Olfactomedin 4 as a circulating biomarker for asthma

An-Soo Jang

Bronchial asthma is a non-communicable chronic long-term characterized by small airways inflammation and narrowing, remodeling in the lungs, and symptoms, such as cough, wheeze, shortness of breath, and chest tightness, which are intermittent and are often worse at night or during exercise. Bronchial asthma is diagnosed based on a characteristic pattern of respiratory symptoms and variable expiratory airflow obstruction, which is confirmed by forced expiratory volume in 1 second reversibility testing in spirometry, variability measurement of peak expiratory flow, bronchial challenge test (including inhaled methacholine, histamine, exercise, and inhaled mannitol), variation in lung function between visits, a significant improvement in lung function after a 4 week therapeutic trial with anti-inflammatory drug, and/or allergy tests, exhaled nitric oxide test, and sputum eosinophils (1).

The use of biomarkers, such as immunoglobulin E, eosinophils, exhaled nitric oxide, periostin, and thymus, activation-regulated chemokine, and chitinase-3-like protein (YLK-40), have been used for the identification of the nature of asthma. Although the monitoring of asthma is relatively confined to real-world situations, many works for seeking new biomarkers have been done for recent years (2,3).

Biomarkers for asthma classify asthma into phenotypes and endotypes, depending on the treatment of asthma (2,3).

The new biomarkers for airway diseases, such as asthma, is left exceedingly extensive and highly heterogeneous. However, research efforts assist the progress of the discovery of various favorable measurement substances, among which a small number have well-qualified diagnostic exactness and can be confidently applied according to medical science and examination of asthma risk stratification and severity prediction. Liquid biomarkers for asthma have been reported in various clinical applications (Table 1) (4-9).

The human respiratory epithelium is lined with a thin layer of liquid covering the luminal surface, which plays a key role in maintaining ciliary function, mucociliary clearance, and the removal of environmental toxins, foreign particles, and antimicrobial properties of the airway (10). Many biomarkers have been associated with airway diseases. Local regional biological fluids, such as sputum, nasal fluid, and bronchoalveolar lavage fluid give themselves as a suitable source of airway local biomarkers (11,12). Peripheral biological fluids, such as blood, serum, and urine, may play additional roles for biomarkers airway diseases (13,14).

Although the main feature in asthma pathogenesis is eosinophilic inflammation, neutrophilic features are also evident, and eosinophils and neutrophils can exist together in certain patients with exacerbated asthma. Asthma is classified into the following 4 phenotypes—eosinophilic dominant, neutrophilic dominant, mixed granulocytic, and pauci-granulocytic types—based on sputum cell differentials. The eosinophilic type provides a rationale for refractory asthma cases, but the neutrophilic type or a combination of the 2 inflammatory types can also reveal a severe asthma phenotype (15).

Diagnostic biological molecules for the neutrophilic inflammatory type of bronchial asthma include increase in sputum neutrophils, blood neutrophils, expression of YLK-40 protein, and hydrogen sulfide in sputum and serum (15,16). Thymic stromal lymphopoietin (TSLP), microbiome, neutrophil extracellular traps, and the activation of the nucleotide-binding oligomerization domain-like receptor family and pyrin domain-containing

Editorial

Olfactomedin 4 as a circulating biomarker for asthma

An-Soo Jang

Department of Internal Medicine, Soonchunhyang University, Bucheon Hospital, Bucheon, Korea

Correspondence to: An-Soo Jang. Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, 170 Jomaru-ro, Bucheon-si, Gyeonggi-Do 14584, Korea. Email: jas877@schmc.ac.kr.

Comment on: Chen X, Khalid K, Chen D, et al. Serum levels of olfactomedin 4: a biomarker for asthma control state in asthmatics. Ann Transl Med 2020;8:494.

Submitted Aug 10, 2022. Accepted for publication Sep 30, 2022.
doi: 10.21037/atm-22-3983

View this article at: https://dx.doi.org/10.21037/atm-22-3983
3 pathways, are phenotypes of neutrophilic asthma. Neutrophilic asthma patients have characteristic features of steroid unresponsiveness, frequent asthma worsening, and persistent or extreme respiratory symptoms. Therefore, treatment focusing on neutrophilic asthma is important. Targeted therapy and biologics for neutrophilic airway inflammation have been studied for the treatment of severe refractory asthma, but most clinical real-world applications have therapeutic options focused on the neutrophilic type. Phosphodiesterase inhibitors, azithromycin, anti-TSLP antibodies, and anticholinergic drugs are promising therapeutic options for the neutrophilic type (15). However, suitable therapeutic investigation targeting neutrophilic airways inflammation is more needed.

Asthma monitoring in clinical situations is commonly done by way of symptom assessment and optimal therapeutic dose requirements, combined with routine lung function tests.

Olfactomedin 4 (OLFM4) is part of the well-conserved olfactomedin domain-containing glycoprotein family and is produced or synthesized in inflammatory cells, including neutrophils, intestinal crypts, and the prostate. OLFM4 is involved in innate immunity, inflammation, and carcinogenesis (17,18). In bone marrow and peripheral blood, OLFM4 as a neutrophil-specific granule protein is solely expressed in neutrophilic cells in humans and mice (19,20).

OLFM4, as a matrix glycoprotein of neutrophil-specific type granules, determine the essential qualities of neutrophil inflammation that might not be a dependent risk factor for poor prognosis in sepsis, and might be expressed increase in a life-threatening condition where the lungs cannot provide the vital organs with enough oxygen and shock condition among adults with sepsis (19). OLFM4 levels can be measured by flow cytometry with featuring of a specific neutrophil subset is detected in healthy adults featuring a specific neutrophil subset (21,22). Recent works have reported that OLFM4 inhibits the activation of several granular proteases important in the innate immune response, including cathepsins C and G, neutrophil elastase, and proteinase 3 (21,23).

In this issue of Annals of Translational Medicine, Chen et al. demonstrate that serum OLFM4 levels could be used to estimate neutrophilic airway inflammation in asthmatic patients (24). Serum OLFM4 levels were found to be increased in patients with asthma. They reported that there was a significant correlation between serum OLFM4 and sputum and blood neutrophil proportion, as well as C-reactive protein. Serum OLFM4 level as a useful biomarker can find the difference between control and uncontrol status in asthmatic patients. Chen et al. suggest that blood OLFM4 is one of the markers being responsible for uncontrolled status in asthmatic patients, and can be used to differentiate specific neutrophilic subtypes of asthma. They suggest that further studies are warranted for examining the role of OLFM4 in evaluating asthma severity and control status. They suggested that the assessment of blood OLFM4 could be a useful marker to diagnose or predict asthma control status, as blood is an easily accessible sample. Unfortunately, Chen et al.’s study was limited due to the small sample size. The effect of drug medication and comorbidity on OLFM4 should also be further clarified.

Increasing research has demonstrated that blood biomarkers can be used in circulating peripheral markers for asthma. Clinical application of OLFM4 as a diagnostic biomarker has used in real world situations. In particular, OLFM4 have a possible advantage for a biomarker for neutrophilic asthma because blood samples have many advantages with regard to easy sample collection, less

| Table 1 Biomarkers using local and peripheral biological samples for asthma |
|-----------------|-----------------|-----------------|
| **Biomarkers**  | **Biological samples** | **Clinical significances** |
| Eosinophils     | Eosinophils, FeNO | Blood, sputum, exhaled air | Association of asthma severity and therapeutic monitoring for biologics |
| Neutrophils     | Neutrophils, YLK-40 | Blood, sputum, serum | Increase in neutrophilic asthma and uncontrolled asthma |
| Micro-RNA       | miR199a-5p, miR142-3p, miR233-3p, miR629-3p | Serum, plasma, sputum | Increase in neutrophilic asthma |
| New serum biomarkers | Nectin-4, Calprotectin, SOX18, Annexin A1 and A5 | Blood | Increase in asthma, association with lung function |

FeNO, exhaled nitric oxide; YLK-40, Chitinase-3-like protein; SOX18, SRY-box transcription factor 18.
contamination and being more acceptable for less accessible populations. OLFM4 is expected to have a diagnostic, monitor, and prognostic value in asthma, in particularly neutrophilic asthma.

Acknowledgments

Funding: This research was supported by Soonchunhyang University 2022.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, Annals of Translational Medicine. The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3983/coif). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References

1. Global Initiative for Asthma. Global strategy for asthma management and prevention [Internet]. Fontana (WI): GINA; 2020 [2021 Feb 23]. Available online: https://ginasthma.org/gina-reports/gina-2020-full-report_-final_-wms/
2. Kuruvilla ME, Lee FE, Lee GB. Understanding Asthma Phenotypes, Endotypes, and Mechanisms of Disease. Clin Rev Allergy Immunol 2019;56:219-33.
3. Roth M, Stolz D. Biomarkers and personalised medicine for asthma. Eur Respir J 2019;53:1802094.
4. Landry V, Coburn P, Kost K, et al. Diagnostic Accuracy of Liquid Biomarkers in Airway Diseases: Toward Point-of-Care Applications. Front Med (Lausanne) 2022;9:855250.
5. Lee PH, Choi S, An M, et al. Recent patents in allergy and immunology: A quantitative real-time polymerase chain reaction method for diagnosing asthma and asthma exacerbation. Clin Transl Allergy 2022;12:e12136.
6. Lee YG, Hong J, Lee PH, et al. Serum Calprotectin Is a Potential Marker in Patients with Asthma. J Korean Med Sci 2020;35:e362.
7. Hong J, Lee PH, Lee YG, et al. Augmented angiogenic transcription factor, SOX18, is associated with asthma exacerbation. J Asthma 2021;58:1143-54.
8. Lee SH, Lee PH, Kim BG, et al. Annexin A5 Protein as a Potential Biomarker for the Diagnosis of Asthma. Lung 2018;196:681-9.
9. Lee SH, Lee PH, Kim BG, et al. Annexin A1 in plasma from patients with bronchial asthma: its association with lung function. BMC Pulm Med 2018;18:1.
10. Lillehoj ER, Kim KC. Airway mucus: its components and function. Arch Pharm Res 2002;25:770-80.
11. Smith AD, Cowan JO, Filsell S, et al. Diagnosing asthma: comparisons between exhaled nitric oxide measurements and conventional tests. Am J Respir Crit Care Med 2004;169:473-8.
12. Fortuna AM, Feixas T, González M, et al. Diagnostic utility of inflammatory biomarkers in asthma: exhaled nitric oxide and induced sputum eosinophil count. Respir Med 2007;101:2416-21.
13. Ahmad Al Obaidi AH, Mohamed Al Samarai AG, Yahya Al Samarai AK, et al. The predictive value of IgE as biomarker in asthma. J Asthma 2008;45:654-63.
14. Zuo H, Xie X, Peng J, et al. Predictive Value of Novel Inflammation-Based Biomarkers for Pulmonary Hypertension in the Acute Exacerbation of Chronic Obstructive Pulmonary Disease. Anal Cell Pathol (Amst) 2019;2019:5189165.
15. Yamasaki A, Okazaki R, Harada T. Neutrophils and Asthma. Diagnostics (Basel) 2022;12:1175.
16. Kobayashi Y, Chu HH, Kanda A, et al. CCL4 Functions as a Biomarker of Type 2 Airway Inflammation. Biomedicines 2022;10:1779.
17. Nicholas B, Guo J, Lee HH, et al. Analysis of cell-specific peripheral blood biomarkers in severe allergic asthma identifies innate immune dysfunction. Clin Exp Allergy 2022. [Epub ahead of print]. doi: 10.1111/cea.14197.
18. Zhang J, Liu WL, Tang DC, et al. Identification and characterization of a novel member of olfactomedin-
related protein family, hGC-1, expressed during myeloid lineage development. Gene 2002;283:83-93.

19. Clemmensen SN, Bohr CT, Rørvig S, et al. Olfactomedin 4 defines a subset of human neutrophils. J Leukoc Biol 2012;91:495-500.

20. ARDS Definition Task Force; Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526-33.

21. Welin A, Amirbeagi F, Christenson K, et al. The human neutrophil subsets defined by the presence or absence of OLFM4 both transmigrate into tissue in vivo and give rise to distinct NETs in vitro. PLoS One 2013;8:e69575.

22. Chen L, Li H, Liu W, et al. Olfactomedin 4 suppresses prostate cancer cell growth and metastasis via negative interaction with cathepsin D and SDF-1. Carcinogenesis 2011;32:986-94.

23. Kangelaris KN, Clemens R, Fang X, et al. A neutrophil subset defined by intracellular olfactomedin 4 is associated with mortality in sepsis. Am J Physiol Lung Cell Mol Physiol 2021;320:L892-902.

24. Chen X, Khalid K, Chen D, et al. Serum levels of olfactomedin 4: a biomarker for asthma control state in asthmatics. Ann Transl Med 2020;8:494.

Cite this article as: Jang AS. Olfactomedin 4 as a circulating biomarker for asthma. Ann Transl Med 2022;10(20):1085. doi: 10.21037/atm-22-3983