Thematic Minireview Series on Molecular Bases of Disease: Asthma*

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Search for the word “asthma” in the archives of the Journal of Biological Chemistry (JBC), and more than 900 matches will come up. That is a testament to the role that JBC authors have played and are playing in the pursuit of a better understanding of the molecular roots of the illness and, ultimately, improved therapies for asthma sufferers.

Asthma is said to have been first identified and named by Hippocrates around 450 B.C., but, for centuries, it was misunderstood and, in some cases, was even attributed to psychological and emotional instability. Although most people today are familiar with the trademark symptoms of asthma (wheezing, coughing, breathlessness, chest tightness) from chronically inflamed airways and passageway spasms, the reality, according to the Centers for Disease Control and Prevention, is that “in most cases, we don’t know what causes asthma, and we don’t know how to cure it.”

According to the American Asthma Foundation, the condition afflicts about 23 million in the United States, and it is one of the most common long-term diseases in children. Most asthmatics use bronchodilators, which reverse airway smooth muscle contraction, and anti-inflammatory drugs, which suppress airway inflammation, but many patients do not respond well to existing therapies.

Shortly before his untimely death in late 2010, JBC Associate Editor Dale J. Benos conceived of this thematic minireview series on the molecular bases of asthma in recognition of important advances that have been made and the important questions that continue to be raised in the pages of JBC. Research into asthma crosses into multiple fields, including immunology, gene expression, signal transduction, and ion channel regulation. It is with great pleasure that we present here the first four parts commissioned by our esteemed colleague Dr. Benos and later shepherded by Associate Editor Luke O’Neill. Additional installments in the series will be published in the near future.

In the first minireview, Miguel A. Valverde, Gerard Cantero-Recasens, Anna Garcia-Elias, Carole Jung, Amado Carreras-Sureda, and Rubén Vicente write about ion channels, the specialized transmembrane proteins that regulate the flow of ions across membranes and determine the tissue physiology that underlies the development of asthma symptoms. The authors stress, “Asthma is a disorder presenting dysfunctional elements at all cellular levels in the airways, and ion channels regulate, one way or another, the function of all airways cells.” The minireview covers animal models, molecular and genetic studies, and clinical observations that relate ion channel activity to the pathogenesis of asthma.

Although many candidate genes have been linked to asthma through various means, including animal models, linkage analyses, and genome-wide association studies, the “allergic” origins of the disease remain poorly defined. Allergic asthma, the prototypical form that is addressed in clinical studies, is generally construed as a syndrome resulting from the interaction between genetic and environmental factors. The second minireview, by Anil B. Mukherjee and Zhongjian Zhang, discusses the current knowledge base for how genetic and environmental factors culminate in allergic asthma. The authors note that the experimental modeling of allergic responses in asthma is problematic. “In contrast with the animal models in which T-helper 2 (Th2) cell response is the dominant feature, in human asthma, an initial exposure to allergen results in Th2-dependent stimulation of the immune response that mediates the production of IgE and cytokines,” the authors write. “Re-exposure to allergen then activates mast cells, which release mediators such as histamines and leukotrienes that recruit other cells, including Th2 cells, which mediate the inflammatory response in the lungs.” The complex array of signaling reactions that underlie asthma are not easily reduced to commonly used aspects of animal models.

The third minireview also discusses certain aspects of allergic asthma and attempts to consider the implications of elevated IgE levels and increased IgE sensitization as disease hallmarks. IgE binding to high-affinity FcεRI and the low-affinity FcεRII/CD23 receptors must be considered in the proper context. “A substantial network of signaling molecules and adaptor proteins that function downstream of FcεRI activation has been defined,” writes author Lawren C. Wu. The author considers elucidation of the cell and membrane biology of FcεRI signaling an important goal of future research. Additional points for investigation include “novel cell surface and intracellular mediators of FcεRI activation, mechanisms of intracellular calcium signaling, and new inhibitory proteins that negatively regulate parts of the signaling network downstream of FcεRI activation.”

In the fourth minireview, author Peter J. Barnes covers signaling pathways involved in existing and quite effective therapies. “β2-Adrenergic receptor (β2AR) agonists are the most effective bronchodilators and relax airway smooth muscle cells through increased cyclic AMP concentrations and directly opening large conductance Ca2+ channels,” Barnes explains. Meanwhile, glucocorticoids are “the most effective anti-inflammatory treatments and switch off multiple activated inflammatory genes through recruitment of histone deacetylase-2, activating anti-inflammatory genes, and through increasing mRNA stability of inflammatory genes.” Barnes writes that our relatively good understanding of how current asthma therapies...
work, in terms of their biochemical mechanisms, opens the

door to both tweaks to existing treatments and invention of

entirely new ones in the future.

As others have before it, this thematic minireview series aims
to link biochemical processes to the understanding of an

important clinical challenge. Over the past half-century, both
the incidence and the severity of asthma have increased world-

wide, further burdening public health service providers in devel-

oped and developing nations alike. Still forthcoming in this the-

matic series are minireviews covering exercise-induced asthma, by

Lisa M. Schwiebert, and myeloid-derived regulatory cells and

redox control in asthma, by David D. Chaplin. We hope that you

will find the collection and its authors’ insights useful.

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