Chapter 12
Overview

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Abstract Although broadly defined in the literature, for the purpose of this section, we define systems biology as the description of the dynamic genomic, proteomic, and metabolomic processes integrated into a functional model of the cell, organelle, or tissue that is capable of accurately tracking the biological system's response to environmental perturbations. The goal of this section is to complete the tripartite description of asthma systems biology, initiated by the previous section (Section II: Genetics and Genomics of Asthma), by reviewing the recent literature—the types and methods of sample collection, processing, analysis, and instrumentation—of metabolomic and proteomic investigations, including functional proteomic studies of the asthma innate immune response and glucocorticoid (GC) receptor signaling with reference to GC resistance in severe asthma.

Keywords Proteomics • Sample prep • Size-exclusion chromatography • Asthma • Airway inflammation • Broncoalveolar lavage • Epithelial lining fluid • Induced sputum • Exhaled breath condensate • Bronchoscopic microsampling

12.1 Introduction

As discussed in this edition and in the supporting literature, asthma is a heterogeneous disease with a complex phenotype that resists clear and absolute classification. To decipher the pattern of symptoms and derive a molecular description of the disease requires multidisciplinary approaches, with an unbiased focus. That is, at a

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basic level, a combination of global analyses spanning genomics, proteomics, and metabolomics may lead to a description of the molecular events that lead to the complex phenotypes collectively defined as "asthma." The integration of the "omics" observations into a coherent "system" would be described as the "systems biology" of asthma and likely lead to astonishing insights into its etiology.

To more precisely define the scope of our review, in this section we review the current literature and examine the tools used to dissect the proteomics and metabolomics of asthma, with specific application to the innate immune response and steroid resistance and the tools uniquely designed to address the special asthma sample types. Since much has been written regarding these topics, our review covers the most recent literature (since 2009), as well as new technical approaches that may facilitate a better understanding of asthma with respect to these "omics" disciplines.

12.2 Metabolomics of Asthma

Low molecular weight metabolites are the result of biochemical processes dictated by the complement of genes expressed constitutively and as a result of signaling pathways that are activated in response to airway insults. As such they may be indicators of early inflammatory response, detectable from conventional airway sample collection strategies discussed throughout this section. In concert with genomic and proteomic studies, metabolomic investigations may be complementary—completing the tripartite description of asthma as a perturbation of the systems biology of the airway. In addition, metabolomics may serve to guide unique insights into biochemical processes that lead to asthmatic airway inflammation and uniquely suggest therapeutic strategies to lessen the degree of asthmatic morbidity.

The first chapter of this section (Chap. 13), Luxon discusses the clinical rationale for investigating the potential role of low molecular weight metabolites in the diagnosis, treatment, and evaluation of therapeutic efficacy in asthma. In addition, Luxon focuses on a review of the recent literature, a description of sample collection approaches with an eye to their unique application in the study of circulating metabolites as well as volatile compounds that may be exhaled, sample preparation and methods of separation and instrumentation used in their analysis.

12.3 Methods of Sample Preparation for Proteomic Analysis of Airway Samples

As proteins are the drivers of cellular responses to environmental perturbations, they are appropriate targets for the study of the biological processes that lead to asthma morbidity. Moreover, their study may lead to insights into the biology

that complements the other "omics" strategies and may provide new therapeutic targets to diminish or abolish the symptoms that lead to the severe morbidity of the disease.

In Chap. 14, Wiktorowicz and Jamaluddin extend the template provided by the preceding chapter to review the current literature that describes the unbiased proteomic investigations and the approaches used to acquire, analyze, and characterize airway samples from the biofluids of bronchoalveolar lavage, to induced sputum and exhaled breath condensates. Particular focus is given to the proteomics tools and approaches for the sample types that are unique to the airway.

12.4 Measurement of the Innate Immune Response in the Airway

With recognition that asthma is a disease mediated by the innate immune response (IIR) to airway insults, interest in the structure and dynamics of this response has been driven by application of new proteomics technologies and approaches in order to better characterize its molecular components.

In Chap. 15, Brasier and Zhao review the recent literature describing the major molecular players involved in the airway IIR leading to asthma, its coupling to adaptive immunity, the molecular events leading to asthmatic morbidity from allergenic insults and viral exacerbations, and finally review the technology used to quantify and characterize the genes and proteins that constitute or impact the IIR.

12.5 Functional Proteomics for the Detection of Impaired Cellular Response to Glucocorticoids

Glucocorticoids (GC) are a major therapeutic avenue used to limit the inflammatory response in asthma. While most asthmatics respond favorably to this therapy, a small number remain resistant to its benefits. The result is increased exacerbations and higher risk of mortality for these individuals.

In Chap. 16, Pazdrak and Kurosky focus on the role of GC signaling in severe asthma with emphasis on the role of T-lymphocytes, eosinophils, monocytes, neutrophils, mast cells, and smooth muscle cells of the airway. The cell function techniques used to characterize these activities are described in addition to estimation of GC receptor function, and characterization of proteomics of GC resistance—including posttranslational modifications and differential abundance measurements.