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Review

Claudins: Gatekeepers of lung epithelial function

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ABSTRACT

The lung must maintain a proper barrier between airspaces and fluid filled tissues in order to maintain lung fluid balance. Central to maintaining lung fluid balance are epithelial cells which create a barrier to water and solutes. The barrier function of these cells is mainly provided by tight junction proteins known as claudins. Epithelial barrier function varies depending on the different needs within the segments of the respiratory tree. In the lower airways, fluid is required to maintain mucociliary clearance, whereas in the terminal alveolar airspaces a thin layer of surfactant enriched fluid lowers surface tension to prevent airspace collapse and is critical for gas exchange. As the epithelial cells within the segments of the respiratory tree differ, the composition of claudins found in these epithelial cells is also different. Among these differences is claudin-18 which is uniquely expressed by the alveolar epithelial cells. Other claudins, notably claudin-4 and claudin-7, are more ubiquitously expressed throughout the respiratory epithelium. Claudin-5 is expressed by both pulmonary epithelial and endothelial cells. Based on *in vitro* and *in vivo* model systems and histologic analysis of lungs from human patients, roles for specific claudins in maintaining barrier function and protecting the lung from the effects of acute injury and disease are being identified. One surprising finding is that claudin-18 and claudin-4 control lung cell phenotype and inflammation beyond simply maintaining a selective paracellular permeability barrier. This suggests claudins have more nuanced roles for the control of airway and alveolar physiology in the healthy and diseased lung.

Contents

Abbreviations: ARDS, acute respiratory distress syndrome; ASL, airway surface liquid; CAR, Coxsackie and Adenovirus Receptor; CC10, club cell specific protein 10; CFTR, cystic fibrosis transmembrane conductance regulator; COPD, chronic obstructive pulmonary disorder; EC, extracellular; ENaC, epithelial sodium channel; JAM-A, Junctional Adhesion Molecule-A; MMP, matrix metalloprotease; PALS, proteins associated with Lin-7; PATJ, Pals1-associated tight junction protein; PDZ, PSD95, Dlg1, ZO-1; SP, surfactant protein; TM, transmembrane; VILI, ventilator induced lung injury; ZO, Zonula Occludens.

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1. Introduction

Epithelia form selective barriers that regulate inner luminal organ spaces, including those found in the respiratory system. Key among the structures which promote epithelial barrier function are tight junctions, structures at cell–cell interfaces composed of transmembrane, cytosolic and cytoskeletal proteins that interact in a coordinated manner to regulate tissue barriers. The core tight junction transmembrane proteins are the claudins. Claudins on adjacent cells associate with each other to form paracellular channels of varying permeability that create a barrier by regulating the paracellular compartment between cells. Importantly, although the cell composition varies throughout the respiratory tree, epithelial tight junctions provide a unified cell-mediated barrier between airspaces and fluid containing tissues.

Several reviews on tight junctions and claudins in the lung have been published over the last few years [1–3]. This review provides an update to current knowledge about the importance of claudin diversity for lung barrier function. This is underscored by recently characterized claudin knockout mouse models demonstrating that multiple claudins play crucial roles in preserving lung barrier function.

2. Multiplicity of epithelial cells lining the respiratory tract

As a conduit for gas exchange, the respiratory tract consists of functionally distinct segments ranging from the conducting airways to the terminal airspaces where gas exchange occurs (Fig. 1). The conducting airways are further divided into functionally distinct anatomical segments: the upper, lower, and distal airways. The upper airway consists of the nasal and oral cavities, pharynx, and larynx and is predominantly involved in sensory function, air humidification and gross filtration of airborne particulates. The lower airway begins with the trachea which then branches into two primary bronchi. Primary bronchi extend and branch through secondary and tertiary bronchi followed by 5–20 generations of bronchioles. The bronchial tree provides a semi-rigid cartilaginous framework to support the terminal airspaces that have the flexibility and compliance required for air influx and efflux.

The main airspace surface of the trachea, as well as conducting airways distal to the trachea, are lined by a pseudostratified epithelium which includes ciliated cells, mucus secreting goblet cells, columnar cells, serous cells and basal cells which altogether form a permeability barrier. Conducting airways are also peppered with submucosal glands containing goblet, duct, and serous cells which contribute to mucus secretion. A major function of the lower airway is clearance of particulates from the lower airspaces. This is facilitated by the concerted efforts of goblet cells and ciliated cells that serve as a "mucociliary escalator" moving foreign material upward and out of the lung [4]. Regulation of the airway surface liquid (ASL) underneath the mucus layer is critical to proper mucociliary clearance [5]. Airway epithelial cells maintain ASL balance by the concerted action of plasma membrane channels (which regulate transcellular fluid and ion transport) and tight junctions (which regulate the paracellular route). Roles for claudins in regulating paracellular ion and water diffusion are described below.

Conducting lower airways are kept open to the atmosphere by supportive cartilaginous rings which gradually thin as the airway

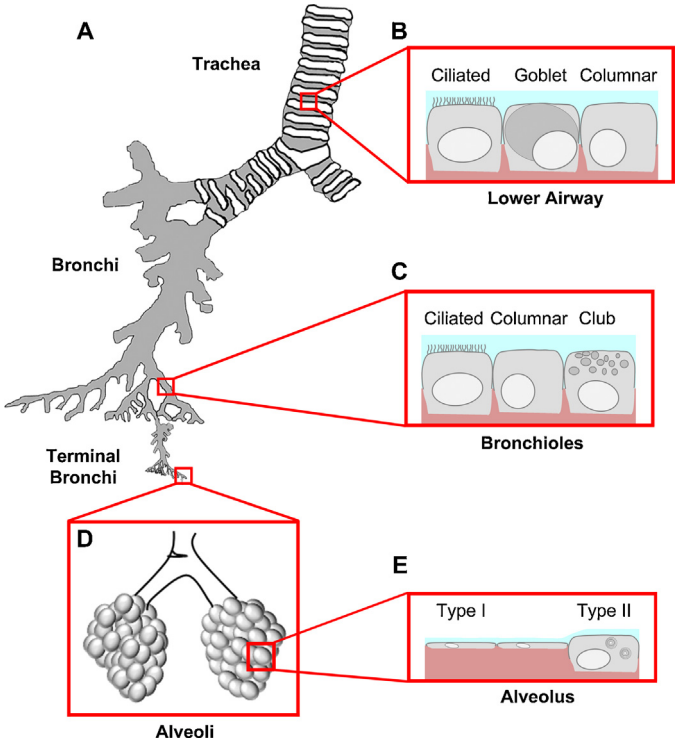

Fig. 1. Epithelial diversity along the respiratory tree. (A) Airways are divided into four main segments: the trachea, the branching bronchi, the terminal bronchi, and the alveolar space. Each segment contains a unique mix of cell types that have specialized functions. (B) The lower airway, proximal to the bifurcation of the left and right bronchus, consists of mostly ciliated cells whose main function is to sweep mucus (blue) secreted by goblet cells out of the airways. Columnar and other cells (*e.g.* serous cells) also contribute to the airway barrier. Basal cells (not shown) are localized to the basement membrane but do not contribute to the tight junction barrier. (C) Distal to the tracheal bifurcation are bronchiolar cells that consist mainly of ciliated, columnar and club cells. Club cells secrete a specialized form of pulmonary surfactant as opposed to mucus and provide a transition zone between the airway and alveolar space. (D). The alveolar space is the location of gas exchange and consists mainly of squamous type I and cuboidal type II cells. Tight junctions between these cells form at apical cell–cell interaction sites. The alveolar sac maintains surface tension through surfactant secreted by type II cells preventing alveolar collapse. (E) Gas exchange occurs efficiently through type I cells, which make up the vast majority of alveolar surface area.

diameter decreases. At the most distal portion of the conducting airways are terminal bronchioles, the smallest branches of the conducting airway with a diameter of 5 mm or less. Terminal bronchioles interconnect the conducting airways with the terminal airspaces, known as alveoli, where gas exchange occurs. In contrast to the conducting airways, the terminal airspaces of the alveolar epithelium are coated with pulmonary surfactant which serves to reduce the surface tension of the air filled alveoli under the pressure of the fluid filled tissue. Thus, bronchioles serve as transition zones from the mucus dominated airspace as reflected by their distinct cellular composition [6,7]. In contrast to larger bronchioles which are dominated by ciliated and goblet cells, terminal bronchioles lack submucosal glands and are enriched for club cells (formerly known as Clara cells [8]). Instead of mucus, club cells are secretory cells that produce a form of pulmonary surfactant containing