Allergy Asthma Immunol Res. 2022 Sep;14(5):441-443
https://doi.org/10.4168/aair.2022.14.5.441
pISSN 2092-7355·eISSN 2092-7363

Allergy, Asthma & Immunology Research AAIR

Editorial

Eosinophil Extracellular Traps Pave the Way for the Identification of Novel Therapeutics in Severe Asthma

Ji-Hyang Lee, You Sook Cho *

Division of Allergy and Clinical Immunology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

▸ See the article "Epithelial Autoantigen-Specific IgG Antibody Enhances Eosinophil Extracellular Trap Formation in Severe Asthma" in volume 14 on page 479.

Received: Aug 11, 2022
Revised: Sep 1, 2022
Accepted: Sep 2, 2022
Published online: Sep 15, 2022

Correspondence to
You Sook Cho, MD, PhD
Division of Allergy and Clinical Immunology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.
Tel: +82-2-3010-3285
Fax: +82-2-3010-6969
Email: yscho@amc.seoul.kr

ORCID iDs
Ji-Hyang Lee
https://orcid.org/0000-0003-4286-3114
You Sook Cho
https://orcid.org/0000-0001-8767-2667

Disclosure
There are no financial or other issues that might lead to a conflict of interest.

The release of chromatin and granule proteins against microorganisms by forming extracellular fibers was first reported in neutrophils, named neutrophil extracellular traps (NETs).[1] Afterward, the release of extracellular traps (ETs) was observed in other immune cells, including mast cells, monocytes, tissue macrophages, and lymphocytes.[2] In contrast to the original concept of ETs as a defense mechanism, accumulated data implicate ETs in the development of numerous medical conditions, especially regarding NETs in infections, autoimmunity, and malignancies.[3,4]

Over the past decade, researches also shed light on the biological role of eosinophil extracellular traps (EETs) in type 2 inflammation. In addition to the presence of EETs during bacterial and fungal infections, they have been found in tissues obtained from patients with allergic and eosinophilic diseases, such as asthma, atopic dermatitis, eosinophilic esophagitis, and chronic rhinosinusitis.[2] With the availability of biologic agents targeting type 2 inflammation in the aforementioned diseases, understanding the contribution of eosinophils in the development, severity, and prognosis of pathologic conditions has become an important research field. In this regard, the biological role of EETs in eosinophilic inflammation needs to be clarified.

In this issue of *Allergy, Asthma & Immunology Research*, Lee and colleagues[5] demonstrated a vicious cycle in severe asthma composed of cytokeratin (CK)-18, its immunoglobulin G (IgG) antibody, and autoantibody-induced EETs, which further enhances the production of CK-18 in airway epithelial cells. The authors noted the elevated level of CK-18 and CK-18-specific IgG in severe asthma using samples from patients and murine models. They also conducted *in vitro* experiments which showed that CK-18-specific IgG enhanced the production of extracellular DNA and eosinophil-derived neurotoxin from isolated eosinophils. In addition, intranasal administration of EETs in mice led to upregulated CK-18 and CK-18-specific IgG in the lungs in a dose-dependent manner, which was not diminished by treatment with dexamethasone. These results collectively indicated the presence of a mutually enhancing autoimmune-EET pathway in steroid-unresponsive severe asthma.

In 2011, the infiltration of EETs colocalized with the major basic protein (MBP) in human asthmatic airways was first reported in all 20 participants of the study.[6] EETs colocalized with

the eosinophil cationic protein (ECP) in the bronchoalveolar lavage fluid (BALF) were observed in patients with asthma, but not in healthy controls. Moreover, the level of EETs in BALF was significantly correlated with lung function and severity of asthma.[7] Among asthmatic patients, the circulating EET levels were significantly higher in patients with poorly controlled asthma than those with well-controlled asthma. Meanwhile, circulating EETs did not differ according to the severity of asthma.[8] However, the proportion of EET-forming eosinophils from patients with severe asthma was higher than those with non-severe asthma during stimulation with interleukin (IL)-5 and lipopolysaccharide (LPS). Further, it was negatively correlated with lung function.[9] These findings suggested the potential of EET as a biomarker in asthma.

Mechanistically, various triggers including IL-5, LPS, reactive oxygen species, autophagy, and viral infections have been reported to stimulate eosinophils to release EETs.[10] Since EETs are web-like structures made up of DNA fibers and granule proteins, namely MBP and ECP, they exert tissue toxicity and recruit or activate inflammatory cells.[11] In asthma, the authors previously identified an association between EETs and type 2 innate lymphoid cells, which stimulate the airway epithelium to release alarmins and consequently exacerbate type 2 inflammation.[12] Most recently, the contribution of EETs in aggravating allergic inflammation by activating pulmonary neuroendocrine cells has been reported.[7] The present study adds a novel pathologic role of EET in asthma progression linked with autoimmunity against the airway epithelium.

The involvement of autoimmunity in asthma has been suggested for decades. In addition to antigens derived from bronchial epithelial cells, including CK-18, endothelial or platelet proteins, extracellular matrix protein, and cellular junction have been reported as self-antigens in asthma.[13] Particularly, immunoprecipitated sputum immunoglobulins from patients with severe eosinophilic asthma reporting elevated anti-eosinophil peroxidase IgG and antinuclear antibodies promoted the production of EET, which was not suppressed by dexamethasone.[14] In the present study, CK-18 served as a key inducer as well as a mediator of persistent eosinophilic inflammation. Given that CK-18 is derived from bronchial epithelium, the study by Lee *et al.*[5] elucidated the impact of EETs on airway structure cells and suggested a possible association with progressive airway remodeling observed in severe eosinophilic asthma, despite treatment with corticosteroids.

EETs have gained attention as a potential therapeutic target in severe eosinophilic asthma due to their involvement in the progress of type 2 inflammation. However, there are many unresolved questions in the pathophysiology of EETs. First, regarding autoimmunity, the initiator of autoreactivity is still unclear. Secondly, under the same stimulation, some eosinophils release EETs, while others do not. This implicates the presence of distinct subtypes of eosinophils. Thirdly, the interaction between DNA fibers and granule proteins in the traps requires further investigation. Fourthly, a methodological way of preventing or dissolving EETs is needed. In addition, the outcomes of depleting EETs should be assessed in terms of efficacy and safety. Finally, working EETs are difficult to determine readily from the patients. Without stimulation, the circulating levels of EETs and the proportion of EET-forming eosinophils were similar between patients with severe and non-severe asthma *in vivo*.[8] Therefore, identifying patients whose asthma is affected by EETs is still challenging in clinical practice.

Although biologics have broadened the therapeutic options for managing severe eosinophilic asthma, there is a subpopulation of patients who show limited response to either corticosteroid or biologics, and a gradual decline of lung function despite anti-inflammatory treatment.[15] For these patients, novel biomarkers and therapeutic agents are necessary.

https://doi.org/10.4168/aair.2022.14.5.441

Beyond the numerical measurement of eosinophils and suppressing type 2 cytokines, more elaborate strategies are required to modulate specific components of eosinophils. At present, EETs are regarded as one of the potential therapeutic targets in severe eosinophilic asthma, which became more cogent with the research by Lee and colleagues.[5] Even though we still have a long way to go before fully understanding the biology of disease-related eosinophils, the accumulated data can enable the search for novel therapeutics in severe asthma.

REFERENCES

1. Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y, Weiss DS, et al. Neutrophil extracellular traps kill bacteria. Science 2004;303:1532-5.
PUBMED | CROSSREF
2. Mukherjee M, Lacy P, Ueki S. Eosinophil extracellular traps and inflammatory pathologies-untangling the web! Front Immunol 2018;9:2763.
PUBMED | CROSSREF
3. Weng W, Hu Z, Pan Y. Macrophage extracellular traps: current opinions and the state of research regarding various diseases. J Immunol Res 2022;2022:7050807.
PUBMED | CROSSREF
4. Keir HR, Chalmers JD. Neutrophil extracellular traps in chronic lung disease: implications for pathogenesis and therapy. Eur Respir Rev 2022;31:210241.
PUBMED | CROSSREF
5. Lee DH, Jang JH, Sim S, Choi Y, Park HS. Epithelial autoantigen-specific IgG antibody enhances eosinophil extracellular trap formation in severe asthma. Allergy Asthma Immunol Res 2022;14:479-93.
CROSSREF
6. Dworski R, Simon HU, Hoskins A, Yousefi S. Eosinophil and neutrophil extracellular DNA traps in human allergic asthmatic airways. J Allergy Clin Immunol 2011;127:1260-6.
PUBMED | CROSSREF
7. Lu Y, Huang Y, Li J, Huang J, Zhang L, Feng J, et al. Eosinophil extracellular traps drive asthma progression through neuro-immune signals. Nat Cell Biol 2021;23:1060-72.
PUBMED | CROSSREF
8. Granger V, Taillé C, Roach D, Letuvé S, Dupin C, Hamidi F, et al. Circulating neutrophil and eosinophil extracellular traps are markers of severe asthma. Allergy 2020;75:699-702.
PUBMED | CROSSREF
9. Choi Y, Le Pham D, Lee DH, Lee SH, Kim SH, Park HS. Biological function of eosinophil extracellular traps in patients with severe eosinophilic asthma. Exp Mol Med 2018;50:1-8.
PUBMED | CROSSREF
10. Choi Y, Luu QQ, Park HS. Extracellular traps: a novel therapeutic target for severe asthma. J Asthma Allergy 2022;15:803-10.
PUBMED | CROSSREF
11. Acharya KR, Ackerman SJ. Eosinophil granule proteins: form and function. J Biol Chem 2014;289:17406-15.
PUBMED | CROSSREF
12. Choi Y, Kim YM, Lee HR, Mun J, Sim S, Lee DH, et al. Eosinophil extracellular traps activate type 2 innate lymphoid cells through stimulating airway epithelium in severe asthma. Allergy 2020;75:95-103.
PUBMED | CROSSREF
13. Mukherjee M, Nair P. Autoimmune responses in severe asthma. Allergy Asthma Immunol Res 2018;10:428-47.
PUBMED | CROSSREF
14. Mukherjee M, Bulir DC, Radford K, Kjarsgaard M, Huang CM, Jacobsen EA, et al. Sputum autoantibodies in patients with severe eosinophilic asthma. J Allergy Clin Immunol 2018;141:1269-79.
PUBMED | CROSSREF
15. Lee JH, Kim HJ, Park CS, Park SY, Park SY, Lee H, et al. Clinical characteristics and disease burden of severe asthma according to oral corticosteroid dependence: real-world assessment from the Korean Severe Asthma Registry (KoSAR). Allergy Asthma Immunol Res 2022;14:412-23.
PUBMED | CROSSREF