Preface

Application of Translational Science to the Clinical Problem of Asthma

The Problem

Asthma is a chronic relapsing airways disease that represents one of the most common chronic diseases worldwide (Busse et al. 2001; Masoli et al. 2004). Currently it is estimated that over 300 M people suffer from asthma, and its prevalence is increasing in both adult and pediatric populations. Asthma therefore represents a major public health problem and is worthy of attention to develop cost-effective prevention and management approaches.

Clinically asthma is a syndrome characterized by episodic, reversible obstructive airways obstruction that variably presents as a myriad of symptoms from cough to wheezing, shortness of breath, or chest tightness. The presence of bronchial muscular hypertrophy, mucous hypersecretion, tissue remodeling, and a T-lymphocyte predominant inflammation are pathogenic signatures of this disease (Busse et al. 2001; Lemanske et al. 2010). Asthma is a disease significantly modified by environmental interactions. Characteristic of asthma is intermittent exacerbations provoked by airway mucosal exposure to proinflammatory stimuli. Here, common cold (RNA viral infections) or inhaled allergens are two of the most common precipitants (Lemanske et al. 2010; Montalbano et al. 2002).

It is widely appreciated that asthma is different from one individual to the next; this heterogeneity is manifested in onset, exacerbating stimuli, severity, and treatment response. Presently, asthma classification methods are largely descriptive, focus on a single aspect or dimension of the disease, and do not lead to actionable intervention. Specifically, the current standard of care treatment for asthma is a stepped-care model; for those with persistent symptoms, anti-inflammatory treatment with inhaled corticosteroids (ICS) remains the first-line treatment. Yet efficacy studies indicate up to 30 % of subjects do not have a response to ICS. Currently, no reliable biomarker has been validated that identify an ICS response (Szefler 2002).

A robust, objective method for diagnosis and measurement of the efficacy for treatment interventions is, therefore, sorely needed.

Molecular Profiling and Personalized Medicine

With the completion of the human genome project, we are now in the era of postgenomic medicine where sensitive measurements of 100s–1,000s of proteins, metabolites, and genes in a single patient can be routinely performed (Hamburg et al. 2010). Properly conducted and interpreted, these multidimensional measurements, a process known as molecular profiling, can identify subtle differences in the pathophysiology of the disease at a level of precision that is not otherwise possible using physiological or clinical measurements. As a result the application of molecular profiling has revolutionized the field of medicine because it identifies robust objective, measurable, and quantitative features associated with disease phenotypes.

The ultimate goal of molecular profiling lies in its translational application to personalized medicine. Personalized medicine relies on measurements of an individual patient's molecular profiles to identify specific tailored interventions that will result in the greatest efficacy and safety, rather than apply generic therapies developed for a large population. The promise of personalized medicine is to individualize the prevention, diagnosis, and treatment of human disease. This individualized approach will result in better treatment responses, thereby reducing morbidity, lowering the rate of adverse drug reactions, enhancing efficacy, promoting better compliance, and reducing healthcare costs (Offit 2011). From a clinical investigative standpoint, the use of molecular profiling can be used to speed the development of therapies in select subgroups of asthmatics. Nevertheless, despite this promise, the full realization of personalized medicine faces significant challenges that will require innovation in basic scientific, regulatory, and translational spheres (Hamburg et al. 2010).

Motivation

We contend that asthma as a complex, heterogeneous and multifaceted disease is well poised for applications of personalized medicine. Recent exciting findings indicate molecular profiling can be applied to identify subclinical phenotypes of asthma that are not readily apparent by conventional assessment (Brasier et al. 2008, 2010). Moreover, these molecular profiles can be used to predict subtypes of asthma that differ in response to pharmacological therapy, cellular inflammatory phenotype, or response to bronchial provocation (Brasier et al. 2010). Upon further validation, these profiling and predictive techniques are ready for meaningful application to the improved prevention and treatment of asthma.

This book is organized into discrete sections edited by established investigators in the field. Part I will introduce asthma as a clinical disease and discuss methods for diagnosis, its epidemiology, environmental interactions, and current therapeutic approaches. Part II will reveal how genetics, epigenetics, and genomics approaches reveal asthma subtypes and etiologies. Part III will focus on methods for molecular profiling asthma, including exciting new developments in protein profiling, quantitative measurements of signaling pathways, and examination of functional responses of airway cells to immunomodulators. Part IV will discuss how complex datasets can be combined and related to disease manifestations and or subclinical phenotypes [or "endotypes," (Anderson 2008)]. Part V will consider how complex and surprising biobehavioral determinants influence the perception and manifestations of asthma. We will conclude with a discussion of next steps and implications.

Readers of this work will acquire advanced understanding how to collect, measure, and visualize multidimensional profiling data in asthma facilitate the understanding of disease modifiers and/or therapeutic intervention. We stand at the door of a revolution in asthma through the application of personalized medicine.

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