Alice Prince *Editor*

Mucosal Immunology of Acute Bacterial Pneumonia

Springer

Mucosal Immunology of Acute Bacterial Pneumonia

Alice Prince
Editor

Mucosal Immunology of Acute Bacterial Pneumonia

Springer

Editor
Alice Prince
Columbia University
New York, NY, USA

ISBN 978-1-4614-5325-3 ISBN 978-1-4614-5326-0 (eBook)
DOI 10.1007/978-1-4614-5326-0
Springer New York Heidelberg Dordrecht London

Library of Congress Control Number: 2012951432

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Introduction

Bacterial pneumonia or lower respiratory tract infection is a major cause of morbidity and mortality worldwide, affecting diverse patient populations ranging from infants to the elderly; previously healthy individuals as well as those with major immunological deficiencies—genetic and acquired. Pneumonia results in a tremendous economic burden estimated at 40.2 billion dollars in the United States alone in 2006 (CDC). Recent tabulations list 4, 447,893 reported cases of pneumonia in USA (not influenza) in patients under the age of 18 in 2007, with another 1,576,376 cases in those over 65 years of age (American Lung Assn. 2010 data). Health care statistics attempt to separate the incidence of pneumonia due to influenza virus versus bacterial pneumonias, although many cases of influenza, particularly those that require hospitalization, are complicated by bacterial superinfection (Chien et al. 2009). Despite the prevalence of bacterial pneumonias, there have been few changes in the approach to either prevention or treatment over the past 50 years. While immunization strategies have been successful for a limited number of organisms, reliance upon antimicrobial agents to kill bacteria once infection is established has been the cornerstone of treatment for the past 50 years. Given the continuing high rates of mortality in selected patient groups, identifying specific targets in the host to prevent destructive immune responses, as is the standard in other pathological processes such as autoimmune diseases and cancer, could provide useful therapeutic adjuncts. Understanding the pathogenesis of pneumonia requires both an appreciation of bacterial virulence factors and the genetics underlying bacterial evolution and adaptation to the host, and an appreciation of the complexities of innate immune signaling in the lung; how the mucosal response to inhaled pathogens is activated and regulated.

The respiratory tract is continually exposed to potential pathogens and very frequently colonized by the very organisms, such as *Streptococcus pneumoniae* and *Staphylococcus aureus*, which can initiate severe infection if they gain access to the lower respiratory tract. The normal innate immune defenses of the respiratory tract provide a potent immunological as well as a physical barrier against bacterial penetration. For bacteria to successfully invade requires not only the expression of specific bacterial virulence determinants, but also requires the appropriate host; a patient with enhanced susceptibility to infection or exaggerated response to airway contamination by inhaled bacteria.

Many common pathogens colonize the upper respiratory tract; *S. aureus* often resides in the anterior nares, lined with a squamous cornified epithelial surface—whereas *S. pneumoniae* and the Gram-negative opportunists that often colonize hospitalized patients more often reside in the posterior pharynx, a mucosal surface. The entire respiratory epithelium is well defended against invading bacteria by an active mucociliary escalator and airway lining fluid replete with small peptides and cytokines with potent antimicrobial activities. Organisms that persist in this milieu are occasionally aspirated and gain access to the lower airways where they initiate the recruitment of phagocytes, predominantly neutrophils to eradicate infection. Most of the organisms that cause pneumonia have the genetic flexibility to actively adapt to the milieu within the airway and ongoing selection for mutants able to withstand the antibacterial activities of airway surface fluid and resist phagocytic clearance then cause infection. The major pulmonary pathogens *S. pneumoniae, S. aureus*, and the Gram-negative opportunists *P. aeruginosa* and *K. pneumoniae* have all evolved multiple and sophisticated mechanisms to counter the many effectors of local mucosal immunity.

Pneumonia, caused by the aspiration of upper airway flora, occurs when these mucosal clearance mechanisms are overwhelmed. Activation of innate immune signaling in the respiratory tract varies substantially depending upon the properties of the specific pathogen as well as the experience of the host with these pathogens. The majority of respiratory bacterial pathogens are extracellular, equipped to replicate in the airway lumen and only occasionally to persist intracellularly, within either a phagocyte or epithelial cell. Major airway pathogens express and shed specific gene products or PAMPs (pathogen-associated molecular patterns) that potently activate innate immune signaling in numerous cell types. Many of these PAMPs are recognized by airway epithelial cells, which have a major role in initiating proinflammatory signaling to recruit and activate immune cells in response to the perceived infection. While some of these PAMPs are recognized by surface-associated receptors, some bacterial products are endocytosed by both immune and stromal cells and stimulate intracellular signaling cascades that mediate type I interferon and inflammasome-mediated signaling.

Each of the major components of the mucosal immune system has a scripted response to the presence of bacterial PAMPs at a site in the lung that is normally sterile. It has become apparent that the nature of the immune response that is elicited is highly variable depending upon the repertoire of virulence factors and PAMPs expressed by specific organisms. The extent of immune signaling is determined by the accessibility and distribution of relevant pattern-recognition receptors. Thus in the airway, resident alveolar macrophages have an important function in the initial recognition of perceived pathogens. For example, the ingestion of *P. aeruginosa* and its flagellin stimulates both TLR5-associated NF-κB proinflammatory signaling and also activates the more potent effectors released by the NLRC4 inflammasome, with resultant caspase-1 activation, generation of IL-1β and IL-18 as well as the induction of pyroptosis, itself a proinflammatory form of cell death. Some of the most virulent pulmonary pathogens, such as *Franciscella tularensis*, replicate to incredibly high levels without evoking an immune conversely, much of the pulmonary damage associated with *Staphylococcus aureus* can be attributed to an excessive proinflammatory response that interferes with respiration.

Many cell types are involved in pulmonary clearance mechanisms. While it is apparent that the rapid influx of phagocytes is critical to contain an acute bacterial pneumonia, the regulation of inflammation is equally critical for a successful outcome. Common to many different causes of lung inflammation, the regulation of proinflammatory signaling is critical to enable efficient removal of pathogens without compromising airway function and gas exchange. The specific roles of major components of innate and adaptive immunity in protection of the lung from bacterial pneumonias were characterized in patients with primary and acquired immune deficiencies; those lacking B cells and antibody who were at substantial risk for pneumococcal pneumonia, patients with T cell defects, and especially CD4+ T cell depletion as a consequence of HIV infection who were especially susceptible to such intracellular pathogens as *Pneumocystis jirovecii*. The importance of neutrophil NADPH oxidase (NOX) activity in protection from *S. aureus* infection was well illustrated in the cohorts of patients with chronic granulomatous disease. Many additional correlations between other less profound immunological defects and susceptibility to specific types of lung infection have been made though the availability of genomic and immune function studies in vitro.

Recruited neutrophils are undoubtedly critical for the clearance of bacteria from the airway, as long as their number and state of activation are not excessive. Bacterial evasion of neutrophil clearance is a major factor in the success of pulmonary pathogens. Moreover, the associated oxidative stress and release of active neutrophil proteases in the airways contribute to tissue damage and further facilitate the establishment of foci of infection where bacteria are protected from the normally efficient removal by phagocytes. The recruitment, activation, and clearance of apoptotic neutrophils are all components of mucosal clearance that could potentially be targeted to regulate the amount of inflammation necessary to clear infection without causing pulmonary damage.

The contribution of other types of immune cells in response to acute bacterial infection in the lung has also been well characterized. The surveillance functions of specific subsets of DCs (dendritic cells) are clearly important in pathogen recognition. DCs also have possibly an even more significant function after they have matured and can traffic to local lymph nodes to inform T cells, both in general and in the context of specific infections. T cells, especially CD4+ T cells have long been recognized as critically important in the handling of intracellular pathogens, as was made evident during the HIV epidemic. The role of Th17 cells and the IL-17 family of cytokines in the recruitment of appropriate immune responses to extracellular bacterial infection in the lung has also become well appreciated. There are also substantial data being generated to understand how these immune cells are able to traffic to the site of infection in the airway. PMN, AM, and DC trafficking often involve the modification of epithelial and endothelial junctions to permit the egress of leukocytes in response to local signals.

Epithelial barrier function is modified as a consequence of TLR signaling to facilitate the transmigration of neutrophils and other phagocytes to the airway (Chun and Prince 2009). This may occur to facilitate immune and phagocyte recruitment or as a direct consequence of specific bacterial gene products. Bacteria activate

changes in barrier function and may invade through the epithelial tight junctions to gain access to receptors that are predominantly found at the basolateral aspects of the airway epithelium (Soong 2011). The common opportunistic pathogens of the respiratory tract have evolved sophisticated mechanisms to actively modulate specific targets of the host; the junctional proteins, Rho GTPases as well as ubiquitinylation systems. With large and flexible genomes, these organisms can acquire genes that enable them to evade with phagocytic clearance, and in some cases persist and disseminate systemically within phagocytes (Gresham 2000).

The host response to these airway pathogens causes much of the pathology associated with bacterial pneumonia. Effective mucosal clearance depends upon the coordinated signaling provided by the major components of the innate immune system in the lung. The relative contribution of each of these effectors has been examined in murine models of acute airway infection, with the caveat that the mucosal immune responses of the mouse do not necessarily replicate what occurs in humans. Studies with transgenic and knockout mouse models have provided important insights into the pathological as well as the beneficial consequences of the innate immune response.

In the subsequent chapters, the components of the innate immunity that participate in response to acute bacterial pneumonia will be reviewed, examining the specific contributions of several different types of immune effectors. How common bacterial pathogens cause pneumonia, either by activating immune signaling or by evading the normal clearance mechanisms will be examined. The goal of this volume is to provide an overview of the complexity of host response to specific bacterial pathogens in the lung and to provide some insights into the intricacies of these host–pathogen interactions. As will be evident, not all of the critical immune effectors are as well characterized as others, particularly in the context of even common bacterial pneumonias. Nonetheless, we can extrapolate from relevant studies of asthma, fungal, or viral infection to explain how these cell types participate in mucosal defenses. By providing reviews focused individually on either the host or the specific pathogen, we hope to provide a balanced compendium of the current understanding of how the lung is defended against acute bacterial infection. The ultimate goal is not only to appreciate the complexities of immune protection of the lung, but also to provide insight into which of these cascades are potential targets to modulate pathological responses to bacterial infection, without compromising the efficiency of pathogen eradication.

References

Chien YW, Klugman KP and Morens DM (2009) Bacterial pathogens and death during the 1918 influenza pandemic. N Engl J Med 361:2582–2583.

Chun J and Prince A (2009) TLR2-induced calpain cleavage of epithelial junctional proteins facilitates leukocyte transmigration. Cell Host Microbe 5:47–58.

Gresham HD, Lowrance JH, Caver TE, Wilson BS, Cheung AL and Lindberg FP (2000) Survival of Staphylococcus aureus inside neutrophils contributes to infection. J Immunol 164:3713–3722.

Soong G, Martin FJ, Chun J, Cohen TS, Ahn DS and Prince A (2011) Staphylococcus aureus protein A mediates invasion across airway epithelial cells through activation of RhoA GTPase signaling and proteolytic activity. J Biol Chem 286:35891–35898.

Contents

Chapter 1
Alveolar Macrophages

David H. Dockrell, Paul J. Collini, and Helen M. Marriott

1.1 Introduction

Macrophages have been recognized as critical immune effectors since the seminal studies of Élie Metchnikoff (Kaufmann 2008). Macrophages also play distinct but equally important roles in tissue homeostasis (Mosser and Edwards 2008). The capacity of macrophages to respond to specific environmental cues and to initiate specific responses arises because of their plasticity.

Alveolar macrophages (AM) are the specialized tissue macrophages that reside in the alveolar space (Fels and Cohn 1986). They represent the major macrophage population in the lung; one study in mice suggested AM constitute 93% of lung macrophages with interstitial macrophages making up the remainder (van oud Alblas and van Furth 1979). AM adapt to a unique environment characterized by relatively high oxygen tensions but must also ensure that their responses do not compromise the precarious physiological balance that permits gas exchange in the alveolus (Piantadosi and Schwartz 2004). In particular the inflammatory response in the airway must be very tightly controlled. As with all tissue macrophages, AM development reflects the influences of differentiation modified by unique environmental honing. This has equipped the AM to perform its fundamental homeostatic roles in the lung and to clear microorganisms, particulate matter, and environmental toxins. The development of bronchoscopy and the ability to isolate AM by bronchoalveolar lavage (BAL) first increased awareness of the unique characteristics of AM some 50 years ago (Finley et al. 1967; Myrvik et al. 1961). Characterization of the AM transcriptome and proteome in healthy cells has expanded our understanding of these cells' functions (Lehtonen et al. 2007; Zaslona et al. 2009; Jin et al. 2004).

D.H. Dockrell (✉) • P.J. Collini • H.M. Marriott
Department of Infection and Immunity, The University of Sheffield Medical School and Sheffield Teaching Hospitals, Beech Hill Road, Sheffield S10 2RX, UK
e-mail: d.h.dockrell@sheffield.ac.uk

A. Prince (ed.), *Mucosal Immunology of Acute Bacterial Pneumonia*,
DOI 10.1007/978-1-4614-5326-0_1,