Tumor Necrosis Factor Alpha-Mediated Asthma?

T. Nabe

Department of Pharmacology, Kyoto Pharmaceutical University, Kyoto, Japan

According to established knowledge, the mechanisms of allergic asthma are as follows: when an inhaled allergen penetrates the airway epithelium, it is detected by dendritic cells, which migrate to the lymph node and present the processed antigen to T cells, and B cells start to produce antigen-specific immunoglobulin E (IgE). IgE binds to Fcε receptors on a variety of cell types including mast cells and basophils. When an allergic individual is subsequently exposed to the specific allergen, the allergen binds to the specific IgE on the cells, causing activation of mast cells and basophils to release chemical mediators, such as histamine, arachidonic acid metabolites and proteases into the airway tissue. These mediators cause an early asthmatic response, which is an airway obstruction induced within 30 min after allergen exposure. There is also a specific population of asthmatic subjects which exhibits a late asthmatic response, i.e. an airway obstruction triggered several hours after allergen challenge and persisting for a relatively long time.

The late asthmatic response has been thought to be based on airway inflammation orchestrated by Th2 cells and eosinophils [1]. In addition to the early and late asthmatic responses, Th2-biased airway inflammation leads to airway hyperresponsiveness (AHR) to nonspecific stimuli and structural remodeling of airway tissues. Various experimental models reproduce these phenotypes of asthma.

Thus the pathophysiology of allergic asthma is traditionally explained by mast cell- and/or Th2 cell-mediated airway inflammation, which is a manifestation of the acquired immune response. On the other hand, recent studies have identified various other important molecules associated with phenotypes of asthma, including tumor necrosis factor (TNF)-α [2, 3], thymic stromal lymphoprotein [4, 5], interleukin (IL)-33 [6, 7] and IL-25 [8, 9]. TNF-α is produced mainly in macrophages and mast cells, and thymic stromal lymphoprotein, IL-33 and IL-25 are mainly from epithelial cells and various leukocytes. Those molecules are considered to play roles in the innate immune response. In order to understand novel pathophysiological mechanisms of asthma, a recent trend has been toward the generation of novel animal models, including asthma associated with both acquired and innate immunity, severe asthma such as steroid-resistant phenotypes [10–12], neutrophilic asthma [13, 14] and the viral exacerbation of allergic inflammation [15, 16]. It is believed that these new asthma models will lead to the development of new strategies for asthma.

In this issue of *International Archives of Allergy and Immunology*, Kim et al. [17] present a well-conducted murine asthma model of AHR, where part of the mechanism reported was TNF-α-mediated airway inflammation. They observed detailed time-course changes in the occurrence of AHR after antigen (ovalbumin) challenge in

sensitized C57BL/6 mice, and found that a late AHR consists of 2 phases, with first and second phases peaking at 10 and 24 h, respectively. It was interesting that the first phase of late AHR was a TNF- α -dependent response because anti-TNF- α antibody and TNF- α knockout animals impaired the response. The second phase of late AHR, however, was not mediated by TNF- α . TNF- α was transiently produced in the airway 1.5–2 h after the antigen challenge, whereas only a single exogenous administration of TNF- α could reproduce the induction of AHR 10 h but not 24 h after administration. They suggested that the cellular source early after antigen challenge could be not only mast cells but also other inflammatory cells, such as macrophages, dendritic cells, eosinophils and platelets (which possess Fc γ receptors on their cell surface), because intratracheal instillation of the immune complex of IgG and antigen markedly developed AHR at 12 h in a TNF- α -dependent manner. In addition, they suggested that TNF- α -induced AHR was mediated by leukotriene B₄, which was produced by the activation of cytosolic phospholipase A₂ and 5-lipoxygenase. Finally, the second phase of late AHR was suggested to be induced by Th2 cell activation because its response (but not the first-phase response) was prevented by CpG-oligonucleotide, a well-established Th1 inducer. Collectively, first- and second-phase late AHR are caused by TNF- α and Th2 responses, respectively.

The first impact of this study is that authors found that late AHR clearly consists of 2 phases. In most studies of AHR in murine asthma, airway responsiveness to a stimulus is normally and conventionally measured 1–2 days after exposure to an allergen. Thus, previous studies may have observed the second phase of late AHR and may have overlooked the phase of a TNF- α -mediated response. Although C57BL/6 mice were mainly used in the study by Kim et al. [17], it is also important to know whether biphasic late AHR is a universal phenomenon in this species.

Striking about this asthma model is the clear data that the first phase of late AHR was mediated by TNF- α [17]. Indeed, elevated levels of TNF- α have been observed in the airway tissues of asthmatic subjects and upregulated TNF- α expression has been detected in alveolar macrophages, mast cells and bronchial epithelial cells [18]. TNF- α exerts a variety of proinflammatory actions in the airway tissues, including the expression of cytokines, chemokines, adhesion molecules and mucins [18]. Some clinical trials have explored the possibility of using TNF- α inhibitors in asthmatic patients. Etanercept, a human dimeric fusion protein composed of a TNF- α type-II re-

ceptor and the Fc portion of IgG1, has been demonstrated to improve asthma pathogenesis, especially in severe asthma patients [19, 20]; there are, however, other clinical trials that reject the role of TNF- α in asthma pathogenesis [21, 22]. It is expected that TNF- α -mediated asthma models, including that reported by Kim et al. [17], could be utilized to further clarify the detailed roles of TNF- α in asthma.

It is also interesting to focus on the relationship between TNF- α and airway neutrophilia because it is well known that TNF- α promotes neutrophil chemotaxis [23]. In the model reported by Kim et al. [17], airway neutrophilia clearly followed the production of TNF- α . This axis of TNF- α and neutrophils may be involved in the induction of the first phase of late AHR. This concept is supported by the findings that (1) the TNF- α inhibitor exhibited efficacy in severe asthma patients [19, 20] and (2) neutrophils are found increasingly in the lungs of patients with severe asthma [24].

Identification of the cellular source of TNF- α is also important. As mentioned by Kim et al. [17], macrophages could be the cellular source of TNF- α produced 1.5–2 h after the antigen challenge. Macrophages can be classified as M1 and M2 macrophages; the former is known to be proinflammatory and induced by chronic inflammation [25]. Although only 2 antigen challenges were carried out in their study [17], chronic exposure to an antigen may induce M1 macrophages to produce more TNF- α and amplify the magnitude of TNF- α contribution to the first phase of late AHR.

It is expected that the TNF- α -induced AHR model reported by Kim et al. [17] will be utilized to elucidate novel mechanisms underlying the pathogenesis of asthma and to develop new strategies against the disease.

References

- 1 Varner AE, Lemanske RF Jr: The early and late asthmatic response to allergen; in Busse WW, Holgate ST (eds): *Asthma and Rhinitis*, ed 2. Oxford, Blackwell Science, 2000, pp 1172–1185.
- 2 Kim YS, Ko HM, Kang NI, Song CH, Zhang X, Chung WC, Kim JH, Choi IH, Park YM, Kim GY, Im SY, Lee HK: Mast cells play a key role in the development of late airway hyperresponsiveness through TNF- α in a murine model of asthma. *Eur J Immunol* 2007; 37:1107–1115.
- 3 Choi JP, Kim YS, Kim OY, Kim YM, Jeon SG, Roh TY, Park JS, Gho YS, Kim YK: TNF- α is a key mediator in the development of Th2 cell response to inhaled allergens induced by a viral PAMP double-stranded

- RNA. Allergy 2012, E-pub ahead of print.
- 4 Al-Shami A, Spolski R, Kelly J, Keane-Myers A, Leonard WJ: A role for TSLP in the development of inflammation in an asthma model. *J Exp Med* 2005;202:829–839.
- 5 Zhou B, Comeau MR, De Smedt T, Liggitt HD, Dahl ME, Lewis DB, Gyarmati D, Aye T, Campbell DJ, Ziegler SF: Thymic stromal lymphopoietin as a key initiator of allergic airway inflammation in mice. *Nat Immunol* 2005;6:1047–1053.
- 6 Hayakawa H, Hayakawa M, Kume A, Tomimaga S: Soluble ST2 blocks interleukin-33 signaling in allergic airway inflammation. *J Biol Chem* 2007;282:26369–26380.
- 7 Kearley J, Buckland KF, Mathie SA, Lloyd CM: Resolution of allergic inflammation and airway hyperreactivity is dependent upon disruption of the T1/ST2-IL-33 pathway. *Am J Respir Crit Care Med* 2009;179:772–781.
- 8 Tamachi T, Maezawa Y, Ikeda K, Iwamoto I, Nakajima H: Interleukin 25 in allergic airway inflammation. *Int Arch Allergy Immunol* 2006;140(suppl 1):59–62.
- 9 Ballantyne SJ, Barlow JL, Jolin HE, Nath P, Williams AS, Chung KF, Sturton G, Wong SH, McKenzie AN: Blocking IL-25 prevents airway hyperresponsiveness in allergic asthma. *J Allergy Clin Immunol* 2007;120:1324–1331.
- 10 Komlósi ZI, Pozsonyi E, Tábi T, Szőko E, Nagy A, Bartos B, Kozma GT, Tamási L, Orosz M, Magyar P, Losonczy G: Lipopolysaccharide exposure makes allergic airway inflammation and hyper-responsiveness less responsive to dexamethasone and inhibition of iNOS. *Clin Exp Allergy* 2006;36:951–959.
- 11 Ito K, Herbert C, Siegle JS, Vuppusetty C, Hansbro N, Thomas PS, Foster PS, Barnes PJ, Kumar RK: Steroid-resistant neutrophilic inflammation in a mouse model of an acute exacerbation of asthma. *Am J Respir Cell Mol Biol* 2008;39:543–550.
- 12 McKinley L, Alcorn JF, Peterson A, Dupont RB, Kapadia S, Logar A, Henry A, Irvin CG, Piganelli JD, Ray A, Kolls JK: TH17 cells mediate steroid-resistant airway inflammation and airway hyperresponsiveness in mice. *J Immunol* 2008;181:4089–4097.
- 13 Wilson RH, Whitehead GS, Nakano H, Free ME, Kolls JK, Cook DN: Allergic sensitization through the airway primes Th17-dependent neutrophilia and airway hyperresponsiveness. *Am J Respir Crit Care Med* 2009;180:720–730.
- 14 Nabe T, Hosokawa F, Matsuya K, Morishita T, Ikeda A, Fujii M, Mizutani N, Yoshino S, Chaplin DD: Important role of neutrophils in the late asthmatic response in mice. *Life Sci* 2011;88:1127–1135.
- 15 Torres D, Dieudonné A, Ryffel B, Vilain E, Si-Tahar M, Pichavant M, Lassalle P, Trottein F, Gosset P: Double-stranded RNA exacerbates pulmonary allergic reaction through TLR3: implication of airway epithelium and dendritic cells. *J Immunol* 2010;185:51–459.
- 16 Tourdot S, Mathie S, Hussell T, Edwards L, Wang H, Openshaw PJ, Schwarze J, Lloyd CM: Respiratory syncytial virus infection provokes airway remodelling in allergen-exposed mice in absence of prior allergen sensitization. *Clin Exp Allergy* 2008;38:1016–1124.
- 17 Kim HK, Lee C-H, Kim J-M, Ayush O, Im S-Y, Lee H-K: Biphasic late airway hyperresponsiveness in a murine model of asthma. *Int Arch Allergy Immunol*, 2012;160:173–183.
- 18 Matera MG, Calzetta L, Cazzola M: TNF-alpha inhibitors in asthma and COPD: we must not throw the baby out with the bath water. *Pulm Pharmacol Ther* 2010;23:121–128.
- 19 Howarth PH, Babu KS, Arshad HS, Lau L, Buckley M, McConnell W, Beckett P, Al Ali M, Chauhan A, Wilson SJ, Reynolds A, Davies DE, Holgate ST: Tumour necrosis factor (TNFalpha) as a novel therapeutic target in symptomatic corticosteroid dependent asthma. *Thorax* 2005;60:1012–1018.
- 20 Berry MA, Hargadon B, Shelley M, Parker D, Shaw DE, Green RH, Bradding P, Brightling CE, Wardlaw AJ, Pavord ID: Evidence of a role of tumor necrosis factor alpha in refractory asthma. *N Engl J Med* 2006;354:697–708.
- 21 Rouhani FN, Meitin CA, Kaler M, Miskinis-Hilligoss D, Stylianou M, Levine SJ: Effect of tumor necrosis factor antagonism on allergen-mediated asthmatic airway inflammation. *Respir Med* 2005;99:1175–1182.
- 22 Morjaria JB, Chauhan AJ, Babu KS, Polosa R, Davies DE, Holgate ST: The role of a soluble TNFalpha receptor fusion protein (etanercept) in corticosteroid refractory asthma: a double blind, randomised, placebo controlled trial. *Thorax* 2008;63:584–591.
- 23 Smart SJ, Casale TB: Pulmonary epithelial cells facilitate TNF-alpha-induced neutrophil chemotaxis. A role for cytokine networking. *J Immunol* 1994;152:4087–4094.
- 24 Foley SC, Hamid Q: Images in allergy and immunology: neutrophils in asthma. *J Allergy Clin Immunol* 2007;119:1282–1286.
- 25 Moreira AP, Hogaboam CM: Macrophages in allergic asthma: fine-tuning their pro- and anti-inflammatory actions for disease resolution. *J Interferon Cytokine Res* 2011;31:485–491.