Chair's Summary: Mechanisms of Relevance to Clinical Heterogeneity of Asthma and Chronic Obstructive Pulmonary Disease

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Systematic analysis of large groups of patients with asthma shows that the clinical features of asthma can be grouped into clusters that vary by traits such as sex, body weight, degree of airflow obstruction, symptoms, skin test responses to aeroallergens, and health care use. Knowledge that clinical traits cluster in this way into distinct patient subgroups has prompted investigators to consider whether distinct pathobiological mechanisms underlie specific clinical phenotypes. As distinct from a disease phenotype, which has no mechanistic implication, a disease endotype is one that is defined by a distinct functional or pathobiological mechanism, and clinical researchers are now moving from studies that describe disease phenotypes to studies that uncover disease endotypes. Progress is slow but evident. For example, analyses of cellular and molecular features of asthma show subgroups with and without evidence of Th2 inflammation. The asthma Th2 endotype is characterized pathologically by excess numbers of eosinophils, mast cells, and activated CD4⁺ T cells in the airway and clinically by responsiveness to corticosteroid treatment. Because 30 to 50% of patients with asthma have noneosinophilic/Th2-low disease subtypes, there is increasing awareness of the need for improved understanding of disease mechanisms in these patients. Understanding of mechanisms of non-Th2 asthma is presently confined largely to hypothesis and speculation. Because some patients with asthma have prominent airway neutrophilia, there is speculation

that airway infection or Th17 inflammation could be disease mechanisms in some patients. It has been difficult to find consistent evidence for such endotypes in asthma, however, a difficulty that suggests a relatively large collection of non-Th2 disease endotypes, each accounting for disease in small patient subgroups. Increasing awareness of the need to conduct studies that reveal disease endotypes is leading to a greater emphasis on collection of biospecimens that allow for cellular and molecular characterization of patients and a greater emphasis on analytic methods that take better account of disease heterogeneity.

Systematic analyses of large groups of patients with chronic obstructive pulmonary disease (COPD) are also revealing distinct clinical and pathologic subgroups. Notable subgroups include one with persistent (non-Th2) systemic inflammation, one with airway Th2 inflammation, and a subgroup with radiographic evidence of emphysema. The subgroups with persistent systemic inflammation and emphysema are important to recognize because they have greater mortality, whereas the subgroup with Th2 inflammation is important because these patients show good treatment responses to corticosteroid medications. There is an additional COPD phenotype—the subgroup prone to frequent exacerbations—that has been shown to respond well to chronic treatment with antibiotics. This subgroup in particular has led to great interest in the airway

microbiome in COPD and to the characteristics of the microbiome that promote exacerbations and that may be amenable to novel treatments.

Advancing knowledge of disease endotypes in asthma and COPD from the research laboratory to the clinic will require the deployment of biomarkers so that clinicians can easily distinguish one disease endotype from another. It will also require a broader range of treatments, especially for non-Th2 disease, so that clinicians can match treatment to endotype and thereby engage in personalized medicine. Such personalization of treatment is currently at a very early stage, because there are few noncorticosteroid medications that can be prescribed for patients with non-Th2-driven airway disease.

This conference describes recent advances in understanding of disease phenotypes and endotypes in airway diseases. While highlighting advances, the papers indicate areas where more research is needed. Although much remains to be done, this collection of papers shows that it is clearly an interesting and rewarding time to be involved in airway clinical research. Increasing awareness that there are unrecognized disease mechanisms that account for clinical phenotypes in significantly sized subgroups of patients provides an exciting challenge for everyone who is working to improve the lives of patients with asthma and COPD. ■

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