Apolipoprotein E in Asthmatic Inflammatory Response: Friend or Foe?

Asthma is a chronic airway inflammatory disease involving many cells and cellular components with complex yet incompletely known etiologic mechanisms. This inflammation is often accompanied by increased airway responsiveness, which causes recurrent wheezing, shortness of breath, chest tightness, and/or cough (1). Allergic asthma threatens the lives and health of 300 million people worldwide, with more than 26 million people being affected each year in the United States alone (2). Despite intense efforts at understanding pathogenic mechanisms and developing strategies to contain this disease in recent decades, the high morbidity and mortality of asthma and subsequent airway remodeling are still difficult to control. Hence, concerted and increased efforts to dissect the pathogenesis, particularly the cellular and molecular mechanisms, are warranted to generate new insight and promote novel ideas for developing more effective prevention and therapeutic approaches.

APOE (apolipoprotein E) is a multifunctional protein, which plays a major role in lipid metabolism and also exerts both pro- and antiinflammatory effects (3). APOE has a high affinity to bind lipoproteins to low-density lipoprotein receptors, which in turn helps to transport cholesterol via the internalization of lipoprotein particles into cells and critically regulate homeostasis of plasma and tissue lipid content by inducing receptor-mediated endocytosis. APOE-deficient mice manifest impaired clearance of plasma lipoproteins and are thus susceptible to development of atherosclerosis and other cardiovascular disorders (4). Interestingly, APOE is a double-edged sword in regulating inflammation, which may be dependent on cell types and disease models. APOE appears to be well established in inhibiting inflammation. In the APOE-deficient mice, oxidized lipids trigger the classical complement cascade, leading to white blood cell infiltration into the choroid plexus, which may increase the propensity for developing neurological disorders (5). This may be because APOE and Factor H interact synergistically in monocytes to reduce complement activation and inflammation in atherosclerotic lesions (6). Studies have also shown that APOE serves as a negative modulator for murine allergic airway inflammation by impeding oxidative stress and inflammasome activity (7).

On the other hand, APOE may facilitate and/or activate inflammatory processes. Studies have shown that APOE can dysregulate asthmatic states by inducing macrophages to actively produce NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasomes and IL-1β in a concentration-dependent manner (8). Complex mechanisms may be associated with APOE molecular actions, such as regulating gata5-mediated IL-13 expression in airway inflammation and affecting a variety of chemotactic regulators of macrophage subpopulations in pulmonary fibrosis and lung injury (9, 10). Previous research has shown that APOE is critically involved in production of proinflammatory mediators in airway epithelium in asthmatic conditions (11). However, how APOE modulates inflammatory responses in different airway cell populations, including epithelial cells, especially the underpinning signaling pathways, has not been well documented.

A timely study from Kalchiem-Dekel and colleagues (pp. 185–197) in this issue of the *Journal* highlights the role of APOE in mediating proinflammatory C-X-C motif chemokine ligand 5 (CXCL5) responses to allergens by activating the Toll-like receptor 4 (TLR4)/transforming growth factor-β–activated kinase 1 (TAK1)/IκB kinase β (IκKβ)/NF-κB/tumor progression locus 2 (TPL2)/c-Jun N-terminal kinase (JNK) signaling pathway in human asthmatic small airway epithelial cells (12). Initially, the authors looked at differential gene expression by RNA sequencing using knockdown of APOE using RNA interference and identified the TLR4/TAK1/IκKβ/NF-κB/TPL2/JNK signaling pathways. Previous studies have shown that APOE is decreased in patients with atopic asthma relative to healthy volunteers (13). This group was able to delineate a new role of APOE in mediating the inflammatory process through enhancement of the proinflammatory response via induction of CXCL5, which can promote neutrophil activation and chemotaxis. CXCL5 was originally believed to be derived from epithelial cells as a neutrophil-activating peptide 78 (ENA-78). Because of the CXC family chemokine ligand with the highest structural homology to IL-8, CXCL5's receptor is called CXCR2 (14). Functionally, CXCL5 can heighten inflammatory processes by recruiting neutrophils to the site. In addition, the binding of CXCL5 to C-X-C chemokine receptor 2 (CXCR2) will activate the PI3K/AKT pathway. Regarding the signaling pathways involved in CXCL5, researchers have recently reported that CXCL5 mediates the activation of signal transducer and activator of transcription 3 (STAT3) and NF-κB, thereby exerting a proinflammatory effect. Adding to the growing list of functions, Kalchiem-Dekel and colleagues demonstrated a novel mechanism by which APOE influences the state of airways in patients with asthma through signaling transduction of the TLR4/TAK1/IκKβ/NF-κB/TPL2/JNK/CXCL5 axis (12). This is a valuable extension of the CXCL5 role in immune response in airway inflammatory diseases.

Although this study provides insight into the mechanisms of asthmatic inflammation and pathogenesis, most of the results only quantified the expression of proteins in *in vitro* models, which may not be sufficient to draw the solid conclusion that APOE can directly activate TLR4 and subsequently drive the underlying signaling transduction involving TAK1/NF-κB/CXCL5 networks *in vivo*. An asthma animal model and perhaps clinically relevant investigation would be useful in clarifying the role and the mechanism of APOE in allergic disease and the homeostasis and inflammatory responses involved in host defense. For instance, an *in vivo* study using knockout mice could be useful in determining the mechanisms by which APOE activates the TLR4/TAK1/IκKβ/NF-κB/TPL2/JNK/CXCL5

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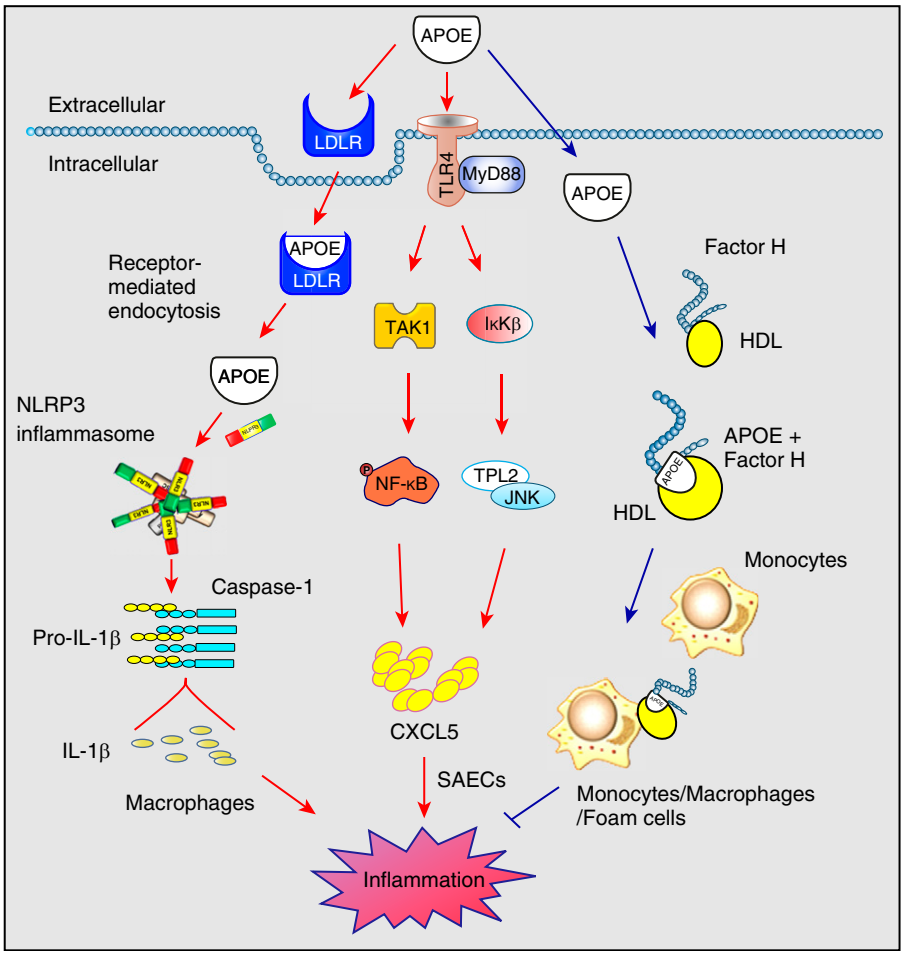

Figure 1. Apolipoprotein E (APOE) exhibits both proinflammatory and antiinflammatory properties. Proinflammatory: APOE is transported through receptor-mediated endocytosis to aggravate asthmatic conditions by facilitating NLRP3 inflammasome activation to release IL-1β by macrophages (8). Meanwhile, APOE promotes the inflammatory response by activating the TLR4/TAK1/IκKβ/NF-κB/TPL2/JNK/CXCL5 pathway in small airway epithelial cells (SAECs) (12). Antiinflammatory: APOE and Factor H interact synergistically in monocytes to reduce complement activation and subsequent inflammatory response in atherosclerotic lesions, leading to attenuated disease states (6). CXCL5 = C-X-C motif chemokine ligand 5; HDL = high-density lipoprotein; IκKβ = IκB kinase β; JNK = c-Jun N-terminal kinase; LDLR = low-density lipoprotein receptor; NLRP3 = NOD-, LRR-, and pyrin domain-containing 3 NLRP3; TAK1 = transforming growth factor-β–activated kinase 1; TLR4 = Toll-like receptor 4; TPL2 = tumor progression locus 2.

signal pathway. To be druggable, the complex signaling axis requires further differentiation to find the key interactions and major factors for targeting. This and future studies will continue to inspire both pharmaceutical teams and basic scientists to look for ways to understand and treat asthma and other prevalent airway diseases. ■

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Shugang Qin, M.Sc.
Qinqin Pu, Ph.D.
Zhihan Wang, M.D.
Min Wu, M.D., Ph.D.
Department of Biomedical Sciences and School of Medicine and Health Sciences
University of North Dakota Grand Forks, North Dakota

ORCID ID: 0000-0003-1205-982X (M.W.).

References

1. Cukic V, Lovre V, Dragisic D, Ustamujic A. Asthma and chronic obstructive pulmonary disease (COPD) - differences and similarities. *Mater Sociomed* 2012;24:100–105.
2. Samarasinghe AE, Rosch JW. Convergence of inflammatory pathways in allergic asthma and sickle cell disease. *Front Immunol* 2020;10: 3058.
3. Huang Y, Mahley RW. Apolipoprotein E: structure and function in lipid metabolism, neurobiology, and Alzheimer's diseases. *Neurobiol Dis* 2014;72:3–12.
4. Kolovou G, Anagnostopoulou K, Mikhailidis DP, Cokkinos DV. Apolipoprotein E knockout models. *Curr Pharm Des* 2008;14:338–351.
5. Yin C, Ackermann S, Ma Z, Mohanta SK, Zhang C, Li Y, *et al*. ApoE attenuates unresolvable inflammation by complex formation with activated C1q. *Nat Med* 2019;25:496–506.
6. Nissilä E, Hakala P, Leskinen K, Roig A, Syed S, Van Kessel KPM, *et al*. Complement Factor H and apolipoprotein E participate in regulation of inflammation in THP-1 macrophages. *Front Immunol* 2018;9: 2701.

7. Zhao CC, Xu J, Xie QM, Fan XY, Fei GH, Wu HM. Apolipoprotein E negatively regulates murine allergic airway inflammation via suppressing the activation of NLRP3 inflammasome and oxidative stress. *Int Immunopharmacol* 2020;81:106301.
8. Gordon EM, Yao X, Xu H, Karkowsky W, Kaler M, Kalchiem-Dekel O, *et al*. Apolipoprotein E is a concentration-dependent pulmonary danger signal that activates the NLRP3 inflammasome and IL-1β secretion by bronchoalveolar fluid macrophages from asthmatic subjects. *J Allergy Clin Immunol* 2019;144:426–441, e3.
9. Chen B, Moore TV, Li Z, Sperling AI, Zhang C, Andrade J, *et al*. Gata5 deficiency causes airway constrictor hyperresponsiveness in mice. *Am J Respir Cell Mol Biol* 2014;50:787–795.
10. Venosa A, Malaviya R, Choi H, Gow AJ, Laskin JD, Laskin DL. Characterization of distinct macrophage subpopulations during nitrogen mustard-induced lung injury and fibrosis. *Am J Respir Cell Mol Biol* 2016;54:436–446.
11. Kalchiem-Dekel O, Figueroa DM, Gordon EM, Kaler M, Barochia AV, Liu P, *et al*. Apolipoprotein E is a concentration-dependent regulator of pro-inflammatory mediator expression by asthmatic airway epithelial cells [abstract]. *Am J Respir Crit Care Med* 2020; 201:A1413.
12. Kalchiem-Dekel O, Yao X, Barochia AV, Kaler M, Figueroa DM, Karkowsky WB, *et al*. Apolipoprotein E signals via TLR4 to induce CXCL5 secretion by asthmatic airway epithelial cells. *Am J Respir Cell Mol Biol* 2020;63:185–197.
13. Bhowmik M, Majumdar S, Dasgupta A, Gupta Bhattacharya S, Saha S. Pilot-scale study of human plasma proteomics identifies ApoE and IL33 as markers in atopic asthma. *J Asthma Allergy* 2019;12:273–283.
14. Layhadi JA, Turner J, Crossman D, Fountain SJ. ATP evokes Ca^{2+} responses and CXCL5 secretion via $P2X_4$ receptor activation in human monocyte-derived macrophages. *J Immunol* 2018;200: 1159–1168.