Allergology International. 2008;57:33-37
DOI: 10.2332/allergolint.R-07-157

REVIEW ARTICLE

Toll-Like Receptors and Airway Inflammation

Yasuhiro Gon[1]

ABSTRACT
The respiratory tract opens to the external environment at the oral side edge, and the other edge of the respiratory tract connects to the closed space (alveoli), and so to preserve the sterility in the terminal respiratory tract is critical for protection against pathogens. The recognition machinery for the invasion of microbes is indispensable for the preservation of the sterility in the lungs. Our general understanding of how microbes are recognized by the innate immune system has increased considerably over the past several years, and the contribution of Toll-Like Receptors (TLRs) to innate immunity is now well documented. In the meantime, it has come to understand that many inflammatory processes may depend on TLR signaling, it has been considered to be involved in the pathogenesis of airway inflammatory diseases such as airway infections, bronchial asthma, and occupational airway diseases. In this review, we focus on physiological roles of TLRs in defense mechanisms of the airways, and pathophysiological roles on airway diseases.

KEY WORDS
airway inflammation, bronchial epithelial cells, innate immune

INTRODUCTION

The alveoli of the lungs that facilitate and are thereby a vital part of the gas exchange process: they are the terminal of the respiratory tree. To carry out efficient gas exchange, the respiratory system and the circulatory system get to within a few microns distance of each other. Alveolar type-I epithelial cells, which occupy 90% of the surface area of the alveoli, are specialized in facilitating the gas exchange process, and therefore they do not have a significant role to play in defending against infections. These particular features of the organizational structure of the alveoli are a disadvantage in terms of the defense against infections, as the invasion of microbes into the alveolar area facilitates the entry of pathogens into the circulatory system, which can result in sepsis and thereby incur the risk of death.

For these physiological and anatomical reasons, the lungs are kept aseptic via various protective mechanisms. The respiratory tract opens to the external environment at the oral side edge, and the other edge of the respiratory tract connects to the closed space (alveoli), in a semi-closed circuit, and so sterility in the respiratory tract increases incrementally from the upper to the lower airway. Neither the trachea nor the relatively large bronchi are aseptic; moreover, because microbes enter frequently from the oral cavity, these organs have to protect themselves from microbes largely through actions like mucous secretions, or mucociliary movements. The final bifurcation of the bronchi is the alveolar bronchiole where the bronchi and the alveoli coexist; it is believed that this area, corresponding to the entrance of the alveoli, is maintained aseptic. The recognition machinery for the invasion of microbes is critical to preserve the aseptic condition.

TLR-MEDIATED INNATE IMMUNE RECOGNITION

Innate immunity refers to a built-in defense system of the host to resist the invasion of microbes. The recognition of microbes by an innate immune system has been considered to play a key role in the maintenance of the aseptic condition. Our general understanding of how microbes are recognized by the innate immune system has increased considerably over the past several years, and the contribution of Toll-

[1]Division of Molecular Cell Immunology and Allergology, Department of Advanced Medical Research Center, Nihon University Graduate School of Medicine, Tokyo, Japan.
Correspondence: Yasuhiro Gon, Division of Molecular Cell Immunology and Allergology, Department of Advanced Medical Research Center, Nihon University Graduate School of Medicine, 30–1 Oyaguchikami-cho, Itabashi-ku, Tokyo 173–8610, Japan.
Email: gon@med.nihon–u.ac.jp
Received 5 October 2007.

Like Receptors (TLRs) to innate immunity is now well documented.[1-5] The discrimination between "self" and "nonself" by TLRs as sensors of pathogen molecules, is a key mechanism of the immune system response. For mammals to be able to detect pathogens, a common strategy used by multiple TLR family members is the targeting of constitutents as an indicator of infectious non-self. It now seems that many inflammatory processes may depend on TLR signaling.[6-8] To date, about 15 mammalian TLRs have been reported.[1,2,4] For example, TLR4 recognizes lipopolysaccharide (LPS) a common constituent of the cell wall of gram-negative bacteria and TLR2 recognises peptidogylcan a common constituent of gram-positive cell walls, both of which are critical for the innate immune response against bacterial invasion.[1-5] TLR3, TLR7, TLR8, and TLR9 recognize pathogen nucleic acids, such as viral RNAs and bacterial DNA.[1-5] TLR activation results in the engagement of signaling intermediates, including the following: myeloid differentiation factor-88 (MyD88); Toll-interleukin (IL)-1 receptor (TIR)-associated protein (TIRAP, also known as MAL); Toll receptor-associated activator of interferon (TRIF); Toll receptor-associated molecule (TRAM); IL-1 receptor-associated kinases (IRAK) and tumour necrosis factor (TNF) receptor-associated factor 6 (TRAF6).[1-5] RNA virus infections such as respiratory syncytial virus (RSV) or influenza virus, are the major causes of virus-induced airway inflammation.[9-11] Detection of the "molecular signature" for RNA viruses has been attributed to TLR3, TLR7, and TLR8. Double-stranded RNA (dsRNA) is a molecular pattern which is associated with viral infection, because it is produced by most viruses at some point during their replication process.[12-16] TLR3 has been shown to recognize dsRNA, and the binding of dsRNA to TLR3 activates signaling to induce anti-viral responses.[17] TLR7 and TLR8 have been described as mediating the immune response to guanine and urachil (GU)-rich single-stranded RNA (ssRNA) viruses.[18-20] TLR3, TLR7, and TLR8 have been shown to be endosomally located.[21,22] TLR3 is also constitutively expressed on the surface of airway epithelial cells.[23] The surface expression of TLR3 recognizes extracellular dsRNA but if TLR3 expression is blocked, the antiviral response to the RNA virus is inhibited which leads to an increase in viral replication and release.[23] TLR3, TLR7, and TLR8 can each signal independently of MyD88, via a Toll/interleukin 1 (IL-1) receptor domain containing adaptor-inducing beta interferon (IFN-β) (TRIF); this independent signaling, leads to NF-kB activation and production of type-I interferon which plays an important role in the innate immune response against viral infection.[13,16]

Not only innate immune responses, different types of adaptive immune responses are also induced via several TLRs expressed on dendritic cells or monocytes. Functioning of the adaptive immune system is based on a diverse set of rearranged T cell receptors and B cell receptors that recognize a wide variety of antigens. Although T and B lymphocytes express receptors of enormous diversity, their activation depends on signals derived from the innate immune system. Immature DCs residing in the periphery are incapable of inducing T cell priming, and TLRs on DC play important role on the DC maturation. When TLRs on DC recognize their ligands, the initiate signaling that lead to DC maturation cause up-regulation of MHC molecules loaded with pathogen-derived peptides and surface expression of co-stimulatory molecules, such as CD80 and CD86. The TLR-mediated control of co-stimulatory molecule expression on DC plays a crucial role in T cell activation.[24]

TLRS IN BRONCHIAL EPITHELIAL CELLS

The lung have multiple regulatory mechanisms to maintain the aseptic condition of the terminal airway, and the alveolar macrophages, which specialize in monitoring microbes in the alveoli, provide complete protection by triggering a strong inflammation reaction when microbes are found.[25,26] On the other hand, regarding the monitoring of microbes in the bronchi, bronchial epithelial cells are on front-line of defense against infections.[27-30] Most TLRs expression in airway epithelial cells have been documented in research using either cell lines, primary cells or tissues,[31-35] but thir exact expression patterns and expression levels are still to be elucidated. From the aforementioned differences in the levels of sterility, the central bronchi and the peripheral bronchi seems to have different roles in terms of how they monitor microbes; however, there have been few reports up until now that have shown any notable differences in TLR expression level between the central bronchial epithelium and the peripheral bronchial epithelium. Additionally, there have been few reports that verify any apparent differences in responsiveness to the TLR ligand in cultured bronchial epithelial cells derived from the central airway or the peripheral airway. The culture experiments, using bronchial epithelial cells, showed differences in responsiveness to the LPS between the bronchial epithelium and the monocyte/macrophage linage. For the macrophages and monocytes, the LPS response was observed with only a minimal nM of concentration. On the other hand, for the tracheal epithelium, the response required more than 100 times that minimal concentration, thus showing a clear difference in sensitivity to LPS.[27,36,37] As to responses to the peptidoglycan and dsRNA, which are ligands within the same TLR, such a significant difference in sensitivity has not been observed.[38-40] It is believed that this difference stems from the different roles of the tracheal epithelial cells and the monocyte/macrophage series in monitoring microbes.

There are some differences in patterns of the se-

creted cytokine response to TLR ligands between the bronchial epithelium and macrophages. For example, TNF is a representative cytokine that is produced from alveolar macrophages when they are stimulated with TLR,[40] but there is little evidence to indicate that the differentiated bronchial epithelial cells can produce TNF.[41] TNF itself has strong inflammation induction effects as well as tissue damage effects. The fact that bronchial epithelial cells do not produce TNF can be rationalized by the fact that the main purpose of the monitoring of microbes by the bronchial epithelial cells is not to induce inflammations strong enough to cause tissue destruction but rather to achieve the recruitment of neutrophils by chemotaxis as an initial response to the entry of microbes.

ALLERGIC AIRWAY INFLAMMATION AND TLRS

Bronchial asthma is a complex inflammatory disease of the airways that is associated with bronchial hyperreactivity, airway obstruction, and increased mucus production. The imbalance between TH1 and TH2 lymphocytes with a predominant TH2-type immune response is a central component in the regulation and perpetuation of the asthma pathology.[42-44] The release of TH2 cytokines including IL-4, IL-5, and IL-13 in response to allergen exposure induces recruitment and, activation of eosinophils, mast cell activation, and the switch to IgE production by B cells in asthmatics.[44,45] The inverse relationship between microbial load in childhood and later development of allergic diseases has led to the hygiene hypothesis,[46-49] this hypothesis was first proposed by David P. Strachan in an article published in the British Medical Journal in 1989.[50] This hypothesis has now been developed to an understanding that frequent exposure to microbial products results in a predominant TH1 phenotype, whereas a lack of such interactions could promote TH2-driven allergic diseases. This "hygiene hypothesis" proposes that infections acquired early in life may protect children against asthma. Gram-negative bacteria, mycobacteria and many viruses strongly induce TH1 responses.[49] These pathogens, or their purified components, have been shown to prevent TH2-type responses in animals.[51] The hygiene hypothesis is strengthened by certain epidemiological evidence and by the recent discovery that polymorphisms in CD14, an LPS coreceptor, are associated with an increased asthma risk in children.[52-54] These genetic variants of CD14 may reduce the intensity of LPS responses, thereby reducing development of TH1-type immunity, LPS though appears to have paradoxical roles depending on the timing and the context of the LPS exposure. Although early exposure to LPS (or other TLR ligands) can decrease the incidence of atopic asthma in later life,[55] many reports have demonstrated an increase in allergen-induced asthma severity following exposure to LPS.[56,57] Viral infection during the first 3 years of life greatly enhances the risk of asthma in children, suggesting that specific interactions between respiratory allergies and viral infections in the respiratory tracts exists; especially, RSV infection in respiratory viral infections, in early childhood, might enhance the development of airway allergen sensitization.[58,59] A replication intermediate of RSV is dsRNA, and several studies have revealed that TLR3 and dsRNA lead to the induction of genes related to the pathogenesis of bronchial asthma. Thymic stromal lymphopoietin (TSLP) has been shown to be highly involved in the pathogenesis of inflammatory diseases in general.[60] High TSLP expression has been found in the skin of patients with acute and chronic atopic dermatitis, while TSLP is not detectable in normal skin or in nonlesional skin of atopic dermatitis patients.[61] In addition, TSLP has been found to be increased in asthmatic airways.[62] High amounts of TSLP have been found in bronchoalveolar lavage fluid in a mouse asthma model and lung-specific TSLP transgenic mice show airway inflammation including massive infiltration of inflammatory cells, goblet cell hyperplasia, and airway hyper responsiveness,[63] whereas mice lacking the TSLPR exhibit strong TH1 responses and fail to develop an inflammatory lung response to antigens.[64] A recent study revealed that TSLP strongly and significantly induced TLR3 ligand and that the combination of IL-4 and dsRNA synergistically enhanced TSLP production in airway epithelial cells;[65] this indicates that respiratory viral infection and the recruitment of TH2 cytokine-producing cells may amplify TH2 inflammation via the induction of TSLP into the asthmatic airway.

ENVIROMENTAL AIRWAY INFLAMMATION AND TLRS

Environmental substances reportedly have a complex effect upon the airway, and epidemiologic studies have shown that asthma-related hospital emergency room visits increase during periods of increased levels of particulate matter less than 10 micrometers in diameter (PM_{10}).[66,67] Residual oil fly ash (ROFA) produced from the combustion of residual fuel oil significantly increases the ambient air pollution. In human airway epithelial cells, ROFA has been shown to induce inflammatory cytokines, such as IL-6, IL-8, and TNF-α.[67] Inhalation of ROFA into the airways of experimental animals, as surrogates, has been an acceptable model to study the biologic effects of PM_{10} air pollution.[68] Furthermore, ROFA reportedly causes increased airway hyperreactivity, neutrophilic inflammation, and hyperpermeability in animal models[68] and can amplify allergic inflammation in mouse models of asthma.[69] Cho HY *et al*. have reported that significant interstrain (genetic) variation was observed in ROFA-induced lung inflammation and hyperpermeability phenotypes.[70] C3H/HeJ (HeJ) mice were most

resistant to the ROFA-induced airway inflammation responses. They observed that ROFA-induced lung injury was significantly greater in CH3/OuJ mice compared with HeJ mice. CH3/OuJ mice have normal TLR4, on the other hand, CH3/HeJ mice have a missense mutation in the tlr4 gene, resulting in nonfunctional TLR4. They also found that ROFA significantly enhanced transcript and protein levels of lung TLR4 in OuJ but not in HeJ mice, and they observed greater activation of downstream signal molecules, such as MYD88, TRAF6, IRAK-1, NF-kappaB, MAPKs, and AP-1 was observed in OuJ mice than in HeJ mice before the development of ROFA-induced airway injury.

Ozone is another ubiquitous urban air pollutant that can significantly contribute to increased pulmonary morbidity and mortality in human populations.[71] Despite the demonstrated clinical relevance of ambient ozone, the biological mechanisms of ozone-induced airway inflammation have remained to be elucidated. Humans exposed to ozone develop neutrophilic inflammation, increased expression of proinflammatory cytokines, and decrements in pulmonary function.[72] Interestingly, TLR4 level has been reported to be strongly linked to the sensitivity of the airway to ozone.[73] This evidence indicates that TLR4 might be a candidate susceptibility gene for environmental airway diseases.

REFERENCES

1. Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. *Cell* 2006;**124**:783-801.
2. Medzhitov R, Preston-Hurlburt P, Janeway CA Jr. A human homologue of the *Drosophila* Toll protein signals activation of adaptive immunity. *Nature* 1997;**388**:394-397.
3. Fritz JH, Girardin SE. How Toll-like receptors and Nod-like receptors contribute to innate immunity in mammals. *J. Endotoxin Res.* 2005;**11**:390-394.
4. Creagh EM, O'Neill LA. TLRs, NLRs and RLRs: a trinity of pathogen sensors that co-operate in innate immunity. *Trends Immunol*. 2006;**27**:352-357.
5. Takeda K, Kaisho T, Akira S. Toll-like receptors. *Annu. Rev. Immunol*. 2003;**21**:335-376.
6. Verstak B, Hertzog P, Mansell A. Toll-like receptor signalling and the clinical benefits that lie within. *Inflamm. Res.* 2007;**56**:1-10.
7. Chaudhuri N, Whyte MK, Sabroe I. Reducing the toll of inflammatory lung disease. *Chest* 2007;**131**:1550-1556.
8. Lakhani SA, Bogue CW. Toll-like receptor signaling in sepsis. *Curr Opin Pediatr*. 2003;**15**:278-282.
9. Ogra PL. Respiratory syncytial virus: the virus, the disease and the immune response. *Paediatr Respir Rev.* 2004;**5**(Suppl A):S119-S126.
10. Hacking D, Hull J. Respiratory syncytial virus—viral biology and the host response. *J. Infect*. 2002;**45**:18-24.
11. Panitch HB. Bronchiolitis in infants. *Curr. Opin. Pediatr* 2001;**13**:256-260.
12. Bowie AG, Haga IR. The role of Toll-like receptors in the host response to viruses. *Mol. Immunol*. 2005;**42**:859-867.
13. Uematsu S, Akira S. Toll-like receptors and Type I interferons. *J. Biol. Chem*. 2007;**282**:15319-15323.
14. Schröder M, Bowie AG. TLR3 in antiviral immunity: key player or bystander? *Trends Immunol.* 2005;**26**:462-468.
15. Sioud M. Innate sensing of self and non-self RNAs by Toll-like receptors. *Trends Mol. Med*. 2006;**12**:167-176.
16. Kawai T, Akira S. Antiviral signaling through pattern recognition receptors. *J. Biochem*. 2007;**141**:137-145.
17. Alexopoulou L, Holt AC, Medzhitov R, Flavell RA. Recognition of double-stranded RNA and activation of NF-kappaB by Toll-like receptor 3. *Nature* 2001;**413**:732-738.
18. Jurk M, Heil F, Vollmer J *et al*. Human TLR7 or TLR8 independently confer responsiveness to the antiviral compound R-848. *Nat. Immunol*. 2002;**3**:499.
19. Hemmi H, Kaisho T, Takeuchi O *et al*. Small anti-viral compounds activate immune cells via the TLR7 MyD88-dependent signaling pathway. *Nat. Immunol*. 2002;**3**:196-200.
20. Diebold SS, Kaisho T, Hemmi H, Akira S, Reis e, Sousa C. Innate antiviral responses by means of TLR7-mediated recognition of single-stranded RNA. *Science* 2004;**303**:1529-1531.
21. Matsumoto M, Funami K, Tanabe M *et al*. Subcellular localization of Toll-like receptor 3 in human dendritic cells. *J. Immunol*. 2003;**171**:3154-3162.
22. Hattermann K, Picard S, Borgeat M, Leclerc P, Pouliot M, Borgeat P. The Toll-like receptor 7/8-ligand resiquimod (R-848) primes human neutrophils for leukotriene B4, prostaglandin E2 and platelet-activating factor biosynthesis. *FASEB J*. 2007;**21**:1575-1585.
23. Hewson CA, Jardine A, Edwards MR, Laza-Stanca L, Jonston SL. Toll-like Receptor 3 Is Induced by and Mediates Antiviral Activity against Rhinovirus Infection of Human Bronchial Epithelial Cells. *J. Virol* 2005;**79**:12273-12279.
24. Kadowaki N. Dendritic cells: a conductor of T cell differentiation. *Allergol. Int*. 2007;**56**:193-199.
25. Reynolds HY. Lung inflammation and fibrosis: an alveolar macrophage-centered perspective from the 1970s to 1980s. *Am. J. Respir. Crit. Care Med*. 2005;**171**:98-102.
26. Fels AO, Cohn ZA. The alveolar macrophage. *J. Appl. Physiol*. 1986;**60**:353-369.
27. Gon Y, Asai Y, Hashimoto S *et al*. A20 inhibits toll-like receptor 2- and 4-mediated interleukin-8 synthesis in airway epithelial cells. *Am. J. Respir. Cell Mol. Biol*. 2004;**31**:330-336.
28. Holgate ST. The epithelium takes centre stage in asthma and atopic dermatitis. *Trends Immunol.* 2007;**28**:248-251.
29. Diamond G, Legarda D, Ryan LK. The innate immune response of the respiratory epithelium. *Immunol. Rev*. 2000;**173**:27-38.
30. Schulz C, Farkas L, Wolf K *et al*. Differences in LPS-induced activation of bronchial epithelial cells (BEAS-2B) and type II-like pneumocytes (A-549). *Scand. J. Immunol*. 2002;**56**:294-302.
31. Hou YF, Zhou YC, Zheng XX *et al*. Modulation of expression and function of Toll-like receptor 3 in A549 and H292 cells by histamine. *Mol. Immunol*. 2006;**43**:1982-1992.
32. Hewson CA, Jardine A, Edwards MR, Laza-Stanca V, Johnston SL. Toll-like receptor 3 is induced by and mediates antiviral activity against rhinovirus infection of human bronchial epithelial cells. *J. Virol*. 2005;**79**:12273-12279.
33. Sha Q, Truong-Tran AQ, Plitt JR, Beck LA, Schleimer RP. Activation of airway epithelial cells by toll-like receptor agonists. *Am. J. Respir. Cell Mol. Biol* 2004;**31**:358-364.
34. Muir A, Soong G, Sokol S *et al*. Toll-like receptors in normal and cystic fibrosis airway epithelial cells. Am. J. Respir. *Cell Mol. Biol*. 2004;**30**:777-783.
35. Oshikawa K, Sugiyama Y. Regulation of toll-like receptor 2 and 4 gene expression in murine alveolar macrophages.

Exp. Lung Res. 2003;**29**:401-412.
36. Schaefer L, Babelova A, Kiss E *et al*. The matrix component biglycan is proinflammatory and signals through Toll-like receptors 4 and 2 in macrophages. *J. Clin. Invest*. 2005;**115**:2223-2233.
37. Punturieri A, Alviani RS, Polak T, Copper P, Sonstein J, Curtis JL. Specific engagement of TLR4 or TLR3 does not lead to IFN-beta-mediated innate signal amplification and STAT1 phosphorylation in resident murine alveolar macrophages. *J. Immunol*. 2004;**173**:1033-1042.
38. Knapp S, Wieland CW, van't Veer C *et al*. Toll-like receptor 2 plays a role in the early inflammatory response to murine pneumococcal pneumonia but does not contribute to antibacterial defense. *J. Immunol*. 2004;**172**:3132-3138.
39. Li J, Pritchard DK, Wang X *et al*. cDNA microarray analysis reveals fundamental differences in the expression profiles of primary human monocytes, monocyte-derived macrophages, and alveolar macrophages. *J. Leukoc. Biol*. 2007;**81**:328-335.
40. Ross AJ, Dailey LA, Brighton LE, Devlin RB. Transcriptional profiling of mucociliary differentiation in human airway epithelial cells. *Am. J. Respir. Cell Mol. Biol*. 2007;**37**: 169-185.
41. Romagnani S. Type 1 T helper and type 2 T helper cells: functions, regulation and role in protection and disease. > *Int. J. Clin. Lab. Res*. 1991;**21**:152-158.
42. Del Prete G, Maggi E, Romagnani S. Human Th1 and Th2 cells: functional properties, mechanisms of regulation, and role in disease. *Lab. Invest*. 1994;**70**:299-306.
43. Nakajima H, Takatsu K. Role of cytokines in allergic airway inflammation. *Int. Arch. Allergy Immunol*. 2007;**142**: 265-273.
44. Romagnani S. Immunologic influences on allergy and the TH1/TH2 balance. *J. Allergy Clin. Immunol*. 2004;**113**: 395-400.
45. Bloomfield SF, Stanwell-Smith R, Crevel RW, Pickup J. Too clean, or not too clean: the hygiene hypothesis and home hygiene. *Clin. Exp. Allergy* 2006;**36**:402-425.
46. Weiss ST. Eat dirt—the hygiene hypothesis and allergic diseases. *N. Engl. J. Med*. 2002;**347**:930-931.
47. Wills-Karp M, Santeliz J, Karp CL. The germless theory of allergic disease: revisiting the hygiene hypothesis. *Nat. Rev. Immunol*. 2001;**1**:69-75.
48. Anderson WJ, Watson L. Asthma and the hygiene hypothesis. *N. Engl. J. Med*. 2001;**344**:1643-1644.
49. Strachan DP. Hay fever, hygiene and household size. *Br. Med. J*. 1989;**299**:1259-1260.
50. Schnare M, Barton GM, Holt AC, Takeda K, Akira S, Medzhitov R. Toll-like receptors control activation of adaptive immune responses. *Nat. Immunol*. 2001;**2**:947-950.
51. Hayden CM, Goldblatt J, LeSouef PN. A novel polymorphism (g1344G>C) in exon 2 of the CD14 gene. *Hum. Mutat*. 2000;**15**:122.
52. Woo JG, Assa'ad A, Heizer AB, Bernstein JA, Hershey GK. The -159 C—>T polymorphism of CD14 is associated with nonatopic asthma and food allergy. *J. Allergy Clin. Immunol*. 2003;**112**:438-444.
53. Leung TF, Tang NL, Wong GW, Fok TF. CD14 and toll-like receptors: potential contribution of genetic factors and mechanisms to inflammation and allergy. *Curr. Drug Targets Inflamm. Allergy*. 2005;**4**:169-175.
54. Woodcock A, Forster L, Matthews E *et al*. Medical Research Council General Practice Research Framework. Control of exposure to mite allergen and allergen-impermeable bed covers for adults with asthma. *N. Engl. J. Med*. 2003;**349**:225-236.
55. Michel O, Duchateau J, Sergysels R. Effect of inhaled endotoxin on bronchial reactivity in asthmatic and normal subjects. *J. Appl. Physiol*. 1989;**66**:1059-1064.
56. Michel O, Ginanni R, Le Bon B, Content J, Duchateau J, Sergysels R. Inflammatory response to acute inhalation of endotoxin in asthmatic patients. *Am. Rev. Respir. Dis*. 1992;**146**:352-357.
57. Welliver RC. RSV and chronic asthma. *Lancet* 1995;**346**: 789-790.
58. Dezateux C, Fletcher ME, Dundas I, Stocks J. Infant respiratory function after RSV-proven bronchiolitis. *Am. J. Respir. Crit. Care Med*. 1997;**155**:1349-1355.
59. Liu YJ, Soumelis V, Watanabe N *et al*. TSLP: an epithelial cell cytokine that regulates T cell differentiation by conditioning dendritic cell maturation. *Annu. Rev. Immunol*. 2007;**25**:193-219.
60. Yoo J, Omori M, Gyarmati D *et al*. Spontaneous atopic dermatitis in mice expressing an inducible thymic stromal lymphopoietin transgene specifically in the skin. *J. Exp. Med*. 2005;**202**:541-549.
61. Al-Shami A, Spolski R, Kelly J *et al*. A role for TSLP in the development of inflammation in an asthma model. *J. Exp. Med*. 2005;**202**:829-839.
62. Zhou B, Comeau MR, De Smedt T *et al*. Thymic stromal lymphopoietin as a key initiator of allergic airway inflammation in mice. *Nat. Immunol*. 2005;**6**:1047-1053.
63. Lee HC, Ziegler SF. Inducible expression of the proallergic cytokine thymic stromal lymphopoietin in airway epithelial cells is controlled by NFkappaB. *Proc. Natl. Acad. Sci. U. S. A*. 2007;**104**:914-919.
64. Kato A, Favoreto S Jr, Avila PC, Schleimer RP. TLR3- and Th2 cytokine-dependent production of thymic stromal lymphopoietin in human airway epithelial cells. >*J. Immunol*. 2007;**179**:1080-1087.
65. Barnett AG, Williams GM, Schwartz J *et al*. Air pollution and child respiratory health: a case-crossover study in Australia and New Zealand. *Am. J. Respir. Crit. Care Med*. 2005;**171**:1272-1278.
66. Quay JL, Reed W, Samet J, Devlin RB. Air pollution particles induce IL-6 gene expression in human airway epithelial cells via NF-kappaB activation. *Am. J. Respir. Cell Mol. Biol.*. 1998;**19**:98-106.
67. Chen CH, Xirasagar S, Lin HC. Seasonality in adult asthma admissions, air pollutant levels, and climate: a population-based study. *J. Asthma* 2006;**43**:287-292.
68. Gavett SH, Madison SL, Stevens MA, Costa DL. Residual oil fly ash amplifies allergic cytokines, airway responsiveness, and inflammation in mice. *Am. J. Respir. Crit. Care Med*. 1999;**160**:1897-1904.
69. ldsmith CA, Hamada K, Ning Y *et al*. Effects of environmental aerosols on airway hyperresponsiveness in a murine model of asthma. *Inhal. Toxicol*. 1999;**11**:981-998.
70. Cho HY, Jedlicka AE, Clarke R, Kleeberger SR. Role of Toll-like receptor-4 in genetic susceptibility to lung injury induced by residual oil fly ash. *Physiol. Genomics* 2005; **22**:108-117.
71. Dockery DW, Pope CA, Xu X *et al*. An association between air pollution and mortality in six U.S. cities. *N. Engl. J. Med*. 1993;**329**:1754-1759.
72. Last JA, Ward R, Temple L, Kenyon NJ. Ovalbumin-induced airway inflammation and fibrosis in mice also exposed to ozone. *Inhal. Toxicol*. 2004;**16**:33-43.
73. Hollingsworth JW, Maruoka S, Li Z *et al*. Ambient ozone primes pulmonary innate immunity in mice. *J. Immunol*. 2007;**179**:4367-4375.