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Lung epithelium: barrier immunity to inhaled fungi and driver of fungal-associated allergic asthma

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Fungi are ubiquitous in the environment. The epithelium that lines our airways is the first point of contact with the frequent encounter of inhaled fungi. Consequently, the lung epithelium has evolved behaviors that instruct the earliest immune events to resist fungal penetration. Although the epithelium efficiently assists in immunity to invasive fungi, it also can be inappropriately triggered, to the detriment of the host, by normally innocuous fungi or fungal components. Thus, there is a tipping point of protective immunity against fungal pathogens versus inflammatory disease caused by an exuberant immune response to harmless fungal antigens. This review will discuss several aspects of barrier immunity to pulmonary fungal infection, as well as situations where fungal exposure leads to allergic asthma.

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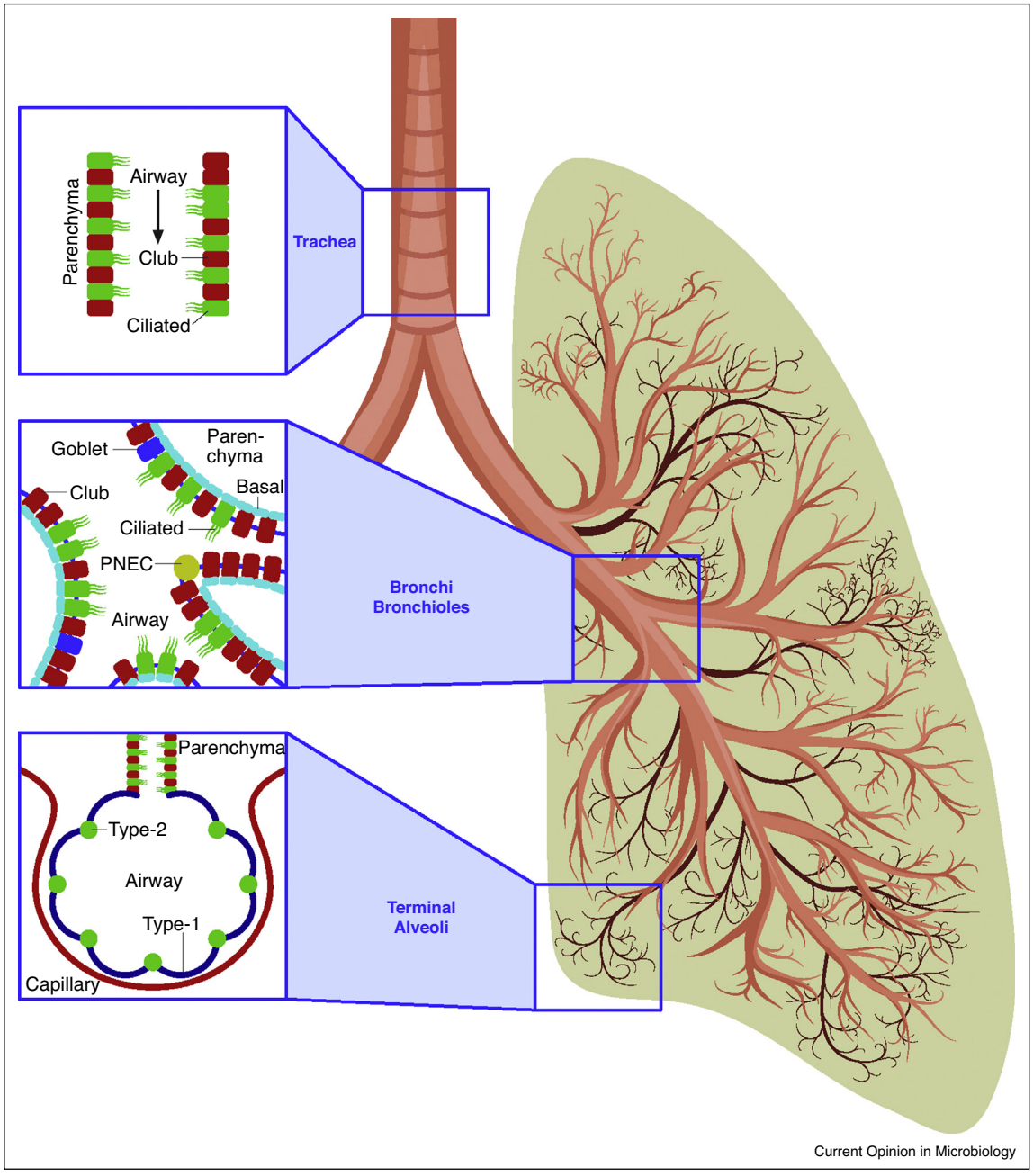
Introduction

For terrestrial vertebrates, the lungs are a primary interface with the external environment. The delicate and moist structures needed for efficient gas exchange between the blood and air also, unfortunately, present a suitable environment for fungal pathogens to invade and cause disease. This vulnerability is partially circumvented by the cavernous, cobbled architecture of the lungs (Figure 1). Particulates must navigate their way through ever winding and constricting passages of the trachea, bronchi, and bronchioles before reaching the fragile site of gas exchange in the terminal alveolar air space. Mucous and cilia lining the airways impose further physical constraints by capturing and reversing the trajectory of inhaled pathogens. Additionally, a heterogeneous assortment of epithelial cell subsets, each with unique functions, are distributed along the airways. Club cells, ciliated columnar cells, basal cells, and pulmonary neuroendocrine cells decorate the proximal airways, whereas type-1 and type-2 alveolar cells populate the distal epithelium. The asymmetric polarization of these epithelial cell subsets also augments their sophisticated behaviors. The apical surfaces of the epithelium expel antimicrobial peptides, mucous, and surfactants into the airway lumen. Conversely, the basolateral surfaces secrete chemotactic factors toward the lung parenchyma, thereby recruiting long ranging leukocytes and initiating the earliest events of immunity. The broad importance of the epithelium as a barrier to microbial invasion is widely recognized. However, the dynamic involvement of epithelial cells and their potent functions in fungal pathogen resistance are only beginning to be understood.

Humans inhale several liters of air every minute, and with each breath, we aspirate numerous fungal yeasts and spores [1]. Ensuing invasive disease is largely determined by the quality and quantity of inhaled fungi, as well as host intrinsic factors like immune status. Primary fungal pathogens (e.g. *Blastomyces*, *Coccidioides*, *Cryptococcus gattii*, and *Histoplasma*) cause symptomatic disease in otherwise healthy individuals, indicating that exposure is a major determinant of mycosis (Figure 2) [2••]. Infections with other fungi (e.g. *Aspergillus fumigatus*, *Cryptococcus neoformans*, and *Pneumocystis*) commonly arise in people with weakened immune systems [2••]. This suggests that opportunistic fungal pathogens are likely less virulent, yet more prevalent in the environment than primary fungal pathogens (Figure 2). In both cases, the earliest events of frontline defense after fungal exposure occur at the epithelial surfaces. Investigations into the evolutionary rivalry between lung epithelial cells and fungi could spur paradigm-shifting treatments that prevent or cure invasive fungal disease.

Asthma is a lifelong illness noted by periodic episodes of respiratory distress. According to the World Health Organization, asthma affects an estimated 235 million people and is the most common chronic disease in children [3]. The initial sensitization and subsequent recurrence of asthmatic events is often triggered by inhalation of environmental allergens [4]. Therefore, allergic asthma can be

Figure 1



Epithelial architecture of the lung. The lung is comprised of three zones. The trachea is lined with ciliated epithelial cells and club cells. The small conducting airways, including the bronchi and bronchioles, are a heterogeneous mix of club cells, ciliated cells, and goblet cells. Basal cells underlie these luminal cells, and pulmonary neuroendocrine cells tend to cluster at bronchiolar branch points. Finally, the terminal airways are occupied by alveolar cells. Type-1 alveolar cells are the primary sites of gas exchange, and as a result, they make up an overwhelming majority of the lung surface area. Type-2 alveolar cells produce surfactants that provide the surface tension to stabilize these delicate alveoli.

operationally defined as an inappropriate response to a normally innocuous extrinsic stimulus. A significant proportion of cases of allergic airway disease are associated with fungal exposure [5–8]. Household molds, like *Aspergillus* and *Penicillium*, as well as the outdoor fungus, *Alternaria*, account for a majority of these fungal-associated allergies [8]. Inhalation of intact fungi and fungal components triggers allergic responses at the respiratory mucosa. Unlike invasive fungal infections, most evidence to date implicates epithelial cells as having a detrimental