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A REVIEW ON CLAUDIN MODULATORS

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ABSTRACT

Claudins are tetra-span integral membrane proteins found in tight junctions. They are expressed in epithelia and endothelia and form paracellular barriers and pores that determine tight junction permeability. The name "Claudin" derived from the Latin word "Claudere", which means "to close". While tight junctions require the coordinated activity of such proteins the specificity of tight junction permeability is regulated by claudins. Claudin-modulators are promising molecules for drug delivery system. They are able to modulate the tight junctions. This review summarizes different types of claudin gene family and discusses the recent advances in their structure, interactions, regulation and physiological functions.

KEYWORDS: *Claudins; paracellular barriers; tight junction; Clostridium perfringens enterotoxin; claudin modulators.*

INTRODUCTION

Development of a new drug is based on pharmacogenomics and molecular target. New tight junction modulators, designed to interact directly with tight junction proteins or regulating molecules are promising candidates to improve the drug delivery. Claudin-modulators are promising molecules for drug delivery system. They are able to modulate the tight junctions. Tight junctions composed of multiple components. In tight junctions consists of the tetra-span integral membrane proteins are known as Claudins. They are essential for tight junction formation and functions. The name "Claudin" derived from the Latin word "Claudere", which means "to close". While tight junctions require the coordinated activity of such proteins the specificity of tight junction permeability is regulated by claudins.[1, 2, 3].

Claudins are integral membrane proteins found in tight junction of all epithelia and endothelia. They were first identified in a purified junctional fraction from chicken liver. They are major structural components of the tight junctions and act as barrier forming proteins. Claudin gene family consists of 24 members which are able to determine the tissue, charge, size selectivity of the paracellular seals. But Claudin-13 is missing in humans. Experimental studies showing that over-expression, knock-out or knock-down and mutations of Claudins, consistently cause changes in paracellular permeability. Down-regulation of Claudins contributes to epithelial transformation by increasing the paracellular permeability of nutrients and growth factors to cancerous cells. In the cases up-regulation of Claudin expression, barrier function of cancerous epithelia changes, as they often display a disorganized arrangement of tight junction strands with increased permeability to paracellular markers.[4,6]

The drug delivery of Pharmaceutical agents was improved through tissue barriers by drug enhancing methods. The methods design to freely modulate the functions of Claudin system and allow delivering drugs to a target tissue via paracellular route. The epithelial and endothelial barriers of the human body are major obstacles for drug delivery to the systemic circulation. Claudins not only used as biomarkers for cancer detection and diagnosis but also possible therapeutic targets for cancer treatments, though the mechanisms of Claudin regulation. These proteins which in turn, provide new approaches for targeted therapy of various diseases.[6,7]

GENE EVOLUTION AND HISTORY OF CLAUDINS

The biological compartments are separated by epithelial or endothelial barrier. The transport of molecules between these compartments can occur by paracellular diffusion. In vertebrates, the tight junctions (TJs) are responsible for forming the seal that controls paracellular transport. TJs are composed of multiple components, but the tetra-span integral membrane Claudins are essential for TJ formation and function. Total 24 Claudin (CLDN) genes have been found in mammals. But Claudin-13 (CLDN-13) is missing in humans and chimpanzees whereas mice and rats have all 24. The exact mechanisms of Claudin evolution remain unknown, although the Claudin multi-gene family expanded and evolved via gene duplications early in chordate development. The genome of the puffer fish “Takifugu” has a large number of Claudin genes (at least 56) as the result of extensive gene duplication. Claudin-like genes also present in lower chordates as well as in invertebrates (Drosophila).

In general, CLDN genes consist of few introns and several lakhs introns altogether. Several pairs of CLDN genes are very similar to each other in sequence and in intron/exon arrangement are located in the human genome, such as CLDN-6 and CLDN-9, which are located on chromosome 16. CLDN-22 and CLDN-24 on chromosome 4, CLDN-8 and CLDN-17 on chromosome 21 and CLDN-3 and CLDN-4 on chromosome 7 are also located. This genomic structure suggests gene duplication as a crucial driving force in the generation of many of these Claudins. Whether the genomic arrangement leads to coordinate regulation is currently unknown but, at least in the case of CLDN-3 and CLDN-4, co-ordinate expression has been reported in several normal and neoplastic tissues and expression of these genes is frequently simultaneously elevated in various cancers. The other Claudin genes are dispersed on several human chromosomes, including the X chromosome. The Claudin proteins show a wide range of sequence similarity. Phylogenetic analysis of the human Claudins demonstrates very strong sequence relationships between some of them, such as CLDN-6 and CLDN-9, whereas other Claudins are more distantly related (Fig. 1). According to expression pattern and functions the Claudin family divided into two, 'classic' and 'non-classic' groups.

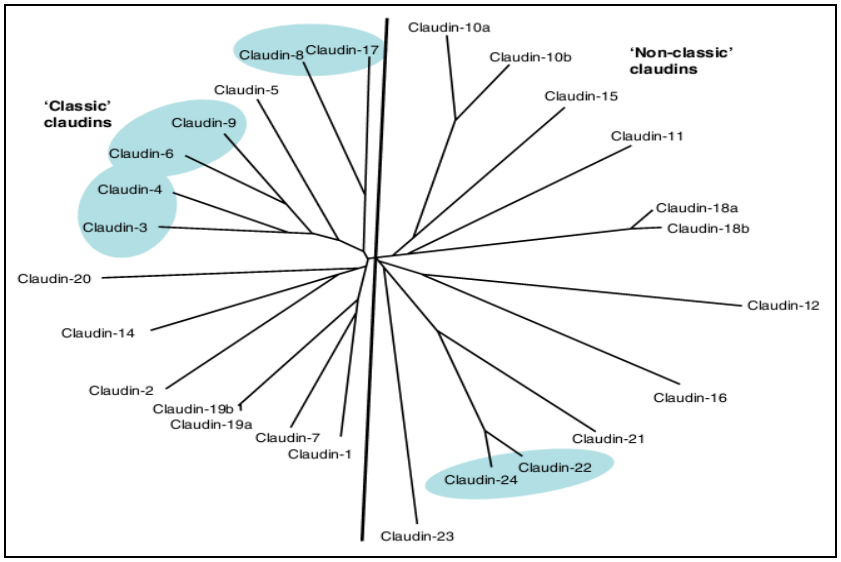

Fig.1 Types of claudins.

STRUCTURAL FEATURES OF CLAUDINS[8]

The Claudins belongs to the Claudin super family of tetra-span membrane proteins with 20 to 30 kDa in size. The structure consists of four trans-membrane helices with their amino and carboxy terminal tails extending into the cytoplasm. The typical Claudin protein contains a short intracellular cytoplasmic amino-terminal sequence followed by a large extracellular

loop (EL1) of 60 residues, a short 20-residue intracellular loop, another extracellular loop (EL2) of about 24 residues and a carboxy-terminal cytoplasmic tail. The amino acid sequence of first and fourth trans-membrane regions are highly conserved among different Claudin isoforms; the sequences of the second and third are more diverse. The first loop contains several charged amino acids and as such influence is thought to influence paracellular charge selectivity. Two highly conserved cysteine residues are present in the first extracellular loop and to increase protein stability by formation of an intracellular disulfide bond. The second extracellular loop, by virtue of its helix-turn-helix motif conformation, can form dimers with Claudins on opposing cell membranes through hydrophobic interactions between conserved aromatic residues. It also contains a PDZ (Protein-protein interaction site) domain-binding motif that allows Claudins to interact directly with cytoplasmic scaffolding proteins such as Zonaoccludens-1 (ZO-1), ZO-2 etc. The PDZ-binding motif required to target the protein to the TJ complex and also function as a determinant of protein stability and function. The carboxy terminal tail is the target of various post-translational modifications, such as serine/threonine and tyrosine phosphorylation and palmitoylation, which significantly alter claudin localization and function.

EXPRESSION OF CLAUDINS[4]

a. Epithelial Tissues

Claudins are expressed in all known epithelial tissues. The different types of Claudins were expressed in the following epithelial tissues in various systems.

- **Kidney**

In the adult glomerulus, visceral epithelial cells (podocytes) form a specialized intercellular junction. True tight junctions form between immature podocytes in the fetal glomerulus. These disappear during development, but can reappear during nephrotic states. Claudin-5 is expressed in the glomerulus and is found throughout the plasma membrane of podocytes. Claudin-6 has also been detected in podocytes, where it is found at the basal membrane and at the base of the slit diaphragm.

- **Gastrointestinal tract**

In the rat stomach, the expression of Claudins 2–5 has been examined. Claudin-3 is most strongly expressed in the surface epithelial cells of the stomach while Claudin-4 is expressed mainly at the tight junction in proximal gastric glands. Claudin-5 is uniformly expressed from

the base of the glands to the surface and like Claudin-3 is located on the basolateral membrane. Claudin-2 was not detected in the stomach. In addition, Claudins 12 and 23 as well as Claudin-18, are also known to be highly expressed in human stomach.

- **Respiratory tract**

In the mammalian proximal airways, Claudins 1, 3, 4, 5, 7, 10 and 18 have been shown to be expressed in bronchi and bronchioles. Claudin-7 was found to be expressed basolaterally. Claudin-3, 4, 7 are expressed in alveolar type-ll cells, and Claudin-5 is expressed in most alveolar epithelial cells. Freshly isolated alveolar cells express Claudin-3 and 5 most abundantly as well as Claudin-18.

- **Other epithelia**- The Table.1 summarizes expression of claudin in epithelial tissues in mammalian species.

Table 1: Expression of claudin in epithelial tissues.

Tissues	Claudins
Cochlea	1, 2, 3, 8, 9, 10, 12, 14, 18
Eye	1, 4, 7
Salivary gland	1, 2, 3, 4, 7, 8, 12
Ovary	1, 5
Exocrine pancreas	1-5, 7
Choroid plexus	1, 5, 11
Urinary bladder	4, 8, 12

b. Endothelia

Vascular endothelial cells also have tight junctions and express multiple Claudins. Claudin-5 is the predominant Claudin, but Claudins-1, 3 and 12 have also been reported. In a purified preparation of brain capillary endothelial cells, Claudins 10 and 22 were also reported to be expressed at significant levels. In brain capillary endothelial cells, Claudin-5 mRNA levels are almost 600-fold higher than Claudin-3. In general, the number of Claudin isoforms that have been identified in endothelia is far less than those in epithelia.

c. Other Tissues

In addition to epithelia and endothelia, Claudins are also found in a variety of other cell types. Claudin-11 and -19 are expressed in inter lamellar strands of myelin sheaths in the central and peripheral nervous system, respectively, where they serve to insulate myelinated nerves and facilitate nerve conduction. Claudin-4 is expressed in pancreatic islet cells, which have tight junction-like strands on their cell surface. In mouse, Claudin-13 is expressed in

hematopoietic tissues, including the bone marrow, thymus, and spleen. Claudins have also been described in lymphocytes and monocytes, dendritic cells, thymocytes, osteoblasts and osteoclasts, astrocytes and even neurons under certain situations.

d. Sub-cellular Localization

In almost all cells, multiple Claudin isoforms are expressed simultaneously at the tight junction, and distributed among all the faces that form cell-cell contacts. Interestingly, though, Dieter cells (DC) and outer hair cells (OHC) in the organ of Corti form a hybrid tight junction/adherens junction in which Claudin-14, Claudin-6/9 partition into distinct sub domains of the junctional complex. Furthermore, Claudin-14 is restricted to heterotypic DC-OHC contacts and is absent from homotypic DC-DC contacts.

REGULATION AND REMODELING[2]

CLAUDIN REGULATION

Tight junctions are composed of a network of strands in which a Claudins are the major trans-membrane constituent. Claudins are organized into a basic hexameric unit. Claudins have been shown to form ladders of stable oligomers in gel electrophoresis.

- **Palmitoylation**

Palmitoylation of integral membrane proteins can affect intracellular trafficking, protein-protein interactions and protein stability. Tight junctional localization of some Claudins can also be modified by palmitoylation (fig.2). Thus in Claudin-14, two palmitoylation sites were identified within the cytoplasmic loop and two further sites within the cytoplasmic COOH terminus, close to the 4^{th} trans-membrane region.

Di-cysteine palmitoylation motifs are conserved throughout the Claudin protein family and were found to enhance incorporation of Claudins into tight junctions. Palmitoylated Claudins more efficiently portion into detergent resistant membranes as compared to non-palmitoylated mutants. Tetraspanins, such as CD-9 and CD-8 are also palmitoylated which is critical to their function as membrane chaperones and organizers of higher order membrane domains. A link between tetraspanins and Claudins is suggested by the demonstration that CD-9 directly interacts with Claudin-1 in a cholesterol sensitive manner whereas CD-81 acts as a co-receptor with Claudin-1, 6 or 9 to facilitate Hepatitis C binding and entry into cells. Also, it is unknown where Claudins oligomerize however, since palmitoylation and

tetraspanin oligomerization occurs predominantly in the Golgi apparatus, this suggests the Golgi apparatus as a potential location for claudin oligomerization.

- **Phosphorylation**

Claudin phosphorylation is another mode of regulating paracellular permeability. Phosphorylation has been linked to both increases and decreases in tight junction assembly and function. Claudin phosphorylation sites for various kinases (PKA, PKC, MLCK, RhoK) using several phosphorylation site detection tools. For instance, Protein Kinase A (PKA) mediated phosphorylation has been shown to decrease assembly of Claudin-3 into tight junctions, yet is necessary for Claudin-16 assembly and function. Claudin-1 and Claudin-4 phosphorylation by protein Kinase C (PKC) is required for assembly into intestinal epithelial tight junctions. Inversely, phosphorylation via myosin light chain kinase (MLCK) and rho kinase is commonly associated with tight junction disassembly and increased paracellular permeability associated with inflammation.

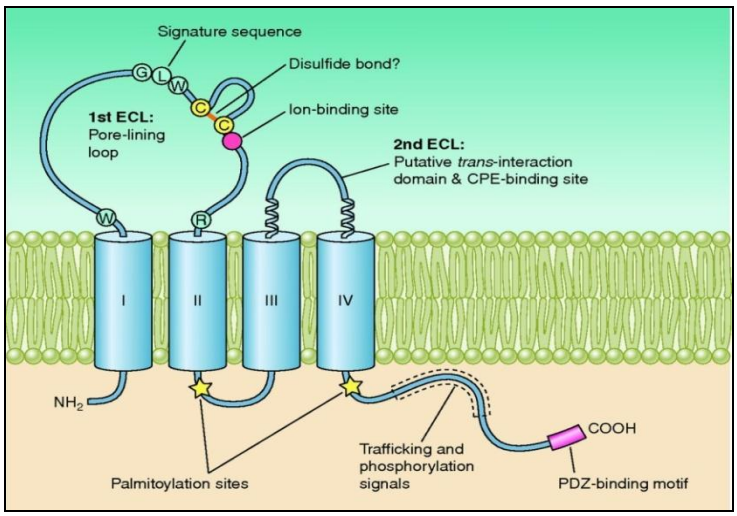

Fig. 2. Regulation of claudins.

CLAUDIN REMODELING

The network of tight junctions is constantly remodelled, the different components have different stability within the strands. Based on fluorescence recovery after photobleaching (FRAP), the majority of claudins are stably integrated into tight junctions, reflecting the strength of intercellular binding and association with the cytoskeleton. In contrast, occludin and ZO-1 are more dynamic. The mobile fraction of occludin is nearly three times greater than that of claudin. ZO-1 is highly dynamic as well, although instead of diffusing along the plane of the membrane, it instead dissociates from tight junctions and diffuses into the

cytoplasm. This is consistent with models where ZO-1 interactions with occludin and claudins are required to stabilize these proteins in junctions.

Tight junctions are also remodelled at a more macroscopic level through strand breaks and reformation. Clathrin-mediated endocytosis plays an important role in this process. Claudins are internalized by a unique mechanism, where the tightly opposed membranes of the tight junction are endocytosed together into one of the adjoining cells, a mechanism also used for gap junction internalization. During internalization, the claudins separate away from occludin, JAM and ZO-1 and generate claudin-enriched vesicles, which has the potential to regulate the claudin composition of tight junctions.

INTERACTION WITH OTHER PROTEINS[2]

- **Claudin-Claudin interactions**

Epithelia and endothelia typically express multiple claudin isoforms in a specific tissue. The interaction between different classes of claudins has the potential to control barrier permeability through the formation of TJs composed of multiple Claudins. Claudin interact in two different ways: laterally in the plane of the membrane (heteromeric interactions) or head to head binding between adjacent cells (heterotypic interactions). Claudin homo-multimers composed of up to six monomers have been observed biochemically and lateral interactions of Claudin-5 within cells has been detected using fluorescence resonance energy transfer (FRET).

Cells with claudin-null backgrounds have helped define specificity in claudin heterotypic interactions. Using this approach, heterotypic and heteromeric compatibility have been found to be determined by distinct mechanisms. For example, claudin-3 and claudin-4 are heteromerically compatible when expressed in the same cell; however, they do not heterotypically interact despite having extracellular loop domains that are highly conserved at the amino acid level. By contrast, claudin-3 heterotypically interacts with other claudins, including claudin-1 and claudin-5.

- **Claudin-occludin interactions**

Occludin is another tetraspan transmembrane protein associated with tight junctions. Occludin is a protein, which formed the physical basis of the tight junction barrier; however, transgenic occludin deficient mice are viable and have normal barrier function which ultimately leads to the identification of claudins as the barrier forming component of tight

junctions. Although occludin-deficiency does not impair barrier function, peptides that mimic the occludin extracellular loop domains can disrupt epithelial barrier function by enhancing junctional disassembly suggesting that occludin associates with tight junctions in a regulatory capacity.

- **Claudin-scaffold protein interactions**

Claudin-ZO (Zonula occludens) protein interactions are required for tight junction assembly. This was demonstrated using cultured epithelial cells in which expression of both ZO-1 and ZO-2 was suppressed. In ZO-1/ZO-2 null cells, claudins failed to localize to tight junctions and the cells had poor barrier function. However, transfection with either ZO-1 or ZO-2 enabled proper claudin localization and function. Thus, ZO-1 and ZO-2 have overlapping function, which suggests that linking claudins to the actin cytoskeleton through these scaffold proteins is essential for tight junction formation. Since most claudins have conserved C-terminal domain, they are likely to interact with zona occludens (ZO) 1, 2 and 3 as demonstrated for Claudin-1 through Claudin-8.

DRUG DELIVERY SYSTEM USING CLAUDIN MODULATORS

With the continued progress in genomic drug discovery, the production of drug candidates has become possible. Today a number of candidates those are extremely effective both in cell- free and in cell models. However, a drug delivery system suitable for the high-throughput production has yet to be fully developed. In tissues, the tight junction plays a pivotal role as both a barrier to restrict various substances and in intra-tissue maintenance. Claudin may be a potential target for use as a drug delivery system via parcellular route. The C-terminal fragment of Clostridium perfringens enterotoxin (C-CPE) is known to modulate the barrier function of Claudin. The C-CPE is a potent absorption-enhancer and that this enhancing activity is 400-fold greater than clinically used enhancers. The enhancing activity examined in the interaction between C-CPE and Claudin-4. This indicates that claudin might be a novel target for a drug delivery system.[3]

CPE AS A TOOL TO STUDY EPITHELIAL TIGHT JUNCTIONS[14]

Clostridium perfringens enterotoxin (CPE), a major cause of food poisoning, forms physical pores in the plasma memgrane of intestinal epithelial cells. The ability of CPE to recognize the epithelium is due to the C-terminal binding domain, which binds to a specific motif on second EC loop of Claudins. The interaction between Claudin and CPE plays a key role in mediating CPE toxicity by facilitating pore formation and by promoting TJ dissembly. The

ability of CPE to distinguish between specific Claudins has been used to develop tools for studying roles for claudins in epithelial barrier function. Moreover, the high affinity of CPE to selected claudins makes CPE a useful platform for targeted drug delivery tumors expressing these claudins.

ROLES OF CLAUDINS

1. IN TIGHT JUNCTIONS[6]

TJs seal the paracellular cleft of epithelia and endothelia and form crucial barriers tissue compartments. TJs consist of integral membrane proteins including occludin, claudins and ZO-1. Of these molecules, claudins are responsible for the formation of tight junction strands. They form the paracellular barrier that controls the transport of ions and small molecules in the intracellular space between epithelial cells. The expression pattern of claudins is highly tissue specific and most tissues express multiple claudins. Claudin can interact with claudins from adjacent cells in a homotypic or heterotypic fashion to form TJs. Claudins can be polymerized together between epithelial cells to form adhesive structure.

2. IN HUMAN DISEASE[4]

Mutation of claudin cause four Mendelian inherited disorders, neonatal sclerosing cholangitis with ichthyosis (Claudin-1 mutations), autosomal recessive, non-syndromic deafness (Claudin-1), familial hypomagnesemic hypercalciuria with nephrocalcinosis (duetoclaudin-16 mutations), ocular disease (Claudin-19). In addition, polymorphisms in claudin genes have been found to be associated with polygenic diseases, including Claudin-1 with atopic dermatitis, Claudin-5 with schizophrenia, and Claudin-14 in kidney stone diseases.

Acquired abnormalities of claudin expression play important roles in clinical disease. For example, Claudin-2 is consistently up-regulated in human inflammatory bowel diseases. Claudins are also expressed on hepatocytes have a role as co-receptors for infection by the hepatitis C virus.

Aberrant expression of claudins is also common in epithelial cancers. Generally, the most common claudins to be affected are claudin-3 and -4, which are usually up-regulated in cancers, and claudin-1 and -7 which can be both up- and down-regulated. *In vitro* studies suggest that dysregulation of claudin expression may play a pathogenic role in tumorogenesis, but the mechanisms seem to vary between different cancers and claudin isoforms and are mostly poorly understood.

3. IN CANCER[2, 11]

The function of claudins is the maintenance of normal epithelial cell homeostasis. However, their role in the process of tumourogenesis is less clear. Cancer cells can spread from the primary site to other parts of the body, a process known as metastasis. During cancer metastasis, several important steps need to be undertaken. An important step in cancer progression is the epithelial–mesenchymal transition. During this process, epithelial cells down-regulate cell–cell adhesion structures, alter their polarity, reorganize their cytoskeleton and become isolated and motile. Tight junctions are involved in this cancer metastatic process. Claudin-6 decreases in breast invasive ductal carcinomas and is inversely correlated with lymph node metastasis. Claudin-2 level is elevated in liver metastasis. The first Claudin-2 extracellular loop is essential for mediating tumour cell-hepatocyte interaction and the ability of breast cancer cells to form liver metastasis *in vivo*. Claudin-3 and -4 control tumor growth and metastasis by sustaining expression of E-cadherin and limiting β-catenin signaling.

Claudin-1 has been found to be reduced in breast cancer as well as in colon cancer. Claudin-7 has also been found to be down-regulated in invasive breast cancer and in head and neck cancers. In gene expression study of ovarian cancer showed that upregulation of claudin-3 and -4. In addition, Claudin-3 and 4 have also been reported to have an increased expression in other cancers such as breast, prostate and pancreatic cancers. Gastric cancer is the most common cancer. The incidence is higher among men and the prognosis is poor. Risk factors include H.pylori infection, smoking, high intake of salt, dietry nitrite, family history of cancer and gender. The functions of claudins in cancer may be highly tissue-specific and may depend on the type and stage of cancer.

CONCLUSION

Claudins are the main structural and functional proteins of tight junctions in epithelial cells. They maintain tissue homeostasis through regulating epithelial barriers, paracellular transport and signal transduction. Modulators of claudins are also useful as a drug delivery system via paracellular route. Clostridium perfringens enterotoxin (C-CPE) is a claudin-modulator. Applications of C-CPE and its derivatives are limited because of their origins in enterotoxin. Therefore development of biocompatible claudin binders and ligands such as chemicals, peptides and antibiotics is crucial for their application as therapeutics. Claudin plays a multiple role beyond acting as a simple paracellular barrier. The modulation of TJs through

the targeting claudins will be a novel strategy for the use of a paracellular route for drug delivery. The role of claudins in cancer, in human diseases (Mendelian inherited disorders, neonatal sclerosing cholangitis, non-syndromic deafness) and its clinical applications in cancer detection, diagnosis and potential therapeutic intervention may become a valid approach in the near future.

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