

A promising approach for asthma treatment by multiwayly modulating toll-like receptors

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Abstract. – Asthma is a major epidemic affecting up to one third people in developed countries over the last decades, and making a crucial impact on morbidity rates. The classical characters of asthma in human are airway inflammation, airway hyperreactivity, and airway remodeling. Hygiene hypothesis, inflammation cells and signaling pathway in asthma were involved in Toll-like receptors (TLRs). TLRs are a kind of pattern recognition receptors, which are important in recognition of various pathogens. TLRs have been seen as a key target for asthma treatment, so a promising approach for asthma treatment was adopted to the multiwayly modulating toll-like receptors way.

Key Words:

Asthma, Approach, Treatment, Toll-like receptors.

Introduction

Asthma

Asthma has become a major epidemic affecting up to one third people in developed countries over the last decades, and making a crucial impact on morbidity rates¹. The essence characters of asthma in human are airway inflammation, airway hyperreactivity, and airway remodeling², while asthmatic patients' airways show the infiltration of eosinophils, degranulated mast cells, and lymphocytes, as well as hyperplasia of goblet cells. The accumulated evidence revealed the above mentioned cells involved in the pathogenesis of asthma by released cytokines, hemokines, chemical mediators and so on. In the progress of asthma research, three major aspects are tempting to speculate the relationship among themselves, which are hygiene hypothesis, inflammation cells, signaling pathway in asthma.

Hygiene Hypothesis

"Hygiene hypothesis", initially proposed by David Strachan³, whose key point is that the increased incidence of allergic diseases in developed countries is explained by the decreased chances of infection during childhood⁴⁻⁵. The exposure to pathogens during bacterial and viral infection may drive the maturation of the immune system in infancy or childhood toward a T helper 1 phenotype (Th1), and away from a T helper 2 phenotype (Th2) associated with allergic diseases. In support of this idea, many animals, clinical and epidemiological studies were observed⁶, according to this theory, certain pathogens can either promote the development of asthma or exacerbate pre-existing asthma inducing by an imbalance in immune homeostasis predisposes to the development of T helper type 2-biased immune responses too. As a result, the balance between Th1 and Th2 is important for asthma pathological immune response to allergens.

Inflammation Cells

Inflammation cells play a crucial role in the pathogenesis of asthma. Moreover, the recruited dendritic cells (DCs), mast cells, eosinophils, neutrophils, T cells, macrophages, respiratory epithelial cells secrete specific cytokines which directly damage the airway epithelium and enhance airway hyperreactivity⁷. For example, mast cells play a cardinal role in anaphylactic reactions by the multivalent binding of allergens to receptor-bound IgE, and release inflammatory mediators such as histamine, prostaglandins, and leukotrienes. In addition, mast cells regulate the levels of allergic airway inflammation by producing cytokines (e.g., Interleukin-4, Interleukin-5, Interleukin-6, Interleukin-10, Interleukin-13, and

Tumor necrosis factor- α , which are important in the pathogenesis of asthma⁸⁻⁹. And other cells also engage in the pathogenesis of asthma through different or similar way, respectively⁷. So inflammation cells are fundamental for asthma inflammation progress too.

Signaling Pathway in Asthma

Evidence suggests that airway smooth muscle (ASM) could be seen as a significant player in the pathogenesis of asthma through many signaling pathway¹⁰. ASM contracts or relaxes in order to regulate airway patency and thus airflow through signaling pathway. Such as: a number of signaling molecules, including (1) tyrosine phosphatases Src homology region 2 domain-containing phosphatase-1 (SHP1) or Src homology region 2 domain-containing phosphatase-2 (SHP2) (both present in the nucleus and cytoplasm), (2) suppressors of cytokine signaling (SOCs previously termed under various names), and (3) nuclear inhibitors called proteins that inhibit activated STATs (PIAS), serve as negative regulators of the JAK/STAT pathways¹¹. G protein coupled muscarinic receptors activate signaling cascades resulting in p42/p44 mitogen-activated protein (MAP) kinase (MAPK), Rhokinase and phosphatidylinositol-3-kinase (PI3K) activity¹². The above mentioned signaling pathway involve in the function regulation of ASM. The signaling pathway also makes cross talk to cooperate with each other in the pathogenesis of asthma.

Toll-Like Receptors

Toll-like receptors (TLRs) are a kind of pattern recognition receptors, which are important in the recognition of various pathogens¹³. To date, eleven TLR family members (TLR1-11) have been identified in the human genome, and different TLRs appear to play crucial roles in the activation of the immune response to distinct pathogen-associated molecular patterns. TLRs can recognize their endogenous and exogenous ligands, then active the signaling cascades to produce the expression of a host of cytokines, chemokines, hematopoietic factors, acute phase proteins, and antimicrobial factors. While all members of this superfamily signal in a similar manner owing to the activation of shared molecules such as TNF receptor associated factors 6 (TRAF6)/nuclear transcription factor kappa-B (NF- κ B), Myeloid differentiation primary response gene 88 (MyD88) [except TLR3, and mitogen-activation protein kinases (MAP)]¹⁴, inter-

action of lipopolysaccharides (LPS) with its receptor TLR4 can also activate a distinct signaling pathway involving TRIF-related adaptor molecule (TRAM) and Toll-IL-1 resistance (TIR) domain-containing adaptor inducing interferon- β [IFN- β] (TRIF), leading to the induction of IFN- α and IFN- β via activation of interferonregulatory factor-3 (IRF-3)¹⁵⁻¹⁷.

Interestingly, a lot of pre-formed toll-like receptors are expressed by mononuclear cells and in particular antigen-presenting cells (APC) and activate these host cells after contact with specific microbial structures, called 'pathogen-associated molecular patterns' (PAMPs)¹⁸. Initially these "molecular patterns" were defined as conserved structure molecules, produced by microbes and not by the mammalian host, which are able to stimulate innate immune reactions by the host. All these show that TLRs is very important for the immune response to pathogens.

Effect of TLRs on Asthma

From existing literatures, TLRs have been seen as a key target for asthma treatment¹⁹. But the mechanisms of TLRs involved in asthma are not clearly understood. From ligands to signaling of TLRs, many studies about effect of TLRs on asthma have been accumulated²⁰. Because most TLRs expression in airway cells have been documented in research using either cell lines, TLRs play a key role in controlling the airway inflammation through trigger TLRs' immune response²¹. More documents have been concerned about molecular mechanism of TLRs on asthma: first some ligands activities of TLRs on asthma were estimated²²; second some effects of cross talk between TLRs and cytokines on asthma were established²³; thirdly different TLRs subtypes effect on asthma were investigated²⁴; finally some clinical experiments between TLRs and asthma were studied²⁵. Collectively, more extensive study on the role of TLRs in patients with asthma is expected to lead not only to controlling the symptoms of asthma, but also to preventing death.

Discussion

Although TLRs are involved in the pathogenesis of asthma, there is not a perfect strategy to explain the approach for asthma treatment. So we hypothesis that a promising approach for asthma treatment was adopted to the multiwayly

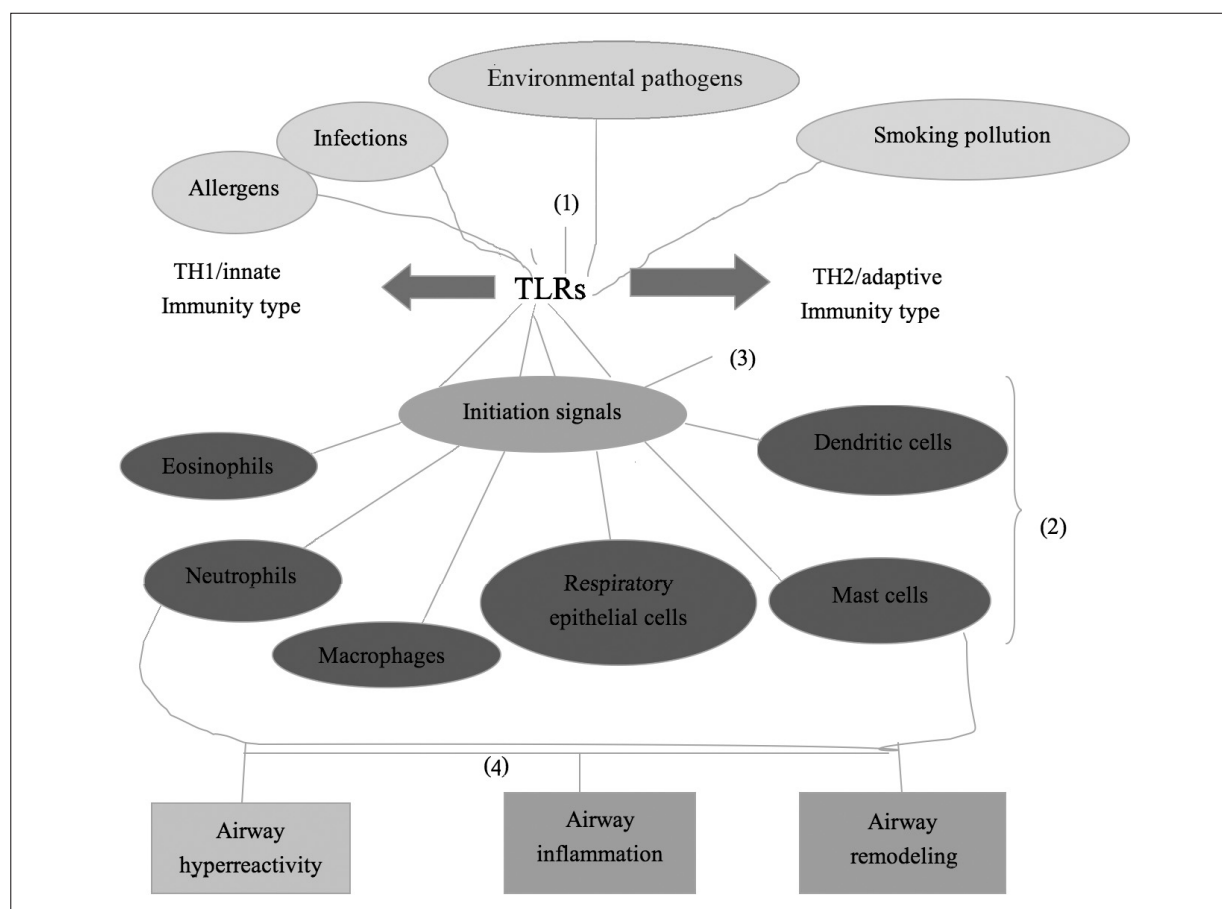


Figure 1. The hypothesis that a promising approach for asthma treatment was adopted to the multiwayly modulating toll-like receptors way: (1) Targeting the TH1/TH2 balance by controlling the expression of TLRs; (2) Targeting the inflammation cells by attuning TLRs in the airway; (3) Targeting the signaling pathway of asthma by regulating TLRs activity; (4) Targeting the classic features of asthma (airway hyperreactivity, airway inflammation, and airway remodeling) by administering special ligands of TLRs.

modulating toll-like receptors way (Figure 1): (1) targeting the TH1/TH2 balance by controlling the expression of TLRs; (2) targeting the inflammation cells by attuning TLRs in the airway; (3) targeting the signaling pathway of asthma by regulating TLRs activity; (4) targeting the classic features of asthma (airway hyperreactivity, airway inflammation, and airway remodeling) by administering special ligands of TLRs. In conclusion TLRs are critical for the future asthma treatment.

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