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Claudins in Normal and Lung Cancer State

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1. Introduction

The epithelial cells form a physical barrier that serves to separate two different environments, and interact with neighboring cells through various kinds of cell-cell communication systems. Among the systems of cell-cell communications have been described 3 types of intercellular junctions: gap-junctions, adherents-junctions and tight-junctions.

The tight junctions are critical for the sealing of cellular sheets and controlling paracellular ion flux. Tight junctions are composed primarily of 3 components: The IgG-like family of junctional adhesion molecules (JAMs), occluding and claudin families. Claudins are the main constituents of tight junctions. The claudin family proteins is composed of approximately 24 transmembrane proteins, all of which are closely related, most of them are well characterized at the level of gene and protein. The claudins are present in variety of normal tissues, hyperplastic conditions, but have also been found in benign neoplasms and cancers that exhibit epithelial differentiation. Loss of claudins expression has been reported in various malignant diseases. The differential expression of several members of the family of the claudins in various cancers has been used to confirm the histological identity of certain types of cancer.

The permeability barrier in the terminal airspaces of the lung is due in large part to tight junctions between alveolar epithelial cells, which regulate the flow of molecules between apical and basolateral extracellular compartments. Disruption of the paracellular alveolar permeability barrier is a significant pathological consequence of acute lung injury. Little is known about the expression and localization of claudins in normal bronchial epithelium and lung cancer. So that is in our interest to describe the expression of claudins in normal and lung cancer, also describe the cellular and molecular mechanisms.

2. Tight junctions

The cellular polarity is critical for a variety of cellular functions, such as directed migration, asymmetric cell division and the vectorial transport of molecules. Polarity is studied in

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epithelial cells where apical and basolateral surface domains with different lipid and protein compositions can be distinguished (Steed, et al., 2010). In vertebrate epithelia, the two membrane domains are separated by tight junctions (TJ), who act as an intramembrane diffusion barrier and also as a paracellular seal that prevents diffusion of molecules across the epithelial cell layer. TJs are structures appearing as discrete sites of fusion between the outer plasma membrane of adjacent cells. The TJ regulates the diffusion of solutes with size and charge selectivity and that it is functionally different in physiologically diverse epithelial cell types. To understand the molecular mechanism controlling TJ structure and function, it is important to determine their molecular composition and organization (Anderson & Cereijido 2001; Steed, et al., 2010).

2.1 Tight junction molecular structure

The molecular components of the TJ have been separated into 3 groups: 1) The integral transmembrane proteins, 2) The peripheral or cytoplasmic and 3) TJ-associated/regulatory proteins. 1) The integral transmembrane proteins are essential for correct assembly of the structure: occludin, claudins and junctional, immunoglobulin superfamily membrane proteins with two extracellular Ig-like domains, including JAM-A, JAM4, coxsackie adenovirus receptor (CAR), and endothelial cell-selective adhesion molecule (ESAM). The integral transmembrane proteins are the critical for correct assembly of the TJ structure and controlling TJ functions via homotypic and heterotypic interactions. 2) The peripheral or cytoplasmic or plaque anchoring proteins: the membrane-associated guanylate kinase (MAGUK) family proteins ZO 1, ZO 2, and ZO 3 bind to the C-terminal cytoplasmic domain of claudins, occludin, tricellulin, and JAM-A. In addition, MAGI-1, MAGI-3, MUPP1, PATJ and ASIP/PAR3 are known to be PDZ domain-containing proteins that directly bind to claudins or other TJ-associated membrane proteins. The plaque anchoring proteins act as a scaffold to bind the raft of TJ molecules together and provide the link to the actin cytoskeleton and the signaling mechanism of the cell. 3) TJ-associated/regulatory proteins – α -catenin, cingulin, paracingulin, etc., (for review see: Blasig, et al., 2006; Furuse 2010; Hamazaki, et al., 2002; Itoh, et al., 1999, Tsukita & Furuse 2000a, 2000b).

2.2 Paracellular transport

Separation of functional compartments is necessary for higher organisms. The structures that separate such compartments, epithelia and endothelia, consist of cell layers with diverse properties according to the organism's actual demands. While such structures prevent uncontrolled diffusion and convection of substances, they also provide selective transport processes via secretion (exocrine and endocrine glands), absorption (intestine), or reabsorption (kidney). Such transport processes are realized via the transcellular pathway involving resorption across the apical membrane, transfer through the cytoplasm, and extrusion at the basolateral membrane. In general, transcellular transport is an energy-dependent process, but it allows the organism to reabsorb substances that are indispensable, even against an existing electrochemical gradient. Moreover, since this pathway is controlled at several steps, it allows fine-tuning according to actual demands. On the other hand, paracellular transport occurs through the intercellular space of

adjacent cells. This transport is passive and dependent on an electrochemical gradient. This form of transport allows bulk reabsorption with a minimum of energy expenditure. The key structure of the intercellular space, and thus the major determinant of paracellular transport, is the tight junction (TJ). The ion conductance of tight junctions varies from tissue to tissue and can be experimentally manipulated by expressing or removing specific pores. The specificity of these pores is determined by the claudin composition and, more precisely, by the properties of their extracytoplasmic loops, such as electrostatic interaction sites. The molecular mechanisms that underlie size-selective paracellular diffusion are unclear. However, several studies reported a functional dissociation between transepithelial electrical resistance and size-selective paracellular diffusion upon specific modifications of either junctional components or signaling pathways that affect permeability. Thus, the molecular bases of ion-selective and size-selective permeation seem to be distinct (see Figure 1) (Amasheh, et al., 2009; Steed, et al., 2010; Tsukita & Furuse 2000a, 2000b; Will, et al., 2008).

3. Claudins

The tight junctions consist of several components: integral membrane proteins, cytoplasmic proteins and cytoskeletal proteins (Brennan, et al., 2010). To date, a number of integral membrane proteins are associated with TJ, occludin, adhesion molecules, claudin family, etc., (Tsukita & Furuse 2000a, 2000b, Dhawan, et al., 2005; Furuse, 2010). Gradually has been shown that the molecular architecture of these complex is more numerous, the TJ is made up of at least 40 different components (Figure 1) (for review see: Schneeberger & Lynch, 2004; <http://www.genome.jp/kegg/pathway/hsa/hsa04530.html>). Among the elements that form part of integral membrane proteins, the claudin family (Clds; present active infinitive of *claudēō*, means close), has attracted the attention because of its relatively recent identification, the family includes 24 members in mammals (Furuse 2010, Brennan, et al., 2010), although Tsukita group recently has reported three new genes that code for Cldns 25, 26 and 27 (Mineta, et al., 2011). The Cldns were identified in 1998 by Dr. Tsukita in membrane fractions from chicken liver (enriched with TJ) through sucrose gradients. Among the protein components two bands of 23 kDa were obtained, with similar in size but not identical. Analysis of the amino acid sequence showed that these proteins were structurally related (30% identical at the amino acid sequence), calling claudin 1 and 2, respectively (Furuse et al., 1998). However, earlier reports this had already been described genes with similar sequences (Briehl & Miesfeld, 1991, Katahira, et al., 1997). This information allowed proposes the existence of a large family of proteins. Currently there are over 558 articles that involve claudins studies (updated to April 20, 2011), describing various aspects of molecular, cellular, regulation, operation, including its expression/co-expression, localization in tissues and organs, and their potential involvement in diseases.

Before the discovery of the claudins, it is believed that the tight junctions were composed mainly of occludin. Even thought that occludin and claudin were members of the same family, but the report of the genetic sequence of the Cldns confirmed that these were different from those occludins proteins, and showed no similarity between them (Furuse, et al., 1998a). To date is accepted that the central part proteins responsible for the paracellular barrier are the claudins (Angelow, et al., 2008, Tsukita & Furuse, 2000).

Claudins are found in the tight junction at the interface of the basolateral and apical membranes of polarized epithelial and endothelial cells, and also at paranodes in compact myelin. Transfected claudins are capable of forming tight junction ‘strands’ or ‘fibrils’, the freeze-fracture descriptions of a branching and anastomosing network of rows of intramembranous particles characteristic of tight junctions. Claudins are also found in the basolateral membranes, possibly as precursors to the fibrils (Peter & Goodenough 2004).

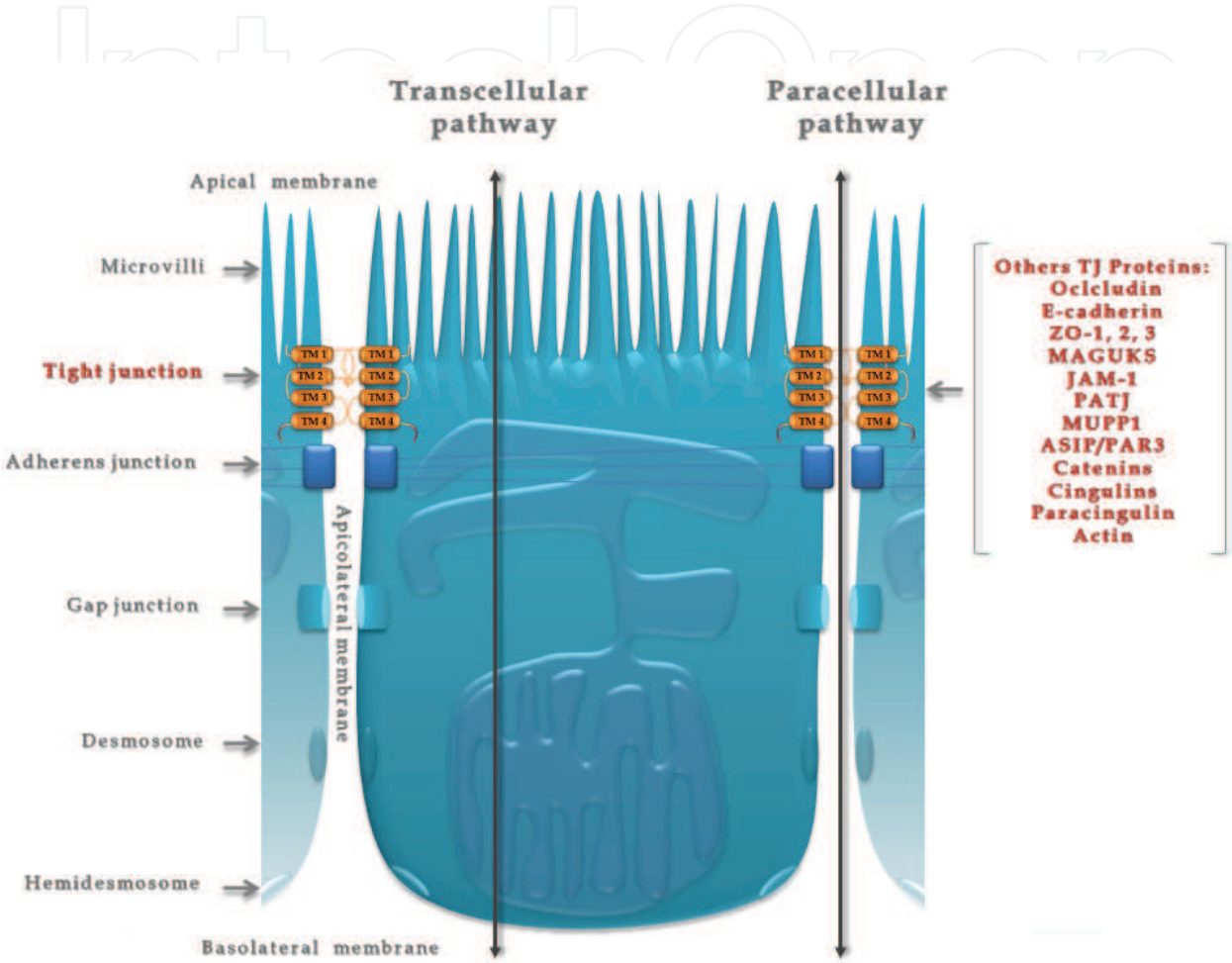


Fig. 1. Schematic diagram of the molecular organization of epithelial.

Cell-cell interactions are mediated by intercellular junctional complexes: gap junctions, adherent junctions, desmosome and thigh junctions, each of which have different had asymmetric distribution in epithelial cells, TJ are located at the apical-basal border and they contribute to maintain cell polarity, regulate the solute and fluid exchange between basolateral and apical domains, and also regulated paracellular permeability. TJ membrane proteins are linked to the cytoskeleton (F-actin) via a complex network of adaptor proteins.

3.1 Claudin evolution

The mechanism by which the family of claudins evolves is unknown; however, the data suggest that this family expanded by gene duplication early in the evolution of chordates

(for review sees: Lal-Nag & Morin 2009, Loh, et al., 2004, Kollmar, et al., 2001). When the septate junctions (the corresponding structure of invertebrates), were replaced by tight junctions. In the same way as other groups of genes were extended, the claudins diversified into the body of vertebrates from the chordates, leading to new structures: the skull, pairs of sense organs and appendages (Kollmar, et al., 2001). The search for claudins in the Genbank of *Drosophyla melanogaster* and *Caenorhabditis elegans* showed no similarity to genes previously reported (Venter & Adams, 2001; Kolmar, et al., 2001). However, in *D. melanogaster*, was recently found three genes, which encode for three different proteins that are required in the paracellular transport: Megatrachea (Mega) Sinuous (Sinu) and Kune Kune. Mega, a transmembrane protein homologous to claudins, and show that it acts in septate junctions, this protein has transepithelial barrier function similar to the claudins, and is necessary for normal tracheal cell morphogenesis but not for apico-basal polarity or epithelial integrity (Behr, et al., 2003). The gene sinuous encodes a protein that is molecularly and functionally similar to vertebrate claudins. Sinuous share several characteristic with vertebrate claudins as has all of the amino acids absolutely conserved across vertebrate claudins and has as much sequence similarity to canonical vertebrate claudins as do some of the more divergent vertebrate claudins. Also has functional similarity because it localizes to and is required for the function of paracellular barrier junctions (Wu, et al., 2004). Kune Kune, this protein localizes to septate junctions and is required for junction organization and paracellular barrier function, but not for apical-basal polarity (Nelson, et al., 2010). In *C. elegans* genome database identified four claudin-related, 20-kDa integral membrane proteins (CLC-1 to -4), which showed sequence similarity to the vertebrate claudins. The expression and distribution of CLC-1 was mainly expressed in the epithelial cells in the pharyngeal region of digestive tubes and colocalized at their intercellular junctions. In CLC-1-deficient worms, the barrier function of the pharyngeal portion of the digestive tubes appeared to be severely in experiments performed with RNA interference. CLC-2 was expressed in seam cells in the hypodermis, and it also appeared to be involved in the hypodermis barrier (Asano, et al., 2003). In addition VAB-9 is a predicted four-pass integral membrane protein that has greatest similarity to BCMP1 (brain cell membrane protein 1, a member of the PMP22/EMP/Claudin family of cell junction proteins) and localizes to the adherents junction domain of *C. elegans* apical junctions. In this nematode *C. elegans* protein VAB-9 regulates adhesion and epidermal morphology (Simske, et al., 2003). In *Danio rerio* (Zebra fish) have been located at least 15 genes for Cldns, some of which have their orthologous in human (Kollmar, et al., 2001), and among non-vertebrate *Halocynthia roretzi* (Sea pineapple) as also found a gene that encodes to claudins (Kollmar, et al., 2001). The presence of these genes suggests that the origin of the claudins may be quite ancient and that a claudin ancestor pre-dates the establishment of the chordates (Kollmar, et al., 2001).

3.2 Claudin structure

The claudins belong to the peripheral myelin protein (PMP22)/ epithelial membrane protein (EMP)/ epithelial membrane protein or membrane protein (MP20)/claudin superfamily of four transmembrane-spanning domains. The 24 mammalian members are 20 to 34 kDa in size (Lal-Nag & Morin, 2009, Peter & Goodenough 2004), and recently others members of the claudin family 25, 26 and 27 were reported (Mineta, et al., 2011). The proteins are

predicted, on the basis of hydropathy plots, to have four transmembranal helices (Morita, et al., 1999; Lal-Nag & Morin, 2009), with their NH₂- and COOH-terminal tails extending into the cytoplasm (Lal-Nag & Morin, 2009). Sequence analysis of Cldns has led to classification into two groups: classic claudins (1–10, 14, 15, 17, 19), and non-classic claudins (11–13, 16, 18, 20–24) (Table 2), according to their degree of sequence similarity to conserved structural features at ECL1 for classic claudins (Krause, et al., 2008). The typical claudin protein contains a small intracellular cytoplasmic NH₂-terminal sequence of approximately 4 to 5 residues followed by a huge extracellular loop (EL1) of approximately 60 residues, a short 20-residue intracellular loop, another extracellular loop (EL2) of about 24 residues, and a COOH-terminal cytoplasmic. The size of the COOH-terminal tail is more variable in length; it is typically between 21 and 63 residues. The amino acid sequences of the first and fourth transmembrane domains are highly conserved among Cldns, and the second and third are more diverse. The first loop contains several charged amino acids and, as such, is thought to influence paracellular charge selectivity, and two highly conserved cysteine residues are hypothesized to increase protein stability by the formation of an intramolecular disulfide bond. It is assumed that the first extracellular loop is critical for determining the paracellular tightness and the selective paracellular ion permeability (see Table 2). It has been suggested that the second extracellular loop, can form dimers with Cldns on opposing cell membranes through hydrophobic interactions between conserved aromatic residues and that the second extracellular loop may cause narrowing of the paracellular cleft (Lal-Nag & Morin 2009; Krause, et al., 2008, 2009).

The region that shows the most sequence and size heterogeneity among the claudin proteins is the COOH-terminal tail. It contains a PDZ-domain-binding motif that allows claudins to interact directly with cytoplasmic scaffolding proteins, such as the TJ-associated proteins MUPP1, PATJ, ZO-1, ZO-2 and ZO-3, and MAGUKs (see figure 1 and 2). Furthermore, the COOH-terminal tail upstream of the PDZ-binding motif is required to target the protein to the TJ complex, and also functions as a determinant of protein stability and function. The COOH-terminal tail is the target of various post-translational modifications, such as serine/threonine and tyrosine phosphorylation and palmitoylation, which can significantly alter claudin localization and function. Most cell types express multiple claudins, and the homotypic and heterotypic interactions of claudins from neighboring cells allow strand pairing and account for the TJ properties, although it appears that heterotypic head-to-head interactions between claudins belonging to two different membranes are limited to certain combinations of claudins, and stoichiometry have yet to be determined (Lal-Nag & Morin, 2009; Peter, & Goodenough 2004).

The extracellular domains of claudins in one cell are thought to interact with those in an opposing cell to form a new class of ion channel (see Figure 1). These channels confer ion selectivity to the paracellular pathway between luminal and basolateral extracellular compartments. The permeability properties of the paracellular pathway have the biophysical characteristics of conventional ion channels, including ion selectivity, anomalous mole fraction effects, pH dependence and a diameter of ~6Å. Exchanging the first extracellular loop between claudin-2 and claudin-4 changes the Na⁺ and Cl⁻ selectivity of the paracellular pathway in cultured epithelial cells (Peter & Goodenough 2004; Ben-Yosef, et al., 2003).

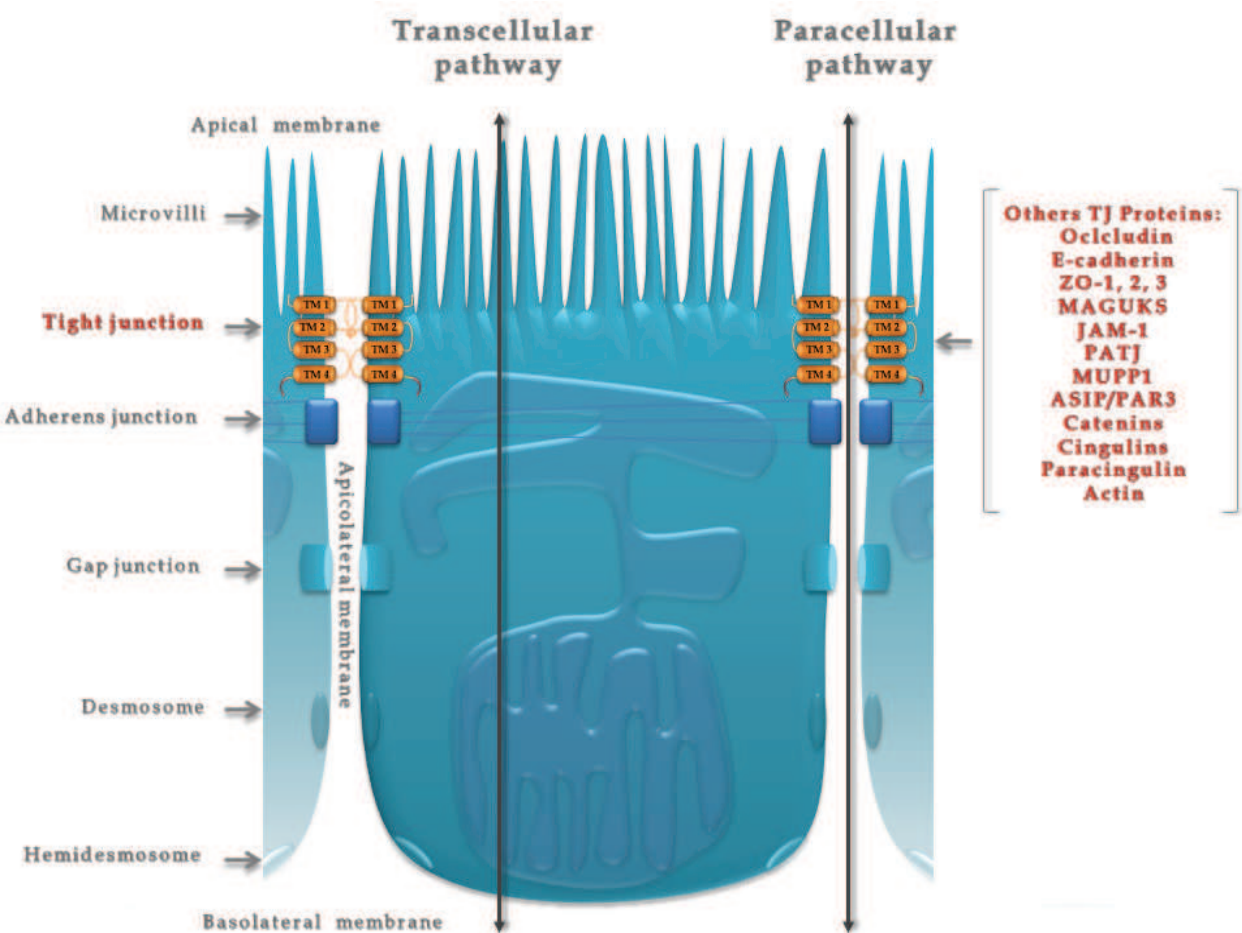


Fig. 2. Schematic representation of structure and molecular interactions of typical claudins. Claudins are proteins with four transmembrane-spanning domains (TM 1, TM 2, TM 3, and TM 4), two extracellular loops (EL1 and EL2) related with paracellular ion selectivity and oligomerization respectively. The NH₂ and COOH terminal are localized in the cytosol, intracellular loops are posttranscriptional modify. COOH terminal contains PDZ-binding domain that is important for signal transduction.

4. Epithelial cells

Epithelia have three basic functions in multicellular organisms, first, cover the outer surface of the body and the cavities and formed a physical barrier that separates two environments. This physical barrier provides protection against mechanical damage, the entry of microorganisms and water losses. Epithelia are also involved in secretion and absorption process. These three functions of epithelia are given primarily by the type of cellular arrangements that characterizes them. Epithelial cells are polarized and form sheets of cells attached to each other through complex mechanisms. Some of these mechanisms of cell-cell interactions will be discussed in this chapter. Thus in an epithelial cell it can distinguish two basic functional components: a) the basal domain and b) the apical domain (Feing & Muthuswamy, 2009). The basal domain participated in cell-

extracellular matrix (ECM) interactions; in particular, it is in contact with a structure formed by type IV collagen, laminin and proteoglycans called basal lamina (Gumbiner, 1996). The basal lamina allows epithelial cells to be attached to the underlying connective tissue. In specialized epithelial tissue basal domain is also involved in endocrine secretion. The apical domain is located in the opposite direction of the basal. Depending on its functions basal domain is involved in exocrine secretion and absorption. Alternatively, another fundamental property of epithelial tissue is the close cohesion between the cells, which allows the formation adherents selectively permeable layers that are at once very strong mechanical barriers. Cell-cell interactions are mediated by intercellular junctional complexes that consist of gap junctions (GJ), adherent junctions (AJ), desmosomes (Ds) and thigh junctions (TJ), each of which have different functions and properties (Itoh & Bissell et al., 2003; Feing & Muthuswamy, 2009). These junctional complexes had asymmetric distribution in epithelial cells, TJ are located at the apical-basal border and they contribute to maintain cell polarity, regulate the solute and fluid exchange between basolateral and apical domains, and also regulated paracellular permeability (Itoh & Bissell et al., 2003; Feing & Muthuswamy, 2009). TJ are widely explained in section 3 of the present chapter. On the other hand, AJ are basal to TJ and they are considered the primary determinants of cell-cell adhesion. AJ are ubiquitously represented by cadherins, transmembranal Ca^{2+} -dependent receptors, which form complex with catenins, cytoplasmic plaque proteins, and actin cytoskeleton. Cell adhesion regulates the organization of cell patters and architecture of tissues (Gumbiner, 1996). In epithelia, it can be found different cell shapes (flat, cylindrical or cubic) in at least three basic forms of cell arrangement, a) simple epithelia (single sheet of cells), b) stratified (multiple cell sheets) and c) pseudostratified (single sheets of cells with several sizes and shapes that give the appearance of true stratified epithelia).

4.1 Lung epithelial cells

The adult human lung is lined by specialized types of airway epithelia organized in tree-like form with three anatomical and functional units: a) trachea and bronchi (tracheobronchial), b) bronchioles and acinar ducts (bronchiolar), and c) peripheral saccular-alveolar structures (alveoli) (Maeda, et al., 2007). Tracheobronchial and bronchiolar units form conducts that provide inhaled gases to alveoli unit, there; epithelial alveolar cells and capillaries exchange oxygen and carbon dioxide required for respiration (Maeda, et al., 2007). Each of these airway units is composed of distinct types of epithelial cells that are important for maintaining normal lung function, in Table 1 is shown a summary of the main types of intrapulmonary epithelial cells with their respective function.

Trachea and bronchi are characterized by pseudostratified epithelia, whereas bronchioles, acinar ducts and alveoli are mainly characterized by simple cubic epithelia. Epithelial cells throughout of airway show major functions such as protection (Ciliated cells), progenitor cells (Basal and Clara cells), exocrine secretion (Goblet, Clara and Alveolar type II cells), endocrine secretion (Neuroendocrine pulmonary cells), and gas exchange (Alveolar type I cells) (Table 1) (Herzog, et al., 2008; Linnoila, 2006; Maeda, et al., 2007; Reynolds, et al., 2007; Rock, et al., 2010; Rogers, 2007).

Airway unit	Epithelia type	Epithelial cell types	Cell function	Biomarkers
T R A C H E O B R O N C H I A L	Pseudo-stratified	Goblet	Mucus secretion	Mucin 5AC (MUC5AC)
		Basal	Attachment with the basement membrane; Progenitor cells	Transcription factor p63, cytokeratins 5 and 14
		Clara	Mucus secretion; Mucocilliary clearance; Detoxify xenobiotics and oxidant gasses; Progenitor of ciliated cells; Regulation of immune system	Uteroglobin, Surfactant apoproteins A, B and D
		Ciliated	Mucocilliary clearance	Calpastatin, ezrin
B R O N C H I O L A R	Simple columnar-cuboidal	Clara	See above	See above
		Ciliated	See above	See above
		Pulmonary neuroendocrine cells	Endocrine and paracrine secretion in lung development; Oxygen sensors	Gastrin-releasing peptide, bombesin, calcitonin gene-related peptide, synaptophysin
A L V E O L I	Simple columnar	Alveolar type I cells (squamous cells)	Mediate gas exchange	T1- α , aquaporin-5 (AQP-5)
		Alveolar type II cells	Synthesis, secretion and recycle the lipid and protein component of surfactant Innate immunity	Surfactant apoprotein C and ATP-binding cassette A3 (ABCA3)

Table 1. Characteristics of intrapulmonary epithelia of human. Sources: Herzog, et al., 2008; Linnoila, 2006; Maeda, et al., 2007; Reynolds, et al., 2007; Rock, et al., 2010; Rogers, 2007.

The complex patterns of intrapulmonary epithelial cells, organization, numbers and types of cells, are regulated by several humoral signals and cell-cell interactions. It is know that

several physiopathological conditions could modify the lung epithelial cell pattern such as infection, cytokines, inflammatory mediators, pollutants and injury that are associated with common airway diseases, including chronic obstructive pulmonary disease, asthma, cystic fibrosis and cancer (Ballaz & Mulshine, 2003; Maeda, et al., 2007; Rock, et al., 2010).

4.2 Lung cancer

Lung cancer is one of the most important epithelial neoplasias in the world with high incidence and mortality (Jemal, et al., 2011). Currently lung cancer is the most commonly diagnosed cancer, as well as, the leading cause of cancer death in males worldwide. Among females, it represents the fourth most commonly diagnosed cancer and the second leading cause of cancer death. Even more, lung cancer is the leading cause of cancer-related deaths around the world, accounting for more deaths than those caused by three of the most diagnosed cancers combined (prostate, breast and colorectal cancers). In 2008 estimated lung cancer related deaths worldwide were 1,378,400 whereas estimated related cancer deaths by prostate, breast and colorectal cancers were 1,004,900 (Jemal, et al., 2011). Moreover, whereas the five-year survivor over time was improved in prostate, breast and colorectal carcinomas in last 15 years, at 99%, the five-year survivor rate of lung cancer was relatively unchanged at 15% (Borczuck, et al., 2009; Schwartz, et al., 2007). The high mortality of lung cancer could be explained in part by histological heterogeneity and late detection (Borczuck, et al., 2009; Schwartz, et al., 2007). On the other hand, smoking is the most important cause of lung cancer, 80-90% of lung cancer cases are associated with smoking but only 15% of the smokers developed lung cancer and 10% of lung cancers occur in never-smokers (Borczuck, et al., 2009; Schwartz, et al., 2007). Other lung carcinogens are asbestos, arsenic, radon, polycyclic aromatic hydrocarbons and air pollution (Jemal, et al., 2011). The World Health Organization (WHO) reported that the cancer is a leading cause of death worldwide and accounted for 7.6 million deaths (around 13% of all deaths) in 2008. The main types of cancer are: lung (1.4 million deaths), stomach (740 000 deaths), liver (700 000 deaths), colorectal (610 000 deaths) and breast (460 000 deaths). More than 70% of all cancer deaths occurred in low- and middle-income countries. Deaths from cancer worldwide are projected to continue to rise to over 11 million in 2030 (<http://www.who.int/mediacentre/factsheets/fs297/en/index.html>).

Lung cancer is divided into two histological types, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC is the most common lung cancer; it represents between 80-85% of cases and consists in a heterogeneous group of cancers that can divide into three major subtypes: squamous cell carcinoma (SCC), adenocarcinoma (AC) and large-cell carcinoma. This histological heterogeneity is only the reflection of lung cancer biology complexity and it has very important implications in initiation, treatment and prognosis.

Multi-step models of carcinogenesis, genetic and genomic approaches are developed to understand lung carcinogenesis (Borczuck, et al., 2009; Schwartz, et al., 2007; Wistuba, et al., 2002). In this way, an emergent field of lung carcinogenesis is open, the role that play the loss of polarity and dysregulation cell-cell adhesion molecules in initiation and invasion process of cancer cells.

CLDN	Aa	MW	CI	Transport	Organism	Detection	Disease
1	211	22,744	C	PT	H, C, R, M, D, Cw	Protein RTi_PCR	Up: LC-S Down: LC-A
2	230	24,549	C	PT: Na ⁺ , K ⁺ , water	H, C, R, M, D,Cw, G	RTi_PCR	
3	220	23,319	C	PB: mono, divalent ions;	H, C, R, M		
4	209	22,077	C	PB: Na ⁺ PT: Cl ⁻	H, C, R, M	RTi_PCR	Up: P-MC
5	218	23,147	C	PB	H, C, R, M	RTi_PCR	Up: LC-A Down: LC-S
6	220	23,292	C		H, C, R, M		
7	211	22,390	C	PB: Na ⁺ PT: Cl ⁻	H, C, R, M	RTi_PCR	
8	225	24,845	C	PBdivalent cations	H, C, R, M	RTi_PCR	
9	217	22,848	C	PT: Na ⁺ , K ⁺	H, R, M	RTi_PCR	
10	a: 226 b: 228	24,251 24,488	NC NC		H, C, R, M H, C, R, M		
11	207	21,993	NC		H, C, R, M		
12	244	27,110	NC		H, C, R, M	RTi_PCR	
13					M		
14	239	25,699	C	PB: K ⁺	H, C, R, M	IE	
15	228	24,356	NC		H, C, R, M		
16	305	33,836	NC	PT: Na ⁺ , cations	H, C, R, M	RTi_PCR	
17	224	24,603	C		H, C, R, M		
18	a: 261 b: 261	27,856 27,720	NC NC		H, C, R, M H, C, R, M	RTi_PCR	
19	a: 224 b: 211	23,229 22,076	C C	PT: Na ⁺ cations	H, C, R, M H, C, R, M		
20	219	23,515	C		H, C, R, M		
21	229	25,393	NC		H, C, M		
22	220	25,509	NC		H, C, R, M		
23	292	31,915	NC		H, C, R, M		
24	205	22,802	NC		H, C, R, M		
25	276				M		
26	223				M		
27	320				M		

Table 2. Molecular characteristics of claudins. Gene; Aminoacids (Az); Molecular Weight (MW); Classification: Classical (C) and Non-Classical (NC); Paracellular Transport (PT) and Paracellular Barrier (PB); Organism: Human (H), Chimpanzee (C) Rat (R), Mouse (M), Dog (D), Cow (Cw), Chicken (G); Lung expression: Real-time PCR (RT_PCR); Disease type: Adenocarcinoma (LC-A), Lung Cancer (LC-S), Pleura (metastatic adenocarcinoma) (P-MC). Source: Amasheh, et al., 2009; Angelow, et al., 2006; Hewitt, et al., 2006; Hou, et al., 2006; 2007, 2008, 2009; Krause, et al., 2008; Milatz, et al., 2010; Mineta, et al., 2011; Singh, et al., 2010; Wen, et al., 2004; <http://www.genecards.org/>.

4.3 Claudins and lung cancer

The tight junctions exist in lung epithelium, but knowledge of their development, normal, disease and cancer phases, but exact function and distribution in the developing and adult human lung is incomplete. Epithelial cells often express multiple claudin types, and they show a variable expression profile in different epithelia. Similarly, expression of different claudins varies between different types of epithelial, endothelial and mesothelial tumors (Kaarteenaho, et al., 2010). The expression of the different claudins during ontogenesis of human lung might vary since they have distinct expression profiles in normal human lung (Kaarteenaho, et al., 2010). Disruption of the paracellular alveolar permeability barrier is a significant pathologic consequence of acute lung injury. The permeability barrier in terminal airspaces of the lung is due in large part to tight junctions between alveolar epithelial cells, which regulate the flow of molecules between extracellular apical and basolateral compartments (Boitano, et al., 2004). In humans, very little is known about the expression and localization of claudins in normal bronchial epithelium and also in lung cancer. The expression of different claudins was studied in freshly excised human airways using immunofluorescence staining and confocal microscopy bronchi and bronchioles expressed claudins 1, 3, 4, 5, and 7, but not claudins 2, 6, 7, 9, 11, 15, and 16 (Coyne, et al., 2003). Claudins 1, 3, 4, 5, and 7 are expressed in developing human lung from week 12 to week 40 with distinct locations and in divergent quantities. The expression of claudin 1 was restricted to the bronchial epithelium, whereas claudin 3, 4 and 7 were positive also in alveolar epithelium as well as in the bronchial epithelium. All claudins studied are linked to the development of airways, whereas claudin 3, 4, 5 and 7, but not claudin 1, are involved in the development of acinus and the differentiation of alveolar epithelial cells (Kaarteenaho, et al., 2010). In human lung tumors by using cDNA microarray and in large cell carcinomas relatively low levels of claudin-4 and 7 expressions were found as compared with other types of lung cancer, such as adenocarcinoma, squamous cell carcinoma and small cell lung cancer (Garber, et al., 2001). Claudin 1 expression was stronger in squamous cell carcinomas than in adenocarcinomas, whereas claudin 4 and claudin 5 expression was stronger in adenocarcinomas (Jung, et al., 2009). 10 Hydroxycamptothecin (HCPT) elicits strong anti-cancer effects and is less toxic making it widely used in recent clinical trials, HCPT-loaded nanoparticles reduced the expression of cell-cell junction protein claudins, E-cadherin, and ZO-1, and transmission electron microscopy demonstrated a disrupted tight junction ultrastructure (Zhang, et al., 2011). Keratinocyte growth factor (KGF) augments barrier function in primary rat alveolar epithelial cells grown in culture, specifically whether KGF alters tight junction function via claudin expression. KGF significantly increased alveolar epithelial barrier functions in culture as assessed by transepithelial electrical resistance (TER) and paracellular permeability (LaFemina, et al., 2010). Alveolar epithelial cells cultured for 5 days formed high-resistance barriers, which correlated with increased claudin-18 localization to the plasma membrane (Kolval, et al., 2010). Bronchial BEAS-2B cells and SK-LU1 cells respond to tobacco smoke by changing their claudin mRNA synthesis and resulting tight junction permeability changes may thus contribute to tobacco induced carcinogenesis both during initiation and progression (Merikallio, et al., 2011). Zeb1 and twist regulate expression of genes which take part in epitheliomesenchymal transition (EMT). Carcinomas metastatic to the lung showed a significantly higher expression of these transcriptional factors than primary lung tumors, indicating their probable importance in the metastatic process. Zeb1 and twist were inversely associated with several claudins, indicating a role in their down-regulation (Merikalio, et al., 2011).

Despite many questions, recent insights into the molecular structure of tight junctions and claudins are beginning to explain their important physiological differences and contribution to paracellular transport and their importance in several disease and neoplasias, as well as, in healthy tissues.

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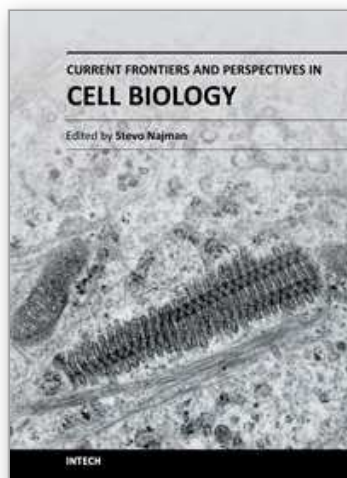
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