs) such as the Toll-Like Receptors (TLRs), innate immune system can recognize some antigenic molecules from microbes, known as Pathogen-Associated Molecular Patterns (PAMP) (Akira and Takeda, 2004). TLRs and Nucleotide-binding oligomerization domain-like receptors (NLRs) are two species of PRRs (Akira and Takeda, 2004; Kawai and Akira, 2010). NF-κB is the main controlling factor to signal the pathway of the TLRs that can get involved in the production of many pro-inflammatory cytokines and chemokines. Some of the most important TLRs are integral membrane glycoproteins, which have leucine-rich repeat motifs in the recognizing domain. TLRs are divided into two groups: 1) TLR1, 2, 4, 5, 6, 10, and 11 are expressed on the cell surface, recognizing proteins, lipoproteins, and polysaccharides in the bacteria and 2) TLR3, 7, 8, and 9 are localized within intracellular vesicles where they sense different types of microbial nucleic acids (Akira and Takeda, 2004; Kawai and Akira, 2010; Tesse et al., 2011).

Up to now, 12 TLRs and more than 20 NLRs have been identified

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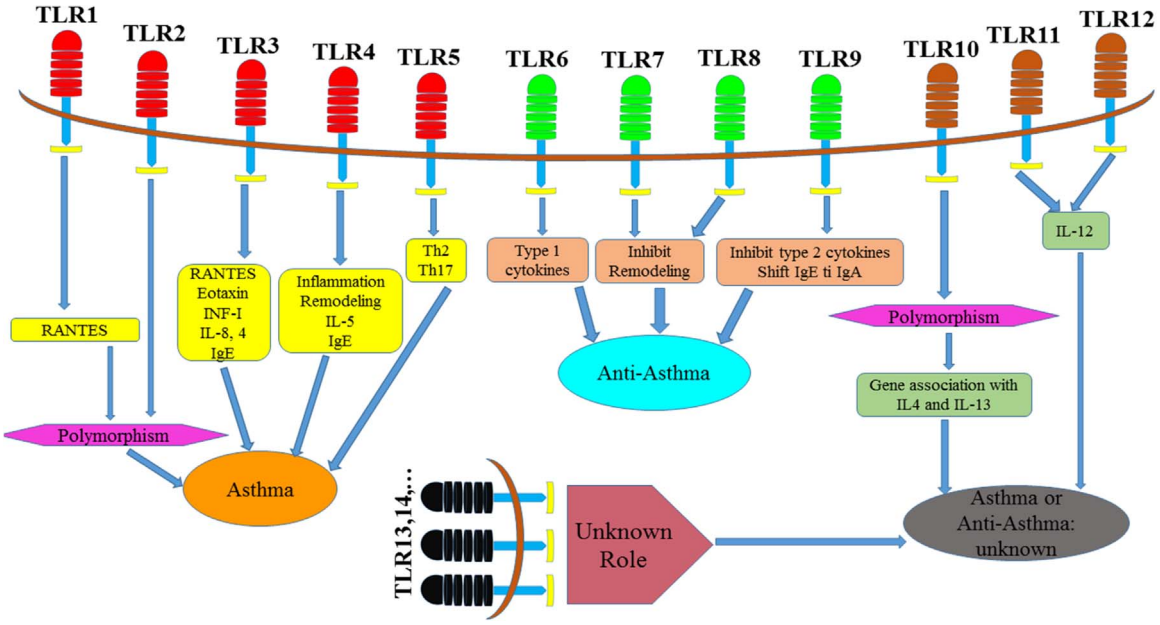

Fig. 1. Toll like receptors signaling through the various pathways with in collaboration with of internal adaptors proteins. Each TLR may induces or influences different functions in allergic asthma.

(Akira and Takeda, 2004; Akira et al., 2006; Tesse et al., 2011). Ligands bind to TLRs through Toll/IL-1 receptor domain (TIR) (Akira et al., 2006; Kawai and Akira, 2010). Most TLRs have been expressed on airway epithelial cells and respiratory track, playing an important role not only to regulate of innate and adaptive immune systems but also to maintain the aseptic condition in the airways (Akira et al., 2006). TLRs can shift immune response towards pro- or anti-allergy responses after successfully recognizing microbial antigens (Akira et al., 2006; Gon, 2008).

As a result, the present review has focused on the role of TLRs in the pathophysiology of allergic asthma and the possibility of using TLRs as a therapy for asthma (Fig. 1). Thus, in the following part we will describe important members of TLRs that have been linked to the pathophysiology of asthma.

2. Toll-like receptor and possible role in pathogenesis of asthma

Activated TLR2 initiates Th2-immune response, thus playing a critical role in asthma (Bezemer et al., 2012; Hussein et al., 2012). Genetic variations in TLRs affect the pattern of immune responses against environmental antigens. Polymorphism in the TLR2 gene is associated with abnormal immune response, making it more susceptible to immune-related diseases such as asthma (Bezemer et al., 2012; Eder et al., 2004; Hussein et al., 2012; Martinez and Holt, 1999). However, TLR2 signaling can also induce the expansion of Treg cells, reducing asthma exacerbations (Liu et al., 2006). TLR2 ligands (Table 1) are a wide spectrum of PAMPs ranging from the molecules on cell membrane of gram-positive and negative bacteria, mycoplasma, mycobacteria, yeasts, and parasites (Bezemer et al., 2012; Hussein et al., 2012; Martinez and Holt, 1999).

TLR2 Arg677Trp polymorphism seems to be a protective factor against replication of *Cytomegalovirus* (CMV) (Brown et al., 2009; Wu et al., 2001); therefore, polymorphisms in TLR genes have been associated with susceptibility to the disease. The heterozygous genotype of the TLR2 with Arg677Trp polymorphism occurs more frequently in CMV-seronegative adult patients than in CMV-infected ones, hence the heterozygous genotype is a protective factor in them. Regarding epidemiological evidence, there is a relationship between respiratory viral infections and asthma exacerbation. As a respiratory pathogen, Murine CMV is capable of altering Th1/Th2 cytokine balance as well as increasing mucus production in allergic airway diseases. On the other hand, it can also activate TLRs and Th1 responses that help regulating viral infection and airway inflammation. However, polymorphisms in receptor genes could be a risk factor for other diseases (Brown et al., 2009; Wu et al., 2001).

Variants of TLR2 are associated with asthma and increased level of IL-9 (and other type 2 cytokines) (Eder et al., 2004; Lee et al., 2011). It is possible that distinct polymorphisms could increase viral replication and inflammation. Chronic inflammation may trigger asthma, leading at the same time to airway remodeling (Bezemer et al., 2012; Eder et al., 2004; Lee et al., 2011); therefore, TLR2 activation by agonists or infectious agents result in allergic asthma conditions.

3. Toll-like receptor 1 (TLR1) and 3 (TLR3) and their role in pathogenesis of asthma

RANTES synthesis is an imminent consequence of TLR1 activation (Lin et al., 1999; O'Neill, 2006). TLR3 stimulation, however, causes the production of type I interferons, IL-8, and RANTES. RANTES production, triggered by TLR3, is lower than the one by TLR1 (Yamamoto et al., 2003). TLR1 recognizes triacyl lipoproteins of bacteria and TLR3, the viral replicative intermediate double-stranded RNA (dsRNA) (Takeda et al., 2003).

In the trachea, TLR3 ligands induce airway responsiveness to bradykinin (Bachar et al., 2004). Activated TLR3 induces pro-inflammatory cytokines, eotaxin, and RANTES, leading to eosinophilic inflammation in the airway (Morris et al., 2005, 2006; Sukkar et al., 2006). Moreover, as a positive feedback, the cytokine pattern, induced by inflammatory cells, enhances the TLRs expression level in the respiratory system (Cooper et al., 2009; Kvarnhammar et al., 2013; Niimi et al., 2007). Rhinoviruses can also increase TLR3 expression in bronchial epithelial cells, triggering exacerbation of the allergic asthma (Hewson et al., 2005; Torres et al., 2010; Wang et al., 2009). As a result, TLR3 plays a critical role in allergic asthma. Long-term activation of TLR3 can cause lung inflammation (Meng et al., 2011; Stowell et al., 2009). TLR3 may increase IL-4 and IgE levels in serum by modulating Th2 immune response, though TLR3 does not alter the total number of cells in broncho-alveolar lavage fluid (Meng et al., 2011; Torres et al., 2010).