

# Preface

Chronic respiratory diseases are complex disorders generally driven by genetic mutations weakening the airways' ability to respond appropriately to inhaled toxins or pathogens. In the case of cystic fibrosis (CF), functional mutations of the cystic fibrosis transmembrane resistance (CFTR) ion channel impair airway hydration, which fosters the formation of infected mucus plugs requiring mechanical stimulation for clearance. These patients suffer from a progressive and irreversible loss of lung function caused by overwhelming and damaging neutrophilic inflammatory responses. On the other hand, frequent exposure to the toxic components of cigarette smoke is considered the primary cause of chronic obstructive pulmonary disease (COPD). Subjects diagnosed with  $\alpha$ 1-antitrypsin deficiency are particularly vulnerable to lung destruction by elastases, and to the development of emphysema. Allergic asthma remains a serious challenge, as this disease incorporates multiple genetic factors and environmental stimuli. The patients experience recurrent episodes of breathless, wheezing, coughing and chest tightness triggered by airway hyperresponsiveness (AHR) to allergens. Over the years, the severity of AHR episodes increases, as chronic inflammatory responses to allergens induce extensive airway remodeling and narrowing of the airway passages. Recently, the discovery of significant overlap between the symptoms of these diseases raised serious concerns with respect to our ability to diagnose and treat the patients efficiently. The scientific community has been mandated to open new avenues for the development of discriminative diagnostic tools and customized therapies for these diseases.

For decades, the most common diagnostic method used to differentiate asthmatics from COPD patients was AHR induced by inhalation of methacholine. Yet, a third of the COPD patients present significant AHR to this drug. As an alternative, The European Respiratory Society Task Force recently endorsed AHR measurements after inhalation of adenosine monophosphate (AMP) as a more specific diagnosis for asthma than methacholine. This finding spiked the interest of the scientific community for the signaling pathways mediating the effects of AMP in the airways of asthmatic patients. We now know that aerosolized AMP must, first, be dephosphorylated by a cell surface enzyme named ecto 5'-nucleotidase (CD73) in order to

generate adenosine, a signaling molecule of the purinergic network. Upon binding to cell surface receptors, adenosine induces histamine release from mast cells, which initiates AHR in asthmatic patients. This narrow window was only the prelude to what would become a major endeavor to expose the purinergic regulation of airway defenses. In the past 15 years, the persistent exponential increase in the number of publications targeting the purinergic regulation of acute lung injury, mucociliary clearance, inflammation, wound healing, remodeling and lung fibrosis is a testimony to the extensive ramifications of this signaling network in chronic respiratory diseases. Clinical and fundamental studies support the existence of disease-specific aberrances in airway concentrations of the signaling molecules, as well as in expression levels of the receptors and related enzymes in lung tissues of asthmatic, COPD and CF patients. This book is a tribute to this exploding field of research, and promises to come for the development of specific diagnostic tools and therapies for the predominant chronic respiratory diseases affecting the general population.

The term “Purinome” was recently ascribed to protein network mediating the effects of extracellular purines and pyrimidines. The composition of each “Purinome” is locally refined by different combinations of signaling molecules (ATP, ADP, Ap<sub>4</sub>A, adenosine), purinergic receptors, cell surface nucleotide-metabolizing enzymes (ectonucleotidases), and nucleoside/nucleotide channels or transporters. These protein clusters mediate tightly concerted actions invested in the maintenance of homeostasis and airway defenses. In chronic disorders, alterations of their global and dynamic equilibrium contribute to the appearance and/or propagation of pathological states.

The vast majority of studies conducted on purinergic signaling are devoted to ATP and its metabolite, adenosine. In a nutshell, the local release of ATP constitutes an alarm signal perceived by surrounding cells through interaction with P2 cell surface receptors. This “communiqué” informs the cells to take action according to their specific roles in the restoration of homeostasis. The cells’ alertness is maintained by the presence of local ectonucleotidases which promptly eliminate the ATP signal and restore receptiveness. The ingenuity of this communication network resides in the subsequent initiation of a negative feedback messenger from the dephosphorylation of ATP into adenosine. This signaling molecule binds P1 cell surface receptors to assist to restrain ATP-mediated responses and restore baseline activities. This sophisticated machinery works in concerts with other signaling networks, such as those supported by cytokines and growth factors, to maintain healthy lungs free of infection. However, chronic disorders associated with the maintenance of excess ATP or adenosine in the airways recruits surface receptors which induce or aggravate lung complications, including hyperinflammatory responses, tissue damage and airway remodeling leading to the loss of lung function.

This book was meticulously designed to systematically introduce the reader to each element of purinergic network, followed by their integration into a mathematical model. Then, evidence is presented for significant aberrances in the regulation of the signaling molecules in chronic respiratory diseases. Three chapters are dedicated to the detailed description of the major respiratory and inflammatory

functions regulated by purinergic signaling, and the aspects affected by chronic disorders. Finally, the reader is presented with the animal models and clinical applications currently used for the development of diagnostic and therapeutic approaches chronic respiratory diseases.

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Chapel Hill, NC

Maryse Picher

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Picher, M.; Boucher, R.C. (Eds.)

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