Commentary

A novel function of IL-33: suppression of innate antiviral immunity

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Asthma is a chronic type 2 inflammatory disease of the airways that is pathologically characterized by persistent structural changes in the airway walls, including goblet cell hyperplasia, thickening of the basement membrane, smooth muscle cell hypertrophy/hyperplasia, increased deposition of extracellular matrix proteins, and abnormally excessive vasculature (1). These structural changes are collectively described as airway remodeling, which causes loss of lung function due to irreversible airflow obstruction, airway hyperreactivity and corticosteroid refractoriness (2). Importantly, structural abnormalities due to airway remodeling are already present in childhood asthma (3).

A number of clinical and experimental studies have reported associations between frequent viral lower respiratory infections in early life and asthma onset in later childhood (4-6). Of note, this association and the development of persistent asthma are markedly more pronounced in children who later become sensitized to various aeroallergens (7). Although the precise mechanisms of how respiratory viral infection links to development of asthma remain poorly understood, one suggested possibility is that asthmatic bronchial epithelial cells have deficient ability to produce interferons (IFNs), which are antiviral cytokines (8,9). This antiviral defect in the asthmatic airway is thought to be closely associated with increased respiratory virus replication and impaired apoptosis of infected airway epithelial cells.

Lynch *et al.* recently demonstrated that aeroallergen-induced IL-33, which is an essential cytokine for development of allergic diseases, including asthma, suppresses antiviral immunity and increases the severity of viral bronchiolitis (10). To investigate whether early-life interaction between a viral respiratory tract infection and allergen exposure causes persistent changes in host immunity in later life, they developed an ingenious mouse model using pneumonia virus of mice (PVM) and a low-dose cockroach extract (CRE).

Mice were inoculated with PVM at 7 days (early life) and 49 days (later life) of age and then repeatedly exposed to CRE to better simulate the natural course of events in humans. Although PVM infection or CRE exposure alone did not induce any features of asthma, co-exposure with PVM and CRE synergized to induce eosinophilic airway inflammation, mucus hypersecretion and airway remodeling, including collagen and periostin deposition and airway smooth muscle cell hypertrophy, in later life. They further found that CRE exposure in early life fundamentally altered the nature of host immunity in later life, because when this early exposure was omitted, all the tested asthmatic features were completely abrogated, even though the mice had been inoculated with PVM in early and later life and then challenged repeatedly with CRE in later life.

Interestingly, IL-33 was found to be crucially involved in the synergistic effect between PVM and CRE. CRE exposure during viral infection in early life induced IL-33 release in the lung as well as impaired anti-viral cytokine production such as IFN-α and IFN-λ, resulting in increased epithelial viral burden, remodeling and type 2 inflammation in the airway. IL-33 blockade by anti-IL-33 treatment of mice effectively prevented the excessive viral load and reversed dampened antiviral immunity by co-exposure to PVM and CRE. By contrast, substitution of CRE with exogenous IL-33 recapitulated the asthmatic features observed in co-exposed mice.

IL-33 is a member of the IL-1 family of cytokines, which can robustly induce type 2 immune responses via the IL-1RL1/ST2 and IL-1RAcP (IL-1 receptor accessory protein) receptors expressed on various effector cells,

including group 2 innate lymphoid cells (ILC2), Th2 cells, eosinophils, basophils, dendritic cells and mast cells (11), as well as airway structural cells such as epithelial and vascular endothelial cells (12). In addition, previous large-scale human genome-wide association studies (GWAS) reproducibly showed that both *IL-33* and its receptor, *IL-1RL1*, are asthma susceptibility genes, without regard to race (13), suggesting that IL-33 may be indispensable for asthmatic airway inflammation.

Although IL-33 was initially described as a nuclear factor expressed in endothelial cells (14), subsequent studies revealed that IL-33 is preferentially and constitutively expressed in the nucleus of tissue structural cells such as epithelial and endothelial cells and is released like high mobility group box-1 (HMGB-1) by necrotic cells after tissue injury and/or trauma (11). Thus, IL-33 seems to be a damage-associated molecular patterns (DAMPs) molecule that has biological functions and provokes local inflammation. This suggests that tissue damage may be crucial for activation of IL-33 in local tissues. Indeed, co-exposure of mice to PVM and CRE increased lung tissue damage (10). Very recently, we demonstrated that platelets constitutively express IL-33 protein and that platelet-derived IL-33 is functionally involved in protease allergen-induced airway eosinophilic inflammation (15). On the other hand, IL-33 has been found to possess anti-inflammatory functions, such as anti-fungal activity (16) and a beneficial effect on murine sepsis model (17).

Thus, IL-33 can act as a multifunctional cytokine that regulates various inflammatory responses. Lynch's report identified a novel function of IL-33 as a potent suppressor of innate antiviral immunity. This function contributes significantly to synergistic associations between frequent viral lower respiratory infections in early life and asthma onset in later childhood. These findings might shed new light on the potential of anti-IL-33 therapy for not only decreasing type 2 inflammation, but also boosting innate antiviral immunity.

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Footnote

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References

1. Hirota N, Martin JG. Mechanisms of airway remodeling. Chest 2013;144:1026-32.
2. Holgate ST, Holloway J, Wilson S, et al. Understanding the pathophysiology of severe asthma to generate new therapeutic opportunities. J Allergy Clin Immunol 2006;117:496-506; quiz 507.
3. Tillie-Leblond I, de Blic J, Jaubert F, et al. Airway remodeling is correlated with obstruction in children with severe asthma. Allergy 2008;63:533-41.
4. Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. Lancet 1999;354:541-5.
5. Kusel MM, de Klerk NH, Kebadze T, et al. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. J Allergy Clin Immunol 2007;119:1105-10.
6. Tregoning JS, Schwarze J. Respiratory viral infections in infants: causes, clinical symptoms, virology, and immunology. Clin Microbiol Rev 2010;23:74-98.
7. Holt PG, Sly PD. Viral infections and atopy in asthma pathogenesis: new rationales for asthma prevention and treatment. Nat Med 2012;18:726-35.
8. Wark PA, Johnston SL, Bucchieri F, et al. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. J Exp Med 2005;201:937-47.
9. Contoli M, Message SD, Laza-Stanca V, et al. Role of deficient type III interferon-lambda production in asthma exacerbations. Nat Med 2006;12:1023-6.
10. Lynch JP, Werder RB, Simpson J, et al. Aeroallergen-induced IL-33 predisposes to respiratory virus-induced asthma by dampening antiviral immunity. J Allergy Clin Immunol 2016. [Epub ahead of print].
11. Nakae S, Morita H, Ohno T, et al. Role of interleukin-33 in innate-type immune cells in allergy. Allergol Int 2013;63:13-20.
12. Yagami A, Orihara K, Morita H, et al. IL-33 mediates inflammatory responses in human lung tissue cells. J

Immunol 2010;185:5743-50.
13. Oboki K, Nakae S, Matsumoto K, et al. IL-33 and Airway Inflammation. Allergy Asthma Immunol Res 2011;3:81-8.
14. Baekkevold ES, Roussigné M, Yamanaka T, et al. Molecular characterization of NF-HEV, a nuclear factor preferentially expressed in human high endothelial venules. Am J Pathol 2003;163:69-79.
15. Takeda T, Unno H, Morita H, et al. Platelets constitutively express IL-33 protein and modulate eosinophilic airway inflammation. J Allergy Clin Immunol 2016. [Epub ahead of print].
16. Le HT, Tran VG, Kim W, et al. IL-33 priming regulates multiple steps of the neutrophil-mediated anti-Candida albicans response by modulating TLR and dectin-1 signals. J Immunol 2012;189:287-95.
17. Alves-Filho JC, Sônego F, Souto FO, et al. Interleukin-33 attenuates sepsis by enhancing neutrophil influx to the site of infection. Nat Med 2010;16:708-12.

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