Editorial

Next steps in precision approaches for asthma-proteomics and asthma endotypes

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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.

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