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Review

Host-pathogen interplay in the respiratory environment of cystic fibrosis

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Abstract

Significant advances have been made in the understanding of disease progression in cystic fibrosis (CF), revealing a complex interplay between host and pathogenic organisms. The diverse CF microbiota within the airway activates an aberrant immune response that is ineffective in clearing infection. An appreciation of how the CF host immune system interacts with these organisms is crucial to understanding the pathogenesis of CF pulmonary disease. Here we discuss the microbial complexity present in the lungs of individuals with CF, review emerging concepts of innate and adaptive immune responses to pathogens that chronically inhabit the CF lung, and discuss therapies that target the aberrant inflammatory response that characterizes CF. A greater understanding of the underlying mechanisms will shed light on pathogenesis and guide more targeted therapies in the future that serve to reduce infection, minimize lung pathology, and improve the quality of life for patients with CF.

Keywords: Cystic fibrosis; Host–pathogen interaction; Microbiota; Innate and adaptive immunity; Lung disease

Contents

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1. Overview of infection and disease

Respiratory failure resulting from chronic infection and inflammation of the airways still represents the primary cause of death for most individuals with cystic fibrosis (CF) [1]. As such, a better understanding of infection and immunity related pathology of the CF airways is needed. *Pseudomonas aeruginosa*, *Staphylococcus aureus*, including the methicillin-resistant (MRSA), *Haemophilus influenzae*, and *Burkholderia cepacia complex*, remain the primary pathogens associated with airway inflammation, although additional important opportunistic pathogens, including *Achromobacter xylosoxidans, Stenotrophomonas maltophilia* and non-tuberculous mycobacteria (NTM), are emerging [2]. Newly developed culture and molecular approaches have allowed for greater appreciation of new and/or emerging pathogens and complex bacterial communities, or microbiota, in the CF airways. Respiratory tract infection contributes toward a dysregulated host immune response in CF, impacting both innate and adaptive immunity and perpetuating a cycle of inflammation and disordered microbiota. Recent research has unveiled the complexity of the relationship between the traditional pathogens, overlooked lung microbiota, and host immune response (Fig. 1), although our understanding is still incomplete. In this article, we review new insights into CF pathogenesis and discuss their potential importance in prevention and treatment of pulmonary disease. The key points presented herein are summarized in the highlights.

2. Role of lung microbiota and pathogenesis

The CF airway represents a permissive environment for microbial colonization [3]. The natural history of CF is characterized by early colonization of the lung by *S. aureus*, followed occasionally by *H. influenzae* [4]. Although the consequences of *H. influenza* remain unclear, evidence suggests that *S. aureus* worsens pulmonary disease [5]. Predisposition and factors contributing to colonization with these early pathogens are still unclear. Although the lungs were classically

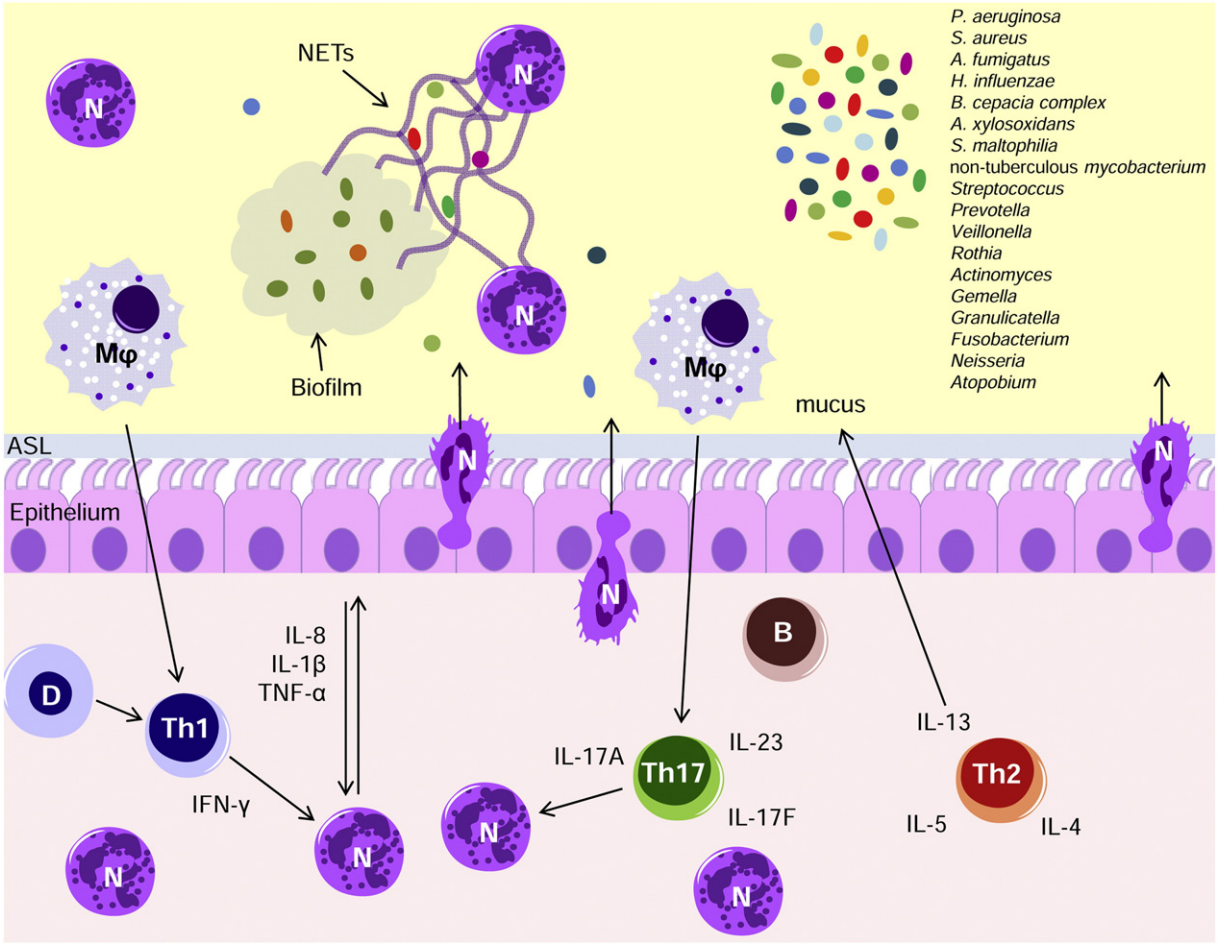

Fig. 1. Innate and adaptive immune response to infections in CF. Infection by several different pathogens triggers perpetual bouts of neutrophil recruitment and breach of the airway epithelium. In the airspace, neutrophils encounter persistent microbial biofilms and release neutrophil extracellular traps (NETs) that are ineffective and ultimately repurposed for the benefit of the microbial biofilms. Following continuous cycles of acute infection or once chronic infection is established, T lymphocytes are recruited and polarized to Th1, Th2 and/or Th17 cells. IL-17A and related cytokines as well as IFN-γ play an important role in the excessive recruitment of neutrophils. The effector phase of allergic bronchopulmonary aspergillosis (ABPA), associated to *Aspergillus fumigatus* infections, is determined by Th2-mediated allergic responses, including eosinophilia, mucus production, and airway hyperresponsiveness. The relevance of other emerging pathogens in CF lung disease progression still remains to be fully elucidated. N, neutrophils; Mϕ, macrophages; D, dendritic cells; B, B cells.