Overview of Bronchial Asthma and Diagnostic Role of Toll-like Receptors Nine and Ten Polymorphisms

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Abstract

Asthma is one of the most common major non-communicable diseases and for many, has a substantial impact on quality of life. Globally, asthma is ranked 16th among the leading causes of years lived with disability as measured by disability-adjusted life years. Around 300 million people have asthma worldwide, and it is likely that by 2025 a further 100 million may be affected. Asthma remains a global public health problem and is a common chronic respiratory disease. It is characterized by airway inflammation related to variable airflow obstruction, airway hyper-responsiveness, and airway wall remodeling. Airflow limitation in asthma is recurrent and caused by a variety of changes in the airway. Airway inflammation is the central driver of the chronic intermittent nature of asthma symptoms eventually ending in severe asthma attacks.Toll-like receptors (TLRs) is a family of pattern recognition receptors that form the cornerstone of the innate immune response. A variety of regulatory factors that control TLR activation have been reported to be involved in the negative feedback of TLR-dependent signaling excessive TLR activation disrupts the immune homeostasis by sustained pro-inflammatory cytokines and chemokine production and consequently contributes to the development and progression of many diseases. Several studies have presented considerable evidences on the contribution of TLR signaling dysregulation to the development and progression of numerous diseases such as autoimmune, chronic inflammatory, and infectious diseases. The aim of the current study to review bronchial asthma and diagnostic role of toll-like receptors nine and ten polymorphisms in pediatrics.

Keywords: Toll-like Receptors; Bronchial Asthma; Pathophysiology; Risk Factors

INTRODUCTION

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation **(1).** According to world health organization reports, Asthma affected an estimated 262 million people in 2019 (1) and caused 455 000 deaths **(2)**.

There is a large geographical variation in asthma prevalence, severity, and mortality. While asthma prevalence is higher in high income countries, most asthma-related mortality occurs in low-middle income countries **(3)**.

Incidence and prevalence of asthma differs by sex across the lifespan. Pre-pubertal boys have a higher asthma incidence, prevalence, and hospitalization rate than girls of the same age, but this trend reverses during adolescence **(1)**.

In Egypt, the snapshot study concluded that over 6.7% and 26.5% of the general adult and pediatric population, respectively, have asthma. The highest prevalence was noted in Greater Cairo and the northern portion of the country, where most urban populations live **(4**).

The 2007 NAEPP guidelines and the 2009 VA/DoD asthma management guidelines use the severity of asthma classification below, with features of asthma severity divided into three charts to reflect classification in different age groups (0-4 y, 5-11 y, and 12 y and older). Classification includes (1) intermittent asthma, (2) mild persistent asthma, (3) moderate persistent asthma, (4) and severe persistent asthma **(5).**

Moreover, the 2022 Global Initiative for Asthma (GINA) guidelines categorize asthma severity as mild, moderate, or severe. Severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbations. Asthma classify according to the level of asthma symptoms control into controlled, partly- controlled and uncontrolled **(1)**.

- **Pathophysiology & different Mediators of Asthma:**

Asthma is a common pulmonary condition defined by chronic inflammation of respiratory tubes, tightening of respiratory smooth muscle, and episodes of bronchoconstriction. During an asthma episode, inflamed airways react to environmental triggers such as smoke, dust, or pollen. The airways narrow and produce excess mucus, making it difficult to breathe **(Figure 1)**. In asthma is the result of an immune response in the bronchial airways **(6)**.

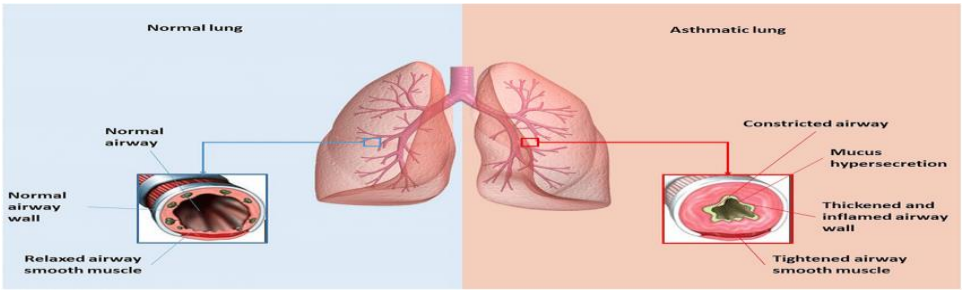

Figure (1): Comparison between the normal and asthmatic lung. Healthy individuals have normal airway walls and relaxed airway smooth muscle. The airways of asthmatic patients constrict upon exposure to innocuous antigens, over express mucus, are inflamed with swollen walls and tightened smooth muscle **(Shastri et al.,2021).**

In asthma, the dominant physiological event leading to clinical symptoms is airway narrowing and a subsequent interference with airflow. In acute exacerbations of asthma, bronchial smooth muscle contraction (bronchoconstriction) occurs quickly to narrow the airways in response to exposure to a variety of stimuli including allergens or irritants. Allergen-induced acute bronchoconstriction results from an IgE-dependent release of mediators from mast cells that includes histamine, tryptase, leukotrienes, and prostaglandins that directly contract airway smooth muscle **(5)**.

In addition, other stimuli (including exercise, cold air, and irritants) can cause acute airflow obstruction. The mechanisms regulating the airway response to these factors are less well defined, but the intensity of the response appears related to underlying airway

inflammation. Stress may also play a role in precipitating asthma exacerbations. The mechanisms involved have yet to be established and may include enhanced generation of pro-inflammatory cytokines **(2)**.

Asthma is characterized by airway hyperresponsiveness (AHR), an exaggerated narrowing of the airway in response to stimuli. AHR can reflect asthma severity, and has been associated with a variety of contributing factors **(4)**

Airway remodeling is the collective term given to the structural changes that occur within the asthmatic airway. These changes include sub-epithelial fibrosis, thickening of the airway smooth muscle (ASM) layer, mucous gland hyperplasia, angiogenesis, and loss of epithelial layer integrity, all of which contribute to a thickened and stiffened airway wall. The development of airway remodeling begins early in the disease course, with structural changes being evident in preschool children with clinically confirmed wheeze, even prior to an asthma diagnosis **(7)**.

The underlying mechanisms driving the development of airway remodeling are largely unclear and likely to be extremely complex and multifaceted. While for many years airway remodeling was thought to result from the presence of chronic inflammation within the asthmatic airway, this has more recently been questioned. Structural changes in the airways of preschool wheezers do not correlate with inflammatory cell counts in bronchoalveolar lavage fluid **(8).**

The inflammation affects all airways from the upper respiratory tract up to the small airways although its physiological effects are believed to be most pronounced in medium-sized bronchi. If not prevented or therapeutically inhibited, inflammatory processes may lead to a deterioration of the disease. Asthma attacks are potentially life threatening **(1)**.

An increased understanding of the development and regulation of airway inflammation in asthma followed the discovery and description of subpopulations of lymphocytes, T helper 1 cells and T helper 2 cells (Th1 and Th2). After the discovery of these distinct lymphocyte subpopulations in animal models of allergic inflammation, in human asthma, a shift, or predilection, toward the Th2-cytokine profile resulted in the eosinophilic inflammation characteristic of asthma **(2)**.

In addition, generation of Th2 cytokines (e.g., interleukin-4 (IL-4), IL-5, and IL-13) could also explain the overproduction of IgE, presence of eosinophils, and development of airway hyperresponsiveness. There also may be a reduction in a subgroup of lymphocytes, regulatory T cells, which normally inhibit Th2 cells, as well as an increase in natural killer (NK) cells that release large amounts of Th1 and Th2 cytokines **(9).**

T lymphocytes, along with other airway resident cells, also can determine the development and degree of airway remodeling. Although it is an oversimplification of a complex process to describe asthma as a Th2 disease, recognizing the importance of n families of cytokines and chemokines has advanced our understanding of the development of airway inflammation **(6).**

Activation of mucosal mast cells releases bronchoconstrictor mediators (histamine, cysteinyl-leukotrienes, prostaglandin D2) **(10)**.

Increases in eosinophils often correlate with greater asthma severity. However, the role and contribution of eosinophils to asthma is undergoing a reevaluation based on

studies with an anti-IL-5 treatment that has significantly reduced eosinophils but did not affect asthma control **(3).**

Neutrophils are central players in the inflammatory process present in asthma and have the capacity to produce transforming growth factor-β1 TGF-β1. Airway neutrophilia is associated with more severe airflow obstruction, lower lung function and thicker airway walls **(8).**

Macrophages are the most numerous cells in the airways and also can be activated by allergens through low-affinity IgE receptors to release inflammatory mediators and cytokines that amplify the inflammatory response **(10).**

Airway smooth muscle (ASM) plays an integral part in the pathophysiology of asthma. It is responsible for acute bronchoconstriction, which is potentiated by constrictor hyperresponsiveness, impaired relaxation and length adaptation. ASM also contributes to airway remodeling and inflammation in asthma **(5).**

The airway epithelium is considered an essential controller of inflammatory, immune and regenerative responses to allergens, viruses and environmental pollutants that contribute to asthma pathogenesis. Epithelial cells express pattern recognition receptors that detect environmental stimuli and secrete endogenous danger signals, thereby activating dendritic cells and bridging innate and adaptive immunity **(6).**

Histamine was the first mediator known to be implicated in pathophysiology of asthma. Histamine is synthesized and released by mast cells and basophils in the airways. Histamine causes mucus secretion and bronchoconstriction which is partially mediated by vagal cholinergic reflex. Histamine also acts as a chemoattractant for eosinophils and activates eosinophils **(7).**

The cysteinyl leukotrienes, LTC4, LTD4, and LTE4, are eicosanoids derived from arachidonic acid by 5-LOX (lipoxygenase) pathway. They are potent constrictors of human airway and have been reported to increase AHR and play an important role in asthma. Potent LTD4 antagonists protect against exercise- and allergen-induced bronchoconstriction, suggesting that leukotrienes contribute to bronchoconstrictor responses **(11)**.

Platelet activating factor (PAF) is a potent phospholipid mediator involved in anaphylaxis and chronic inflammatory disorders, including bronchial asthma. PAF is able to act both, directly as a chemotactic factor and indirectly through the release of other inflammatory agents **(10).**

Prostaglandins are lipid products synthesized from nuclear and plasma membranes via by the metabolism of cyclooxygenase (COX) enzymes through the arachidonic acid metabolic pathway**.** Increased concentration of PGF2, PGD2, and thromboxane B2 in bronchoalveolar (BAL) fluid of asthmatics is found. When inhaled, they cause bronchoconstriction **(8).**

Elevated levels of MMP-9 (metalloproteinase-9), a protease released by eosinophils and alveolar macrophages, are found in bronchoalveolar fluid from asthmatic patients **(5).**

Kinins are vasoactive peptides secreted from kininogens by the action of kininogenase during the inflammatory response. Bradykinin is an important kinin that has many effects on airway functions mediated by direct activation of B2 receptors of airway smooth muscles. Bradykinin activates alveolar macrophages to release LTB4 and PAF

and activates nociceptive nerve fibers in the airways of asthmatic patients only which may mediate cough and chest tightness characteristic features of asthma **(6)**.

Cytokines are extracellular signaling proteins secreted by almost every cell under certain conditions and play a critical role in orchestrating all types of inflammatory response in asthma**.** The important cytokines in asthma are lymphokines secreted by T-lymphocytes: IL-1β, IL-3, IL-4, IL-5, IL-6, IL-9, IL-13, TNF-α, etc. where IL-3 is reported to be crucial for the survival of mast cells in tissues, but IL-4 plays an important role in switching B-lymphocytes to produce IgE and expression of vascular cell adhesion molecule-1 VCAM-1 on endothelial cells. IL-5 plays a critical role in differentiation, survival, and priming of eosinophils, thus promoting eosinophilic inflammation, and present in BAL fluid during allergen induced late-phase asthma **(11).**

Chemokines are chemotactic cytokines responsible for recruitment of inflammatory cells in the airways. Chemokines have been categorized into two main groups, (a) CXC (α-type) and CC (β-type) chemokines, and exert their effects through G-protein-coupled chemokine receptors (CCR) **(4).**

Tachykinins are neuropeptides derived from preprotachykinins (PPTs). They are released by sensory nerves of airways and stimulate mucus secretion, plasma exudation, neural activation, bronchoconstriction, and structural changes. These peptides activate macrophages and monocytes to release inflammatory cytokines, IL-6. Higher concentration of a tachykinin, substance-P (SP), has been found in BALF of asthmatic lungs **(3).**

Endothelins are peptide mediators secreted via endothelin-converting enzyme (ECE) through mRNA present in airway epithelial cells and regulated by a number of proinflammatory cytokines in asthma. Endothelins are potent bronchoconstrictors and induce airway smooth muscle cell proliferation and fibrosis and play an important role in chronic inflammation of asthmatic airways **(10)**

Several nonadrenergic-noncholinergic (NANC) nerves and neuropeptides have been identified in the respiratory tract. Thus, chronic asthma may be associated with increased neurogenic inflammation, which may provide a mechanism for prolonging the inflammatory response even in the absence of initiating inflammatory stimuli **(11)**.

Antibodies are protein molecules released by immune system in response to foreign bodies, allergens. Five classes of antibodies, namely, IgM, IgG, IgA, IgD, and IgE are known. Of these IgE is the predominant antibody in asthma in humans. IgE is the antibody responsible for all types of allergic reaction and pathogenesis of allergic asthma and development of inflammation in the human body. Elevated levels of IgE are found in bronchial asthma. Monoclonal antibodies against IgE have shown the reduction of IgE and associated asthma symptoms in asthmatics **(2)**.

- **Etiology of and risk factors for asthma:**

Asthma comprises a range of heterogeneous phenotypes that differ in presentation, etiology and pathophysiology. The risk factors for each recognized phenotype of asthma include genetic, environmental and host factors. Although a family

history of asthma is common, it is neither sufficient nor necessary for the development of asthma **(1).**

Genome-wide linkage studies and case–control studies have identified 18 genomic regions and more than 100 genes associated with allergy and asthma in 11 different populations. In particular, there are consistently replicated regions on the long arms of chromosomes 2, 5, 6, 12 and 13. Association studies of unrelated individuals have also identified more than 100 genes associated with allergy and asthma, 79 of which have been replicated in at least one further study **(6).** Extensive heterogeneity in the genetic basis of asthma, and in gene-by-environment interactions, is likely. Failure to identify and precisely quantify environmental exposures and their timing may account for some of the difficulty that researchers have had in replicating genetic associations **(12).**

Risk factors in the prenatal period are multifactorial. Assessment is complicated by the variety of wheezing conditions that may occur in infancy and childhood, only some of which evolve to classical asthma **(12).**

Observational studies examining prenatal nutrient levels or dietary interventions and the subsequent development of atopic disease have focused on foods with anti-inflammatory properties e.g., omega-3 fatty acids and antioxidants such as vitamin E and zinc. Several studies have demonstrated that higher intake of fish or fish oil during pregnancy is associated with lower risk of atopic disease specifically eczema and atopic wheeze up to age 6 years **(6).**

Similarly, higher prenatal vitamin E and zinc levels have been associated with lower risk of development of wheeze up to age 5 years**.** However, no protective effect against the development of atopic disease in infants has been shown for maternal diets that excluded certain foods (e.g., cow's milk, eggs) during pregnancy **(2).**

A greater risk of persistent wheeze and asthma in early childhoodand a dose–response relation between number of antibiotic courses and risk of wheeze or asthma **(5).**

Potential reasons for these findings include maternal stress and differences in the infant's gut microflora associated with different modes of delivery **(12).**

The other 3 phenotypes have been described primarily by age of onset in cohort studies, and their genesis in early infancy is largely unknown. Distinguishing among these different phenotypes in early childhood is critical to understanding the role of risk factors and their timing in early infancy **(12).**

The influence of breastfeeding on the risk of childhood atopy and asthma remains controversial. Some studies have shown protection**,** whereas others have reported higher rates of allergy and asthma among breastfed children **(11).**

Exclusive breastfeeding for at least 3 months was associated with lower rates of asthma between 2 and 5 years of age, with the greatest effect occurring among those with a parental history of atopy **(2).** Also, an association between reduced airway function in the first few weeks of life and asthma in later life **(4).**

Maternal smoking with in utero nicotine exposure has been correlated with this type of lung dysfunction, but the effects of other exposures have been less well studied. **(2).**

Family size and the number and order of siblings may affect the risk of development of asthma. Although large family size (more than 4 children) is associated with a decreased risk of asthma, birth order is not involved **(6)**.

Socio-economic status is as relevant to the incidence of allergy and asthma as it is to the expression, severity and management of these diseases remains unclear. Parental stress has also been prospectively associated with wheezing in infancy **(5)**.

The use of antibiotics has been associated with early wheezing and asthma in several studies **(13)**.

Viral infections of the lower respiratory tract affect early childhood wheezing. Whether lower respiratory tract infection promotes sensitization to aeroallergens causing persistent asthma is controversial: childhood viral infections might be pathogenic in some children but protective in others **(1).**

The role of the innate immune system in handling and presentation of antigens and suggests that polymorphisms in Toll-like receptors may play a greater role than previously recognized in the development of the skewed immune responses associated with persistent asthma **(8).**

Nutrition and diet (e.g., folic acid, vitamin B_{12}), smoking, exposure to microbial products, maternal stress and maternal care are potential factors influencing fetal genetic expression, and a further window for epigenetic modification in early life may allow environmental factors to modify a child's genome with the potential to cause or prolong allergy and asthma. Further work is needed to verify and understand these risks. **(11).**

A greater incidence of asthma among adolescent and young adult females and a greater proportion of males with remission of asthma. In contrast, adult females have more severe asthma than males, with more hospital admissions, slower improvement, longer hospital stays and higher rates of readmission **(11)**

The influence of some environmental risk factors such as allergens may be modified by sex. In one study of adults, 18% of women with asthma, but only 2.3% of men with asthma, had normal results on common tests related to atopy (negative skin prick tests, immunoglobulin E < 100 IU/mL and eosinophilia < 5%) which suggested different disease mechanisms between the sexes **(5).**

Finally, the influence of obesity on the development of asthma is greater among women than among men and has not been shown to be influenced by caloric intake or physical activity **(2).**

- **Diagnosis of asthma**

The diagnosis of asthma involves a thorough medical history, physical examination, and objective assessments of lung function in those ≥ 6 years of age (spirometry preferred, both before and after bronchodilator) to document variable expiratory airflow limitation and confirm the diagnosis. Bronchoprovocation challenge testing and assessing for markers of airway inflammation may also be helpful for diagnosing the disease, particularly when objective measurements of lung function are normal despite the presence of asthma symptoms **(14).**

The modified Asthma Predictive Index (mAPI) is a useful tool for identifying young children with recurrent wheeze who may be at high risk of developing asthma. A positive mAPI in the preschool years has been found to be highly predictive of future school-age asthma **(15).**

Chest radiography is the initial imaging evaluation in most individuals with symptoms of asthma. The value of chest radiography is in revealing complications or alternative causes of wheezing in the diagnosis of asthma and its exacerbations. It usually is more useful in the initial diagnosis of bronchial asthma than in the detection of exacerbations, although it is valuable in excluding complications such as pneumonia and asthma mimics, even during exacerbations **(16).**

Because of the variability of asthma symptoms, patients will not exhibit reversible airway obstruction at every visit and a negative spirometry result does not rule out a diagnosis of asthma. This is particularly true for children who experience symptoms predominantly with viral infections, or who are well controlled on asthma medications. Therefore, to increase sensitivity, spirometry should be repeated, particularly when patients are symptomatic **(6).**

Once airflow obstruction has been confirmed, obtaining evidence of excessive variability in expiratory lung function is an essential component of the diagnosis of asthma. In general, an increase in FEV_1 of > 12% and, in adults, a change of > 200 mL from baseline after administration of a rapid-acting bronchodilator is accepted as being consistent with asthma **(14).**

Allergy skin prick (epicutaneous) testing is recommended to identify possible environmental allergic triggers of asthma, and is helpful in identifying the asthma phenotype of the patient. Testing is typically performed using the allergens relevant to the patient's geographic region. Although allergen-specific IgE tests that provide an in vitro measure of a patient's specific IgE levels for specific allergens have been suggested as an alternative to skin tests, these tests are less sensitive, more invasive (requires venipuncture), and more expensive than skin prick tests **(1).**

- **Toll like receptors**

Toll-like receptors (TLRs) is a family of pattern recognition receptors (PRRs) that form the cornerstone of the innate immune response**.** Toll was originally discovered as a gene controlling the dorsal–ventral polarity of the Drosophila embryo, but was later found to be involved in anti-fungal immunity **(17).**

They can recognize both the external pathogen-associated molecular patterns (PAMPs) and the internal damage-associated molecular patterns (DAMPs) **(18).**

The main function of TLRs is the ability to recognize numerous pathogens. TLR function in innate immunity is through the induction of antimicrobial activity and the production of inflammatory cytokines **(19)**.

Upon activation by PAMPs or DAMPs, TLRs recruit adapter proteins that act as a platform to recruit IL-1R-associated protein kinases (IRAK) 1, 2, 4, and M and TAB2 and TNF receptor-associated factor 6 (TRAF6) which finally leads to nuclear translocation of pro-inflammatory transcription factor, nuclear factor kappa-B (NF-kB), activator protein 1 (AP-1) and interferon regulatory factor 3 (IRF3) **(20).**

Each transcription factor is responsible for the transcription of specific genes that encodes different set of proteins such as pro-inflammatory cytokines [tumor necrosis

factor alpha (TNF-α), interleukin (IL)-1β and IL-6] and type 1 interferon (IFN-α, β), chemokines (CXCL8 and CXCL10), and antimicrobial peptides **(18).**

- **Implication of TLRs in Asthma**

Some studies suggest that asthma is considered as a multifactorial disorder influenced by genetic factors and environmental factors. However, its exact mechanisms are still largely uncertain **(21).**

The immune system has been reported to play a crucial role in disease progression. The acknowledgment was that asthma is primarily involved in IgE related T helper type 2 regulation and recruitment of mast cells and eosinophils **(5).** The importance of the B cells, macrophages, dendritic cells, and natural killer T cells in asthma progression**.** Therefore, the immune regulatory is shown to be responsible for the pathogenesis of asthma, and it is correlated with immune system activation **(11).**

Toll-like receptors (TLRs) as pattern-recognition receptors mediate signal transduction and the maturation and activation of the innate immune cells. TLRs also involve in allergic responses by recognizing microbial or endogenous molecules and airborne allergens in the improper environment. Thus, TLRs influence immunity and host physiology. TLRs are associated with the pathogenesis of allergic diseases such as asthma **(22).**

Because the airways are regularly exposed to inhaled suspended environmental allergens and PAMPs, asthma susceptibility may be at least partially associated with disordered immune responses to common environmental inhalants.Thus, asthma susceptibility might also be associated with variation in genes encoding components of innate immunity, making them biologically plausible candidate genes for asthma **(23).**

- **TLR9 and asthma:**

It is a member of the toll-like receptor (TLR) family. TLR9 is an important receptor expressed in immune system cells including dendritic cells, macrophages, natural killer cells, and other antigen presenting cells (**19).**

TLR9 is expressed on endosomes internalized from the plasma membrane, binds DNA (preferentially DNA containing unmethylated CpGs of bacterial or viral origin), and triggers signaling cascades that lead to a pro-inflammatory cytokine response **(22).**

Th2 immune response have been reported to be suppressed by CpG-oligonucleotides (ODNs), which are TLR9 agonists **(24).**

Clinical trials using CpG-DNA have been conducted to treat allergic asthma patients. In the trials, a certain improvement effect has been reported **(23).**

AZD1419 is a TLR9 agonist that has been developed to achieve immune modification by reducing the asthmatic response to allergic triggers and, potentially, as observed in murine models of airway allergic inflammation, induce a sustained clinical improvement in airway function and asthma symptoms after a relatively short course of treatment **(25)**.

- **TLR10 and asthma**

TLR10 does not activate the immune system and has instead been shown to suppress inflammatory signaling on primary human cells. This makes TLR10 unique among the TLR family **(26)**.

TLR10 was thought to be an "orphan" receptor, however, recent studies have identified ligands for TLR10 and these include HIV-gp41 **(27)**.

TLR10 is unique among the TLR family in having an anti-inflammatory function, rather than a pro-inflammatory function. This was discovered by over-expressing TLR10 in human cell lines and using antibody-mediated engagement of the receptor on primary human cells. When TLR10 is activated in this manner, it suppresses the amount of cytokines produced, as compared to control cells. TLR10 engagement also has long-term effects on monocyte and B cell activation/differentiation by suppressing the transcription of activation markers. TLR10's mechanism of action is not yet known but activation of the receptor has been shown to suppress NF-κB, MAP kinase and Akt signaling events stimulated by TLR and CD40 ligands **(28)**.

Conclusion:

Asthma is a chronic and complex disorder of the respiratory system characterized by airway obstruction and inflammation.

Several risk factors are important determinants of asthma; numerousstudies have revealed that asthma has a strong genetic component.

Toll-like receptors are an essential family of innate immunepattern recognition receptors that play a pivotal role in host defense against microbes.

TLRs (TLR-9, TLR-10) are involved in various signaling pathways of the immune system that protect from asthma or develop asthma phenotypes.

No Conflict of interest.

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