Chair's Summary: Innate and Adaptive Immune Responses in Airway Disease

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The lungs are constantly exposed to the external environment, which contains myriad particles and molecules that are potentially antigenic. The respiratory immune system must maintain a state of tolerance, discriminating between potentially harmful pathogens that could promote infectious disease while ignoring innocuous particles such as dust or pollen. These immunological control systems develop during early life and are greatly influenced by genetics, infection history, age, and environmental conditions such as smoking, diet, and pollution. Asthma, emphysema, chronic obstructive pulmonary disease (COPD) and pneumonia are thought to occur as a consequence of disruption of these control systems and disturbance of respiratory tolerance. Conversely, excessive immunological tolerance may lead to ineffective clearance of infectious agents such as influenza, tuberculosis, respiratory syncytial virus, or *Streptococcus pneumoniae*, which in turn may lead to inflammatory lung disease, bronchitis, pneumonia, and sepsis. Respiratory diseases represent an important cause of morbidity and mortality globally, and deaths due to these diseases are increasing worldwide. Moreover, the very young and the elderly are disproportionately represented at the more severe end of the disease spectrum, with asthma being more common in children and COPD and emphysema occurring later in life. It is clear that a better understanding of the basic mechanisms underlying respiratory immune homeostasis is vital to developing novel therapeutic agents and vaccines for disease prevention and control.

Traditionally, diseases have been associated specifically with either innate or adaptive immune pathways—for example, innate immunity for infections and COPD or adaptive immune systems for asthma. However, the distinction between the different arms of the immune system is becoming less apparent, and it is clear that most diseases involve contributions from both sides of the immune system. Understanding these interactions is critical in the search for more effective therapies for diseases, which are common and ever-increasing. The focus of the 29th Transatlantic Airway Conference was how innate and adaptive immune system pathways contribute to the development of a variety of lung diseases, such as asthma, COPD, and respiratory infections. The papers that the speakers presented at the meeting covered the broad areas of epithelium–immune system interactions, early effector mechanisms, the influence of the microbiome and host defense mechanisms, and immunomodulatory and regulatory pathways. The talks highlighted novel aspects of the immune system and revealed the complexity of interactions that operate within the lung.

Epithelium–Immune System Interactions

The airways are protected by a number of different cells that are resident within the lungs, such as the epithelial cells that line the airways and macrophages that reside in the airway lumen. The location of both of these cell types is such that they are constantly exposed to the

external environmental milieu and are able to act as sensors to detect changes in this environment and thus to function as sentinels to maintain immune system homeostasis. It is increasingly recognized that interaction between components of the immune system and resident lung stromal cells are critical in driving pathology in a number of different respiratory conditions. The interaction of pulmonary epithelial cells and immune cells was elegantly outlined by Bart Lambrecht, who focused on how the interface between epithelial and dendritic cells provides a bridge between innate and adaptive immunity within the lung. Local dendritic cell populations can receive instructions via the respiratory epithelium to promote inflammation. Although the pulmonary epithelium represents a physical barrier to the external environment, the cells incorporated within this layer express a wide variety of receptors that are important in detecting and responding to molecules encountered within the inhaled environment. Loss of epithelial integrity after exposure to infection, chemicals such as cigarette smoke or pollution, or allergens signal the onset of inflammation in susceptible individuals. In these people, a common virus becomes a major health problem with long-term consequences and the associated economic burden on health services. Donna Davies showed examples of how epithelial cells from patients with asthma were more susceptible to injury by cigarette smoke and infection with common respiratory pathogens such as rhinovirus. Moreover, the profound effect of cigarette smoke on gene expression was shown by Ron Crystal, who reported

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that even healthy smokers have an altered transcriptome in their pulmonary basal epithelial cells. Interaction between the epithelium and cells of the immune system is an essential component of the maintenance of respiratory homeostasis. A role of epithelial cells in reestablishing immune system homeostasis was outlined by Kodi Ravichandran, who showed how epithelial cells might limit inflammation by phagocytosis of apoptotic cells following exposure to allergens.

Early Effector Mechanisms

An efficient and effective response to potentially harmful particles is important because even a small amount of inflammation may compromise lung function. A number of different cell types are thought to contribute to these early effector responses. Andrew McKenzie introduced innate lymphoid cells and how they contribute to allergic immune responses, and neutrophil inflammation during lung disease was discussed by Moira Whyte. The vast vascular supply to the lung ensures constant traffic of cells of the immune system through the lungs, which can respond efficiently and effectively to environmental change. In addition, the increased resistance of the pulmonary microvasculature results in a large pool of marginated neutrophils. These neutrophils are able to regulate immune responses via molecules such as the proteases which they release. The particular effect of fibrinogenolysis on allergic responses was discussed by David Corry.

Influence of Host Defense Pathways

A robust and coordinated immune response is necessary for host defense against respiratory pathogens. Jay Kolls outlined the vital role that T cells play in this regard. Effector T cells such as Th17 as well as IL-17⁺ $\gamma\delta$ T cells are important for a range

of pulmonary infections induced by bacteria and fungi. Several presenters discussed how infection exacerbates immune responses to allergens or other environmental exposures, such as cigarette smoke. Michael Holtzman showed that acute infection has long-term consequences for individuals' pulmonary health in that viral infections may prime them for allergic responses and enhance the effects of exposure to cigarette smoke. Infection with Sendai virus results in increased IL-33 expression, which is maintained even after viral clearance. Moreover, viral infections increase the number of progenitor cells in the lung. The relationship between viral infections and cigarette smoke and its consequences for developing COPD were discussed by Phil Hansbro, who highlighted the involvement of the interferon pathway by blockade of phosphoinositide 3-kinase. Fungal infections are increasingly recognized to be problematic for people with underlying respiratory conditions, often resulting in enhanced disease severity. Cory Hogaboam outlined a role for the TAM (Tyro3, Axl, and Mer) receptors in modulation of fungal asthma and also during infection with respiratory syncytial virus. These regulators of Toll-like receptor expression are important for control of innate immunity in the inflamed lung.

Regulation and Modulation of Inflammation

It is hoped that a better understanding of the molecular mechanisms involved in maintaining respiratory immune tolerance, and also of those pathways dysregulated during common inflammatory lung diseases, will lead to the development of novel avenues for therapeutic intervention. It is known that there are sophisticated mechanisms in place to promote active suppression of immune responses to these airborne particles, such as regulatory T cells (Tregs) and plasmacytoid dendritic cells, as well as expression of

molecules such as CD200R on airway macrophages. The exploitation of these pathways is a potential method of downregulating inappropriate immune responses. This strategy has been employed successfully to ameliorate allergic responses by using immunotherapy to promote antigen-specific tolerance. Mark Larche discussed the latest results of a trial in patients with cat allergies. He described the efficacy of the tested therapy and its good safety profile. Similarly, Mick Croft showed that viral infection suppresses Treg activity in the lung, thus enhancing allergic responses. Tolerance in the lung is mediated by a complex array of molecules expressed on a range of immune cells. In fact, pulmonary macrophages are able to induce the development of Tregs and downregulate allergic responses. Kasia Hawrylowicz showed how nutrition affects regulatory pathways, with the number of FoxP3⁺ T cells correlating with the levels of Vitamin D in the circulation. She proposed that enhancing Vitamin D levels in chronic, steroid-refractory asthma patients might be of benefit. Guy Brusselle rounded off the meeting with a discussion of treatment developments in COPD and stressed the necessity of investigating both innate and adaptive pathways to maximize treatment options.

Respiratory diseases are very common, and, although symptoms are not life-threatening for a large number of patients, severe asthma or COPD is debilitating and shortens life expectancy for a growing number of patients. Few novel treatments are available for patients with these diseases. However, the next generation of therapeutics can be discovered and developed only by gaining a basic understanding of the mechanisms of respiratory immune tolerance, how changes in lung structure affect function, the influence of genetic background versus environment, and the impact of the aging process on respiratory health. ■

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