Asthma is a chronic relapsing disease of the airways affecting over 300 million people worldwide (1). The pathogenic processes of acute exacerbation and remodeling are influenced by genetic predisposition modified by environmental exposures (2). A body of literature now supports the contention that Th2 paradigm is insufficient for explaining the entire spectrum of this disease (3). Distinct spectrum of T cell subsets (Th17), exercise-induced or aspirin sensitivity are a few notable examples.

I read with great interest the review by Xu et al. that describes the advances in proteomics technologies that have been applied for the diagnosis and treatment of bronchial asthma (4). Reviewed in the article, proteomics is a rapidly evolving field that enables a comparison of protein abundances between patients with bronchial asthma versus controls. The authors detail the studies that have been conducted comparing protein changes in blood (serum), bronchial lavage fluid and sputum using gel-based or “bottoms-up” mass spectrometry proteomics. Because proteomics is not a fully mature technology nor is it completely an unbiased profiling technology, analysis of each of these sample types has its own challenges and limitations. For example, the background of high abundance proteins in serum makes identification of pathogenic proteins from the lung a challenging endeavor. Mucus and salivary contamination in complicates proteomic analysis of sputum. Making this problem more challenging has been the findings that analyses of the different types of protein sources show that the most informative sampling is from bronchoalveolar lavage (BAL). This is an invasive approach that yields proteins produced by the airway mucosa and is a very attractive fluid for identification of pathogenic proteins. Having said this, Xu identifies that collecting bronchoalveolar lavage fluid (BALF) in a standardized manner that can be used to compare across patients has not yet been developed.

The authors emphasize that the major impact of proteomics is not in the arena of diagnostics, but rather in understanding disease-promoting pathways, colloquially referred to as “endotypes” (5). The authors review studies that identify differentially expressed proteins that have been identified including complement factors in serum, lipocalin in BAL, S100A in sputum and b-2 globulin in nasal lavage fluid. Although these studies are an important first step, more work will be required to achieve the goal of identifying those proteins that are drivers of disease, including demonstration that modifying the protein or its pathway affects clinical outcomes in asthma.

A major question remains how to link differential protein expression with actionable information. How might we do this? Further advances in proteomics coupled with mechanism-focused experimental design are needed. For example, applications of proteomics to asthmatics after provocation using segmental allergen challenge or naturally induced exacerbations will be more robust for identifying activated pathways driving disease. Studies conducted since the publication of this review using paired segmental allergen challenge coupled with invasive BAL sampling show the presence of allergen-elicited fibrin cascade (6). An important observation from this work is that...
markedly diverse protein patterns are present during the exacerbation than what could be identified by analysis of stable disease. Additionally, studies employing the approach of pharmacoproteomics will help to identify pathways that are affected by the application of disease-modifying drugs. A pharmacoproteomics study confirmed elucidated the role of a chromatin remodeling pathway in severe asthma and associated with airway remodeling (7,8). Finally, integration of multiple omics datasets (e.g., genomics with proteomics or proteomics with metabolomics) provide independent information about disease pathogenesis. One or several of these approaches will be necessary to unlock the enigma and spectrum of asthma endotypes.

In summary, the review by Xu identifies the promise of proteomics to understand the complexity of asthma and stimulates an important discussion about the goals of proteomics technologies and its current limitations. This is a rapidly advancing field. Greater information will be obtained by attention to profiling technological advances, mechanism-based experimental design, and integration with other profiling technologies.

Acknowledgments

Funding: This study was supported by NIH/NIAID AI062885, AI136994, AI159702 and NCATS UL1TR002373.

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-22-4198/coif). ARB reports funding of NIH/NIAID AI062885, AI136994, AI159702, and NCATS UL1TR002373; and patents unrelated to the content of this editorial (Patent No. 6,699,459 and Patent No. 8,053,199). The author has no other conflicts of interest to declare.

Cite this article as: Brasier AR. Next steps in precision approaches for asthma-proteomics and asthma endotypes. Ann Transl Med 2022;10(19):1047. doi: 10.21037/atm-22-4198

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. The Global Asthma Network. The Global Asthma Report 2014. Auckland: Global Asthma Network, 2014:28-36.
2. Busse WW, Lemanske RF Jr. Asthma. N Engl J Med 2001;344:350-62.
3. Durrant DM, Metzger DW. Emerging roles of T helper subsets in the pathogenesis of asthma. Immunol Invest 2010;39:526-49.
4. Xu P, Wang L, Chen D, et al. The application of proteomics in the diagnosis and treatment of bronchial asthma. Ann Transl Med 2020;8:132.
5. Kuruvilla ME, Lee FE, Lee GB. Understanding Asthma Phenotypes, Endotypes, and Mechanisms of Disease. Clin Rev Allergy Immunol 2019;56:219-33.
6. Zhu Y, Esnault S, Ge Y, et al. Airway fibrin formation cascade in allergic asthma exacerbation: implications for inflammation and remodeling. J Proteomics 2022;19:103415.
7. Zhao Y, Tian B, Sun H, et al. Pharmacoproteomics reveal novel protective activity of bromodomain containing 4 inhibitors on vascular homeostasis in TLR3-mediated airway remodeling. J Proteomics 2019;205:103415.
8. Tian B, Hosoki K, Liu Z, et al. Mucosal bromodomain-containing protein 4 mediates aeroallergen-induced inflammation and remodeling. J Allergy Clin Immunol 2019;143:1380-94.e9.