International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Claudins in Respiratory Health and Disease

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Abstract: ***The respiratory epithelium is at the center of respiratory health and disease. The disruption of its barrier function contributes to the pathophysiology of respiratory diseases such as asthma, interstitial lung disease, infections, or cancer. Claudins are one of the major players in epithelial junctions. They can be affected by external environmental factors and induce alterations in the epithelial barrier. The profile of claudins is different in different stages of development or diseases of the lung.***

Keywords: Claudins, respiratory disease

1. Introduction

The respiratory epithelium in continuously exposed to a wide range of potentially damaging agents, such as infectious agents, pollutants, gas, car emissions, tobacco smoke, toxins, or pollens. (1, 2) The first barrier defending the respiratory tract against these offenders is the epithelial barrier. Several elements are the constituents of this barrier: surface liquids, mucus layer, cellular integrity, and junctional complexes formed between adjacent cells. (1) The integrity of each structure conditions the functionality of the barrier.

Respiratory epithelium and its functions

The respiratory tract is paved by epithelium with different characteristics based on its localization. The respiratory airways have different structures and roles in respiration.

- Conducting airways starts from the trachea and includes bronchi to the 16th generation. They can be cartilaginous or non - cartilaginous. Their role is to humidify the air, sense the irritant, and, due to mucociliary clearance remove all the foreign particles. In cartilaginous airways, the epithelium is pseudo - stratified columnar and ciliated, with many gands that produce mucus. In non - cartilaginous airways, the club cells appear and the glands disappear. (1)
- Respiratory airways continue the conducting airways, from the 17th to 23 generations of the bronchial tree. They have non - ciliated epithelium and only a few mucus secretory glands. (1)
- The alveolar epithelium consists of two types of cells - alveolar type I and type II cells with the main role in gas exchange. It also separates two main compartments, the air - filled compartment, and the liquid interstitial compartment. (1)

The cell - cell contact is of extreme importance in respiratory epithelium to ensure intact integrity and its barrier function. The epithelial cells are mechanically connected by intracellular junctions. Based on their composition and localization, the cellular junctions are:

- Tight junctions – composed of membrane proteins and scaffolding proteins. The membrane proteins can have one (junctional adhesion molecules - JAMs) or four transmembrane domains (claudins, occludin, tricellulin). Scaffolding proteins are zona occludens - 1 (ZO - 1), ZO - 2, ZO - 3, membrane - associated guanylate kinase with inverted orientation - 1 (MAGI - 1), multi - PDZ domain protein 1 (MUPP1) and cingulin and have as main role the mediation of signals from surface to cytoskeleton. (3, 4)
- Adherens junctions are represented by a transmembrane protein - E - cadherin with the role of adhesion molecule as well as intracellular signaling. (4)
- Desmosomes bond filament cytoskeleton from neighboring cells. (4)

To exercise its separatory function, the epithelium is crossed by solutes and water in a regulated manner. Transport pathways across the epithelium can be transcellular and paracellular. The transcellular pathway implies the ion movement from one side of the apical and basolateral membrane to another depending on ion channels and transporters. Paracellular transport is based on diffusion dependent on electrochemical gradients. (5)

The tight junctions are the main element that regulates cells permeability. This property is closely correlated with its protein composition. The most important perms electivity regulator is claudin composition. The thickness of tight junctions is variable along the epithelium based on the cell type. (5)

Claudins

Claudinsare a family of proteins known as regulators of the permeability of cells. This family consists of 27 members described in mammals, named 1 - 27. Claudin 13 is missing in humans. (3, 5)

In the human normal respiratory tract and lungs are expressed a number of claudins, but their disposition is different in different anatomical segments. They control the permeability of the epithelium and can be affected in various pathological conditions. The expression and level of claudins are variable with lung organogenesis stage. While claudins 1, 3, 4, 5 and 7 can be identified in the pseudoglandular and canalicular periods in the epithelium of the bronchioles, claudin 5 is lost in the alveolar period. (3, 5)

The localization and functionsof the respiratory system claudins are detailed in the following table. (1, 3, 6, 7)

Table 1: Claudins in respiratory system - localization, functions and regulatory factors (1, 3, 6, 7)

Claudin	Localization	Function	Regulation
CLAUDIN 1	Bronchial cells, alveolar cells type 1 Lateral membranes	• Sealing function • Regulate the adhesion between neighboring cells • Supressor of tumor invasion and metastasis	• Protease - activated receptor 2 • Thymic stromal lymphopoietin • Peroxisome prolifertator - activated receptor
CLAUDIN 2	Bronchial cells, alveolar cells type 2 Intracellular	• Formation of pores for water movement	• TNF - α
CLAUDIN 3	Bronchial cells, alveolar cells type 1 (represents 31%) and alveolar cells type 2 (represents 67%) Tight - junctions complexes	• increases paracellular permeability • opposite effects than claudin 4	•
CLAUDIN 4	Bronchial cells, alveolar cells type 1 (represents 10%) and alveolar cells type 2 (represents 23%) Lateral membranes	• decreases paracellular permeability • sealing function • increase alveolar water resorbtion • homeostasis of the alveolar liquid layer	•
CLAUDIN 5	Bronchial cells, alveolar cells type 1 and 2 Tight - junctions complexes	• increases paracellular permeability • increases liquid accumulation and lung injury	• NFkB • TNF - α • Virus infection
CLAUDIN 7	Bronchial cells, alveolar cells type 1 and 2 Tight - junctions and basolateral membranes	• Organisation of adhesion junctions	•
CLAUDIN 8	Bronchial cells, alveolar cells type 1 Tight - junctions complexes	• Decreases paracellular permeability • Prevents paracellular leakage of sodium • Sealing properties	• glucocorticoids
CLAUDIN 18.1	Bronchial cells, alveolar cells type 1 (represents 56% and alveolar cells type 2 (represents 18%)	• not fully defined	

Factors affecting respiratory claudins and respiratory health

Tobacco smoke increases the permeability of the tight junctions. The exposure suppressed claudin gene expression, most affected being claudin - 1, claudin - 3, claudin - 4, and claudin - 7. (3, 8, 9, 10, 11)

Pathogens such as viruses and bacteria affect tight junctions by decreasing the expression of proteins, redistribution or disruption of claudins. R*hinovirus* suppresses the expression of claudin 1 in nasal epithelial cells, *adenovirus* produces an increased permeability by matrix metalloproteinase 9. *Pseudomonas aeruginosa* destroys tight junctions that permit the invasion of respiratory epithelium. *Influenza A virus subtype H3N2* and *Respiratory Syncytial Virus* promote downregulation of the expression of claudin 1. *Varicella zoster virus* induces a decreased activity of claudins 2 and 18 in alveolar epithelial cells and H5N1 subtypes determine the loss ofclaudin4. *SARS - CoV - 2* interferes with the function of barrier of respiratory endothelium by dicreasing claudin 5 expression. (3, 5, 12, 13, 14)

Claudins, pathological conditions, and respiratory disease

Interstitial lung diseases are characterized by chronic inflammation and fibrosis that modifies the structure and function of the lungs. Changes in claudin functions were identified especially in alveolar cells or metaplastic alveolar epithelium. While in normal alveolar epithelium claudins 3, 4 and 7 are found, in metaplastic epithelium claudins 1, 2, 3, 4 and 7 could be identified. (3)

*Asthma*isa chronic inflammatory disease that affects almost 300 million people and creates a huge burden on the medical system worldwide. The pathophysiology of asthma is continuously enriched by novel discoveries. The modern approach propose a framework based on biomarkers, phenotypes, endotypes, and genotypes consistent with the description of the intimate mechanisms involved. Epithelial permeability and its constituents contribute to the development, severity, progression and treatment response in asthma. There is evidence that place airway epithelium dysfunction as a main feature in asthma. (6, 15)

Claudins participate to the epithelial dysfunction in asthma.

- Claudin 1 plays a central role in asthma pathogenesis. Studies show that in sensitized mice, claudin1 in the epithelial cells of the lung was reduced, while its

expression was increased in airway smooth muscle. It is involved inairway remodeling in asthma by regulatory effects on ASM cell proliferation, angiogenesis, and inflammation. (16, 17)

- Claudin 4 –even though this protein is described in detail for lung injury or cancer, its role in asthma pathogenesis remains unclear. Recent studies reveal that plasma levels of claudin 4 were almost 2 fold higher for asthmatic patients compared to healthy subjects. The exacerbated patients had plasma levels significantly higher than patients with stable asthma. More than that, plasma levels were correlated with FEV1%, total IgE and eosinophils. (2, 18)
- Claudins 5 and 8 are decreased in experimental asthma - eosinophilic, neutrophilic and mixed granulocytic. (4, 18)
- Claudin 18 gene in codes two variants of this protein. They are different by their first exon. Claudin 18.1 is exclusively identified in respiratory epithelium. Recent studies reveal that claudin 18.1 levels are decreased in subjects with asthma associated with T_H2 inflammation and related to total Ig E levels and blood eosinophils count. The claudin 18 levels are inversely associated with sensitization to inhaled antigens and withT_H2 inflammation. (6, 15, 19)

Lung cancer - the profile of claudins identified in tumor cells are different depending on the type of tumor. The claudin expression may be influenced by various growth factors. Claudins 1, 2, 3, 4 and 7 have different expressions: (3)

- *small cell lung carcinoma* - a sixteen times higher levels of claudin 3 were identified*;*
- *squamous cell carcinoma* – decreased claudin 1 mARN and claudin 3, 4 and 7 compared to the normal lung; (3, 20, 21)
- *adenocarcinomas* - decreased claudin 1 mARN, claudins 1, 3, 4 and 7 and increased claudin 5. In this type of cancer, the decreased expression of claudin 1 is associated with poor survival expectancy. (3, 20, 21)

In non - small cell lung carcinoma low claudin - 6 expression correlates with poor prognosis. (22)

COVID - 19– the infection induces a down - regulation of claudin 5 and this is associated with severe vascular leakage and vascular barrier dysfunction. The studies show that claudin 5 expression is almost abolished in the lungs of COVID - 19 patients. The serum levels of claudin 5 were higher in patients with moderate forms of disease compared to those experiencing severe forms. The same conclusion regarding down - regulation of claudin 5can be extended to multi system inflammatory syndrome and neuro inflammation folowing COVID - 19. (5, 23, 24)

2. Conclusion

The respiratory epithelium appears to play a central role in preserving respiratory health. Claudins, as important constituents of cellular junctions, are the new molecules of interest for many pathological conditions of the respiratory system.

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