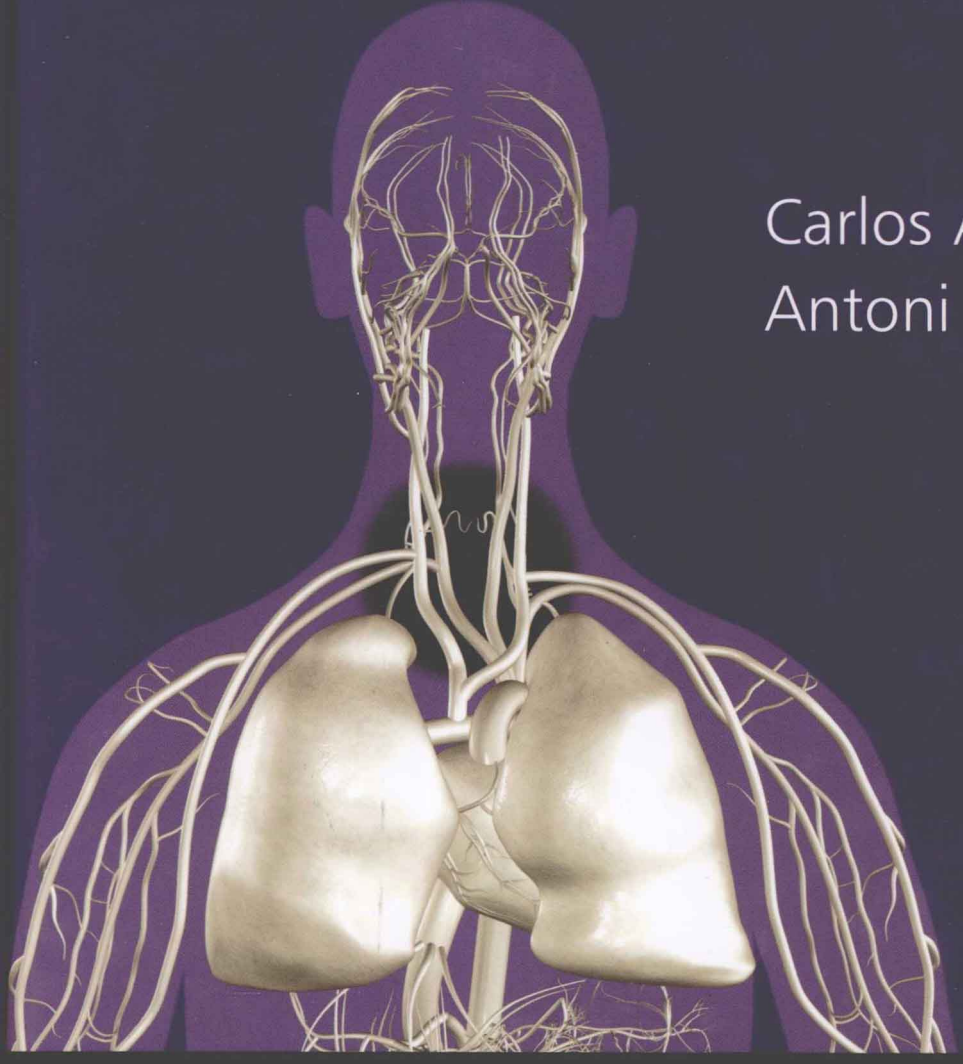

Carlos Agustí
Antoni Torres

Pulmonary Infection in the Immunocompromised Patient

STRATEGIES FOR MANAGEMENT

WILEY-BLACKWELL

PULMONARY INFECTION IN THE IMMUNOCOMPROMISED PATIENT

STRATEGIES FOR MANAGEMENT

Editors

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PULMONARY INFECTION IN THE IMMUNOCOMPROMISED PATIENT

Preface

The number of immunocompromised patients has increased over the last decade. Improvements in solid-organ and haematopoietic stem cell transplantation techniques, the expanded use of chemotherapic treatments and glucocorticoids use, and the appearance of new immunomodulatory therapies are some of the reasons that justify this increase. The success of the different transplant techniques has generated a great deal of interest in the management of immunocompromised patients among clinicians and basic scientists. The recognition and management of pulmonary complications that result from immunosuppression is a challenging task. The lungs may be injured directly through an infectious or toxic insult. Conversely, lung disease may result as a secondary event. Pulmonary complications in these patients require a multidisciplinary approach that often involves different specialists. This includes an appreciation of the epidemiology of post-transplant pulmonary complications, the differential diagnoses for these processes, the appropriate diagnostic explorations, and the specific treatments and potential interactions.

Our goals in this book are to provide an integrated discussion of progress in a comprehensive fashion. The general aspects of the lung immune defences are reviewed by Drs Patel and Koziel. Microbiological diagnosis and respiratory sampling in this population are a very important issues, related to the adequacy of treatment and mortality. Dr Ieven and Dr Baughman have reviewed both chapters in depth. The radiological approach to the diagnosis of respiratory complications is of particular importance and Dr Franquet presents the different tools that we currently have in our hands.

The remaining chapters of the book are dedicated to the review of respiratory infections regarding different types of immunosuppression: HIV infected patients, neutropenia, haematopoietic stem cell transplantation and chronic steroid treatment. Finally, intensive care management, antibacterial, antifungal and antiviral treatments are updated by experts in these subjects.

As in any multi-author book, the success of the endeavour relates to the commitment and creativity of the collaborating authors; we are extremely thankful for the hard and careful work of each of our contributors. We would also like to thank our colleagues at John Wiley & Sons, Ltd who provided outstanding support for this project.

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1

Lung immune defences in the immunosuppressed patient

Naimish Patel and Henry Koziel

Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA

1.1 Introduction

The respiratory tract is constantly exposed to environmental elements and potential pathogens on a daily basis during the obligatory process of breathing or through subclinical aspiration. To avoid infectious disease pathogenesis in the respiratory tract, a number of elegant, complex and interdependent systems of host defence mechanisms are in place to prevent microorganism colonization of the respiratory epithelium, promote efficient microbe elimination, and maintain sterility of the lower respiratory tract in the healthy host. The layers of host defence mechanisms include physical barriers and secreted chemical factors (operant immediately), innate immune system (operant within minutes to hours), and the adaptive immune system (operant within days). Disruption of any of these components of lung host defence may lower critical threshold for microbial invasion and promote disease pathogenesis. Several acquired immunodeficiency states are associated with frequent and severe respiratory tract infections, and lung infections with opportunistic pathogens. This chapter will review the components of lung host defences in health with particular focus on human data, and discuss perturbations of host defences associated with select specific immunodeficiency states that may promote susceptibility and contribute to pathogensis of respiratory tract infections.

1.2 Host defence function in health

In health, host defence function is provided by three critical integrated components, including (1) physical (or mechanical) and chemical mechanisms; (2) innate immunity; and (3) adaptive immunity. Physical and chemical mechanisms are present and operate continuously and serve as an immediate protective function to microbial challenge. For microbes that circumvent or bypass physical and chemical mechanisms, the innate

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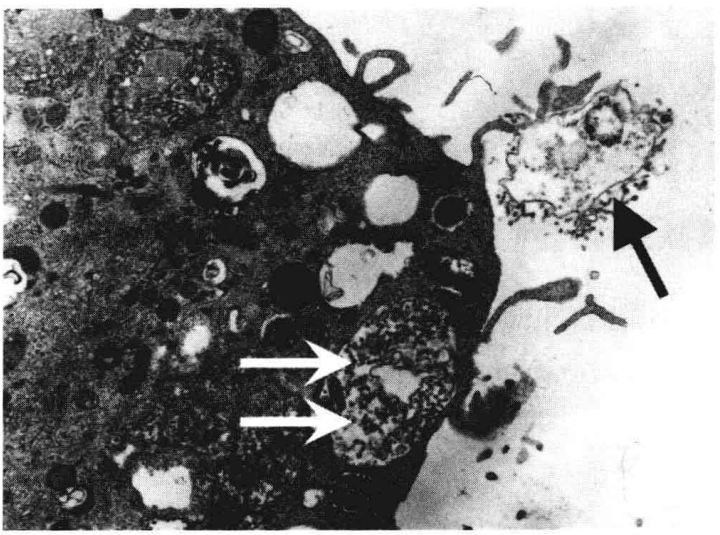

Figure 1.1 Electron micrograph of human alveolar macrophage engaging pneumocystis organisms. Alveolar macrophages represent the predominant immune cells in the alveolar airspace, and critical effector cells in pathogen recognition and elimination. Pneumocystis trophic forms are seen in the process of engagement by macrophage pseudopodia (arrow) and ingested in the macrophage (arrows). *Pneumocystis* is a major opportunistic pathogen responsible for severe pneumonia in the immunocompromised host. (Electronphoromicrograph courtesy of Angeline Warner, Harvard School of Public Health, Boston, MA).

immune system represents another layer of the host defence response. Cellular and soluble components of innate immunity are constantly present, and are capable of recognizing, engaging and eliminating a broad array of microbes (through molecular recognition of conserved molecular patterns expressed by pathogens but not host cells) within minutes to hours of microbial challenge (Figure 1.1). Through a relatively limited number of secreted and host-cell associated recognition molecules, innate immunity can detect and generate an appropriate antimicrobial response to a broad range of bacteria, fungi and viruses. In health, the majority of daily microbial challenges are likely effectively cleared by these first two layers of host defences, as the majority of living creatures have only mechanical and chemical defences, and innate immunity. If clearance of microbes is not achieved despite activation of innate immune mechanisms, the adaptive immune system can be activated within days to provide an amplified and specific immune response. The adaptive immune response is composed predominantly of B-lymphocytes and T-lymphocytes that recognize specific antigen determinants on pathogens, and ultimately provide lifelong memory against repeated challenges with the same pathogen.

Physical (mechanical) and chemical mechanisms of host defence

Physical barrier and mechanical host defence mechanisms, and chemical host defence mechanisms are constantly available for immediate action in the healthy host. Particle size in part determines fate, as particles and microbes generally exceeding 5 μm can be entrapped as air flows through the tortuous channels of the nasopharynx and by nasal

hairs, and through inertial forces are impacted along the tonsilar pillars, glottis, trachea and branching bronchi and bronchioles. Entrapped particles and microbes may be expelled through coughing and sneezing mechanisms. The complex glycoprotein mucins lining the airway epithelial surfaces facilitate particle entrapment, and promote elimination by the cephalad respiratory epithelial cell ciliary movement that allows expectoration or swallowing of mucin-entrapped pathogens. In general, particles and potential pathogens smaller than 5 μm can bypass these mechanical obstacles and gain access to the terminal bronchioles and alveoli. In addition, the respiratory epithelium serves as a critical barrier function. Similar to the function of the skin, the integrity of the mucosal surfaces including the respiratory epithelial cells and associated tight functions remains critical to protective host defence function. The importance of these mechanisms, which operate constantly, is underscored by conditions that interfer with proper function such as mucociliary disease (dynein arm dyskinesia), bronchiectasis (anatomical distortion and scarring of epithelium), and neurological disorders or pharmacological agents that prevent effective cough reflexes.

A number of secreted airway products also contribute to antimicrobial functions by several mechanisms including direct antimicrobial activity, opsonization and agglutinization (Table 1.1). Microbes that pass the physical and mechanical barriers may be eliminated by a range of chemical mediators that are constantly expressed and may be further induced. These mediators include molecules capable of direct antimicrobial effect (ex. lysozyme, lactoferrin, SLPI, complement, α-, β- and θ-defensins and cathelicidins), agents that inhibit microbial growth (ex. transferrin), and molecules that serve as opsonins that facilitate host cell recognition (ex. complement, fibronectin, collectins, SP-A, SP-D, IgA and IgG) or modulate host cell response to pathogens (ex. LPS-binding protein) (Crouch, 1998; Shepherd, 2002; Zhang and Koziel, 2002; McCormack and Whitsett, 2002). Lung collectins, such as surfactant components

Table 1.1 Secreted antimicrobial factors in the airways.

Cathelicidin
Collectins
SP-A
SP-D
mannose binding protein (MBP), or mannose binding lectin (MBL)
Complement
Defensins (α and β)
Fibronectin, vitronectin
Ficolins
Immunoglobulins
IgA (predominant in upper airways)
IgG (predominant in lower airways)
Lactoferrin
LPS binding protein (LBP)
Lysozyme
Transferrin

SP-A and SP-D can serve as opsonins and enhanced phagocytosis, agglutination of microbes, and increased bacterial membrane permeability promoting pathogen elimination (Shepherd, 2002). Classical pathway complement proteins C3, C4, C1q and alternative complement pathway component factor B are expressed in the lung alveolar fluid (Watford, Ghio and Wright, 2000), and can provide opsonization of microbes in the respiratory tract.

Innate immunity in the lungs

Innate immunity is an evolutionarily conserved ancient defence mechanism that comprised components that are constantly expressed and available, can be activated within minutes to hours, and can engage potential pathogens upon initial encounter (Martin and Frevert, 2005; Zaas and Schwartz, 2005). The principal cellular components of lung innate immunity include alveolar macrophages, neutrophils, NK cells, dendritic cells and eosinophils. Alveolar macrophages represent the predominant immune cell in the alveolar airspace, accounting for >85% of mobile cells in the alveoli. Neutrophils and eosinophils are generally not present in the alveoli but are recruited in response to chemotactic signals. Natural killer (NK) cells participate in early innate defence through cytotoxic activity against pathogen-infected cells and secretion of cytokines and chemokines that modulate subsequent steps in the adaptive immune response (Biron *et al.*, 1999). Recognition of microbial products by dendritic cells triggers functional dendritic cell maturation and leads to initiation of antigen-specific adaptive immune responses.

The innate immune response is mediated through interactions of microbes or microbial products with the germline-encoded host cell receptors. Innate immune cells such as alveolar macrophages recognize potential pathogens through surface recognition receptors such as mannose receptors, β-glucan receptors, scavenger receptors and Toll-like receptors (TLRs). The family of mammalian TLRs serves a critical role in the early host defence response through recognition of conserved molecules derived from microbial pathogens (Imler and Hossmann, 2001), leading to activation of NF-κB (Beutler, 2000) and MAP kinases (Barton and Medzhitov, 2003), and subsequent transcription and translation of host defence genes (Medzhitov, 2001; Aggarwal, 2003). Expressed on cells near mucosal portals of entry including macrophages (Jones *et al.*, 2001) dendritic cells (Muzio *et al.*, 2000) and lung epithelial cells (Armstrong *et al.*, 2004), mammalian TLR1 through TLR9 represent critical molecules in the first line of host defence to microbes in the lungs. Functional deficiency or genetic deletion of TLR4 increase susceptibility to *H. Influenza*, *S. pneumoniae*, and *K. pneumoniae* respiratory tract infection in murine models (Wang *et al.*, 2002; Branger *et al.*, 2004). Humans with TLR4 mutations are hyporesponsive to inhaled LPS (Arbour *et al.*, 2000). Alveolar macrophage and alveolar epithelial cells exhibit limited responsiveness to TLR4 stimulation due to relatively low membrane expression of the adaptor molecule MD-2 (Jia *et al.*, 2004; Kajikawa *et al.*, 2005). TLR5 polymorphism ($TLR5^{392stop}$) in the ligand binding domain increases susceptibility of humans to *Legionnella* pneumonia (Hawn *et al.*, 2003).

Regulation of activating pattern recognition receptors

Control of inflammatory responses to infectious challenge is of particular importance for the continued normal gas exchange function of the lungs. In general innate receptor activation promotes proinflammatory responses, and cellular innate immune responses (such as macrophages) to antigenic challenge can result in enhanced innate immune response upon future rechallenge by the same antigen (Bowdish *et al.*, 2007). However, concurrent with innate surface membrane and intracellular receptor activation to promote proinflammatory responses, a number of counter regulatory molecules are also activated that likely limit the proinflammatory response to maintain homeostasis and limit collateral damage. Examples of these regulatory molecules for TLRs include: TOLLIP, IRAK-M, sMyD88, ST2, SIGGR, SOCS-1, NOD2, MIF, PR105 and TAM receptor family (TYRO3, AXL and MER) (Rothlin *et al.*, 2007; Liew *et al.*, 2005). Whether these molecules are modulated by immunosuppressive agents or medical conditions associated with immune suppression is not completely understood.

Regulation of innate immunity by secreted products

In addition to serving antimicrobial functions, soluble products can also serve to modulate cellular innate immune response in the lungs. For example, lung collectins such as SP-A can modulate the innate immune response, such as regulating macrophage pattern recognition receptor expression (Beharka *et al.*, 2002) and regulating the generation of macrophage reactive oxygen species (Crowther *et al.*, 2004). SP-A and SP-D bind LPS and prevent interaction with LBP and TLR4-CD14 complex on alveolar macrophages (Borron *et al.*, 2000; Sano *et al.*, 2000) and thus limit activating responses. In addition to hepatic production as an acute phase reactant, LBP is expressed by pulmonary artery smooth muscle cells (Wong *et al.*, 1995) and type-II alveolar epithelial cells (Wong *et al.*, 1995; Dentener *et al.*, 2000). Alveolar lining fluids contain high concentrations of sCD14 and LBP (Martin *et al.*, 1992; Martin *et al.*, 1997b) and thus can modulate TLR4-mediated signaling.

Epithelial cells

Alveolar epithelial cells, in addition to providing a physical barrier function, also contribute to the innate immune response in the lungs. Epithelial cells express defensins HBD-1 and HBD-2 (McCray and Bentley, 1997; Hiratsuka and Al, 1998), and defensins also stimulate IL-8 production by epithelial cells (van Wetering *et al.*, 1997). Epithelial cells express TLRs and CD14, and can thus respond to microbial products analogous to TLR signaling in leukocytes, with release of IL-1β, IL-6, TNF-α, IL-8 and RANTES, GM-CSF, and TGF-β (Diamond, Legarda and Ryan, 2000). Microbes and microbial components (such as lipopolysaccharide, peptidoglycan and flagella) can interact with innate receptors (such as TLR2) expressed on the apical surface of epithelial cells (often in the context of lipid rafts) (Soong *et al.*, 2004), which in turn can promote Ca^{2+} release (Chun, Soong and Prince, 2006) and activate epithelial cell transcription factors such as