Amino Acids (2025) 57:48
https://doi.org/10.1007/s00726-025-03479-w

REVIEW ARTICLE

Exploring claudin proteins: from sequence motifs to their impact on tight junction-mediated signaling pathways

Lingling Bao[1] · Siqi Yang[1] · Wenhua Zhao[1,2] · Yongchun Zuo[1]

Received: 18 April 2025 / Accepted: 27 August 2025 / Published online: 23 September 2025

Abstract

Claudin (CLDN) proteins are extensively studied due to their critical role in maintaining tissue barriers and cell polarity. However, significant gaps remain in understanding the functional mechanisms of their sequence motifs and the molecular mechanisms of their interactions with other tight junction proteins**.** This review systematically examines the multifunctional properties of the CLDN protein family from the perspectives of sequence and structure. During evolution, CLDN family members have developed highly conserved structural features, particularly key conserved sites within the first extracellular loop (ECL1) and the C-terminal PDZ-binding domain, which play a central role in regulating the barrier function of tight junctions, ion selectivity, and protein–protein interactions. Furthermore, the distribution pattern of acidic and basic amino acids in ECL1 has been shown to directly determine ion selectivity and paracellular permeability. Meanwhile, the assembly and functional stability of tight junctions are precisely regulated by the C-terminal PDZ-binding domain through its interactions with the ZO protein family. Additionally, the study further elucidates how CLDN proteins modulate critical signaling pathways governing cellular proliferation, survival, and permeability, thereby participating in diverse physiological and pathological processes. These insights have deepened the understanding of the functional diversity of CLDN proteins and provided a new theoretical basis for developing disease diagnostic markers and designing targeted treatment strategies based on CLDN proteins.

Keywords CLDN protein · Tight junctions · Conserved sequence motif · Barrier function · Ion channel · Signaling pathway

Introduction

The CLDN protein family, encoded by the CLDN gene family, comprises a group of four-pass transmembrane proteins predominantly localized in the tight junctions of epithelial and endothelial cells. These tight junctions play a pivotal role in establishing selective barriers that regulate the paracellular movement of ions, molecules, and cells across distinct physiological compartments (Furuse et al. 1998a; Krause et al. 2008; Reviews 2013; Tsukita et al. 2001; Van Itallie et al. 2003). In mammals, the CLDN family encompasses 27 members, with CLDN13 being exclusive to rodents, while humans possess 26 CLDN subtypes (Mineta et al. 2011). Structurally, human CLDNs are composed of 207 to 305 amino acids, exhibiting a molecular weight ranging from 21 to 34 kDa (Günzel and Yu 2013). Characterized by four transmembrane domains (TMD1–TMD4), these proteins possess a short cytoplasmic N-terminus, an extended C-terminal cytoplasmic domain, two extracellular domains (the

Lingling Bao and Siqi Yang contributed equally to this work.

Handling editor: J. Rebehmed.

✉ Wenhua Zhao
848192702@qq.com

✉ Yongchun Zuo
yczuo@imu.edu.cn

[1] State Key Laboratory of Reproductive Regulation and Breeding of Grassland Livestock, Institutes of Biomedical Sciences, School of Life Sciences, Inner Mongolia University, Hohhot 010021, China

[2] Reproductive Medicine Centre, Inner Mongolia People's Hospital, Hohhot 010017, China

larger ECL1 and the smaller ECL2), and a brief intracellular loop (Morin 2009; Tsukita et al. 2019) (Fig. 1). Given that protein function is intrinsically linked to molecular architecture, CLDNs serve as critical intercellular barriers and fences, ensuring the proper spatial organization of membrane phospholipids and proteins. Dysregulation of CLDNs has been implicated in a spectrum of pathological conditions, including cancer, inflammatory disorders, and metabolic syndrome (Angelow et al. 2008; Morin 2005; Zhang et al. 2024).

The functional diversity of CLDN proteins stems from their highly conserved structural motifs, including critical domains within the extracellular loops and the C-terminal PDZ-binding motif. These structural elements not only mediate interactions between CLDN proteins and other tight junction components but also play a pivotal role in regulating paracellular transport (Itoh et al. 1999; Jeansonne et al. 2003; Piontek et al. 2008; Rosenthal et al. 2010). Although significant progress has been made in elucidating the crystal structures and functions of CLDN family members, the evolutionary relationships among different CLDN isoforms and the sequence determinants underlying their functional specificity have yet to be fully elucidated. For instance, the relationship between the diversity of sequence motifs across species and their functional conservation remains unclear; the dynamic binding mechanisms between CLDN proteins and scaffolding proteins such as ZO-1 and MUPP1 require further investigation; and notably, the regulatory role of phosphorylation in modulating these interactions demand deeper exploration. In the context of disease, extensive research has established a clear link between aberrant CLDN expression and tumorigenesis (Hou et al. 2012; Villagomez et al. 2025). CLDN proteins participate in disease pathogenesis through modulating multiple signaling pathways: (1) regulating cell polarity and proliferation via interactions with ZO protein family members (Brunner et al. 2023); (2) influencing cytoskeletal reorganization through small GTPases such as Rac1/RhoA; (3) controlling cell survival by interacting with apoptosis-related proteins including Bcl-2/Bcl-xL; and (4) maintaining intercellular permeability in coordination with Occludin/JAM complexes (Taylor et al. 2021). However, current investigations demonstrate marked imbalance in research depth. While existing studies predominantly focus on elucidating molecular mechanisms of canonical pathways like PI3K/AKT and Wnt/β-catenin, understanding of other potential pathways and their network-based regulation remains substantially limited (Bakir et al. 2020; Kay et al. 2017; Ohta et al. 2012). Particularly noteworthy is the pressing need to clarify the interaction mechanisms between CLDN proteins and critical signaling pathways including Notch and Hippo—aberrant activation of these pathways may lead to uncontrolled cell proliferation, tight junction dysfunction, and subsequent tumor progression and metastasis. Furthermore, currently available therapeutic strategies targeting CLDN-associated signaling pathways show limited clinical efficacy, highlighting the urgent demand for developing more precise targeted interventions.

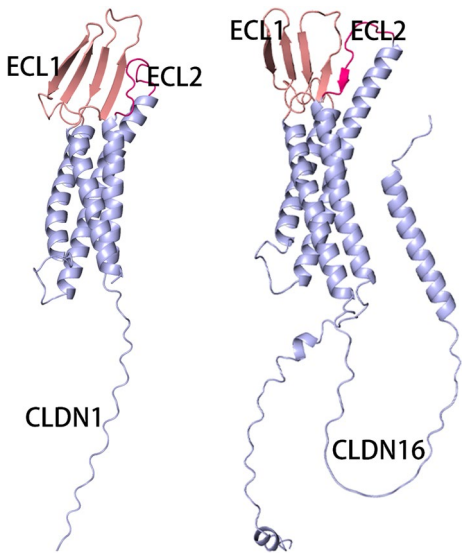


Fig. 1 Three-Dimensional Structure of CLDN Proteins. The figure illustrates the three-dimensional structures of CLDN1 and CLDN16 proteins. CLDN1 (AF-O95832-F1), as a representative of classical CLDN proteins, and CLDN16 (AF-Q9Y5I7-F1), as a representative of non-classical CLDN proteins, each consist of four transmembrane domains (TM) and two extracellular loops (ECL1 and ECL2)

Within the CLDN protein family, despite sequence and structural variations among individual members, highly conserved amino acid motifs are consistently observed. These motifs are predominantly localized in two key regions: (1) the extracellular loop domains, where they mediate paracellular barrier and pore functions, and (2) the C-terminal cytoplasmic tail, which harbors conserved binding sites for scaffolding proteins such as ZO-1, ZO-2, and MUPP1. Through motif discovery and consensus sequence analysis, the conservation and variability of these motifs across different CLDN members can be systematically outlined. The primary mechanisms through which these functional motifs operate are further examined, offering a comprehensive overview of the structural determinants that underlie the functional diversity of CLDN proteins. Such an analysis not only deepens the understanding of the molecular foundations of CLDN protein functions but also sheds light on the evolutionary adaptations that have shaped their diversity. By clarifying the sequence motifs and their arrangements, this perspective aims to advance the field of epithelial biology and provide a foundation for future investigations into the roles of CLDN proteins in both health and disease.

Methods

Data sources and processing

All protein sequence and structural data are sourced from the following databases:

UniProT Database (https://www.uniprot.org/): For obtaining protein sequences and AlphaFold predicted structures. PDB Database (https://www.rcsb.org/): For obtaining the experimental resolution of protein structures. PLIP Database (https://plip-tool.biotec.tu-dresden.de/): For analy zing the interaction between ligands and proteins and key amino acid information.

During the process of data processing and analysis, ensure the integrity and consistency of the data. All analytical results are verified multiple times to guarantee their reliability.

Sequence alignment and evolutionary analysis

To investigate the evolutionary relationships of the target protein, we retrieved homologous protein sequences from related species in the UniProT database. Using MEGA software (version 11.0), we performed multiple sequence alignment with the ClustalW algorithm. Based on the alignment results, we constructed a phylogenetic tree using either the Maximum Likelihood (ML) or Neighbor-Joining (NJ) method in MEGA, selecting the appropriate method based on the data size and the purpose of the construction. The reliability of the tree was assessed with a Bootstrap value set to 500 replicates. To further enhance the visualization of the evolutionary tree, we utilized the iTOL (Interactive Tree Of Life) online tool to refine and annotate the phylogenetic tree, highlighting key evolutionary nodes and branches.

Molecular structure visualization and analysis

In this study, the PyMOL software (version 2.5.2) was utilized for the visualization and analysis of molecular structures. The three-dimensional structural data of the target protein were primarily sourced from the following two databases:

AlphaFold Database: Obtain the AlphaFold predicted structure of the target protein from the UniProT website for analyzing the overall conformation and functional domain distribution of the protein.

PDB Database: Download the experimentally resolved structures of target proteins (such as X-ray crystal structures or cryo-electron microscopy structures) from the RCSB Protein Data Bank to validate the accuracy of AlphaFold predicted structures.

The data on ligands and key amino acid interactions are sourced from the PLIP database (Protein–Ligand Interaction Profiler), through PLIP analysis, the interaction patterns between ligands and proteins are examined, including hydrogen bonds, hydrophobic interactions, and more.

In PyMOL, we conducted 3D visualization of the protein's overall structure, functional domains and ligand binding sites, analyzed hydrogen bond and salt bridge networks using built-in measurement tools, generated an electrostatic potential map to study charge distribution and potential ligand binding sites, and analyzed key amino acid sites for protein interactions.

Through the aforementioned methods, we have systematically analyzed the structural characteristics, ligand binding patterns, and evolutionary relationships of the target protein, laying a solid foundation for subsequent functional research and applications.

Other protein function prediction

Utilize InterPro to analyze protein function and predict conserved sites and use the KEGG database platform for enrichment analysis of CLDN-related proteins and their signaling pathways and functions.

Phylogenetic relationships and motif composition of CLDN proteins

Phylogenetic analysis provides valuable insights into the functional differences and diversity within protein families. By tracing the evolutionary trajectories of proteins across species, it systematically reveals their functional conservation and specificity, thereby deepening our understanding of evolutionary dynamics and functional diversification processes. The claudin proteins show a wide range of sequence similarity. Our phylogenetic analysis of tight junction proteins across seven species—human, mouse, cattle, sheep, pig, horse, and dog—demonstrates that certain members (e.g., CLDN1-10, 14, 17, and 19) exhibit high sequence homology. Notably, CLDN1 and CLDN7 form a distinct evolutionary clade, while CLDN2 and CLDN14 constitute another, suggesting that these proteins may have undergone similar selective pressures during evolution. However, their specific functional relationship requires further experimental validation (Fig. 2A). A subdivision of the claudin family into 'classic' and 'non-classic' groups has been suggested from sequence analysis of the mouse claudin proteins (Krause et al. 2008). Our analysis of these seven species also suggests that some demarcation can be made between claudins on the basis of sequence homology, although the exact members of the 'classic' and 'non-classic' classes are slightly different from the ones suggested by Krause et al.

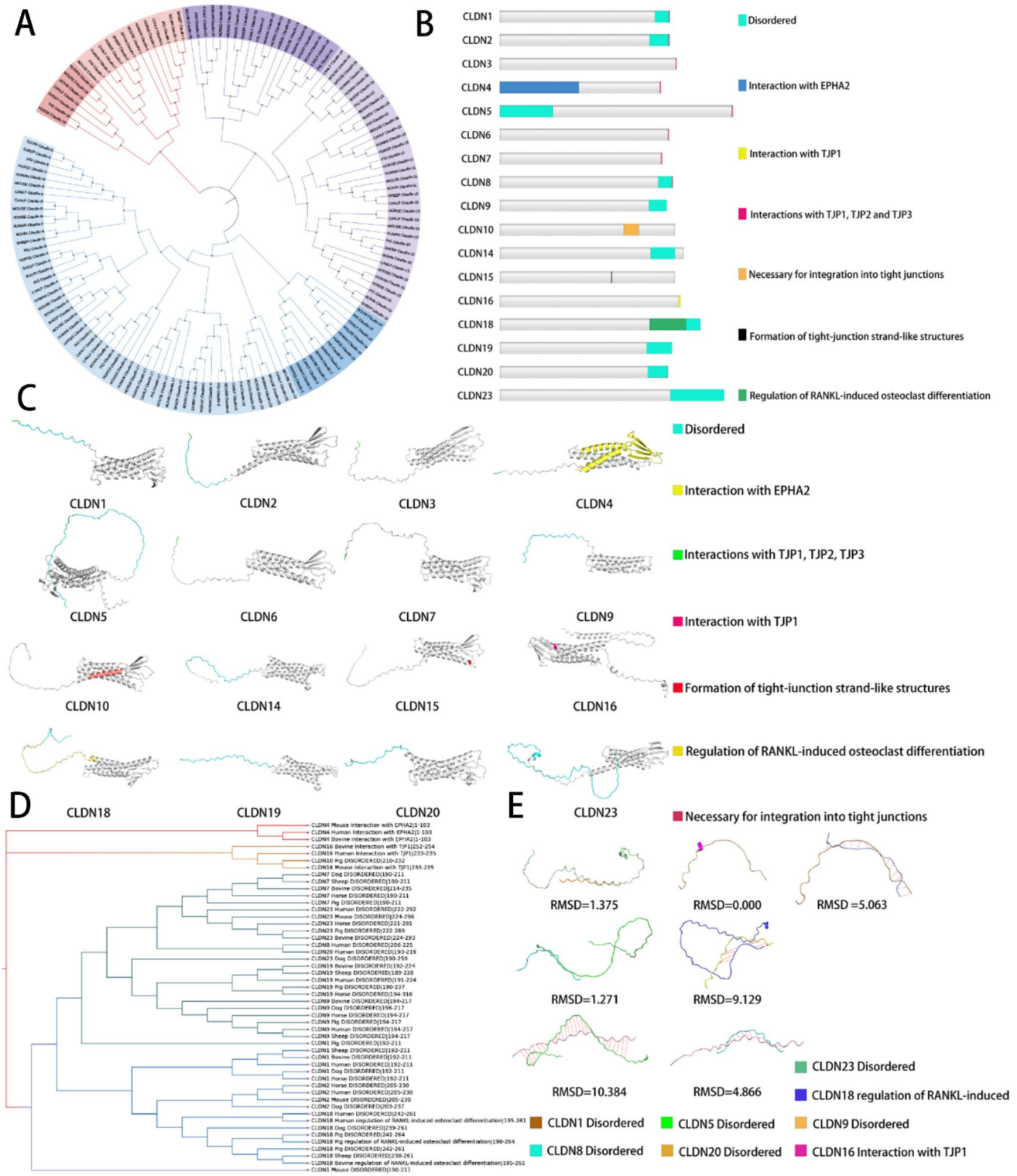


Fig. 2 Phylogenetic relationships and motif compositions of CLDN proteins. **A** The evolutionary history of CLDN proteins was inferred using the neighbor-joining method. **B**, **C** Distribution of domains in CLDN proteins. **D** The evolutionary history of CLDN protein domains was inferred using the neighbor-joining method. **E** Schematic representation of domains based on the phylogenetic tree of CLDN protein domains. Domains with closer evolutionary relationships typically have smaller RMS (root-mean-square) values, indicating greater similarity in their spatial structures. However, there are some exceptions where domains with closer evolutionary relationships have larger RMSD values. This may be related to the specificity of protein functions, interactions between domains, or other biological factors

(Krause et al. 2008) for the mouse proteins. With the progressive elucidation of claudin protein expression profiles and functional characteristics, it may be possible and more appropriate to subdivide the claudins according to these parameters.

Sequence motifs serve as the structural foundation for the diverse functionalities of proteins. Within the CLDN protein family, a systematic examination of motif composition highlights key characteristics, where both conservation and variability are assessed across its various members (Fig. 2B, C). CLDN proteins contain two critical functional motifs: a disordered region, potentially involved in dynamic conformational changes and functional regulation, and a C-terminal region interacting with TJP1, TJP2, and TJP3, likely contributing to intercellular connections and barrier functions. These findings highlight the functional mechanisms of the CLDN protein family. Notably, both functional regions localize to the termini of CLDN proteins, with the TJP-interacting region exhibiting a clustering pattern in classic CLDN proteins. This pattern correlates closely with the conserved YV motif at the C-terminus, indicating its key role in mediating CLDN-TJP interactions (Itoh et al. 1999).

Through comprehensive characterization of the evolutionary relationships and structural features of these domains, with particular emphasis on their evolutionary conservation and three-dimensional structural similarity profiles, we have uncovered a significant phenomenon: the phylogenetic trajectories of the domains exhibit marked divergence from those of their corresponding full-length proteins (Fig. 2D). This discrepancy likely stems from distinct selective pressures acting on functional motifs throughout evolutionary history. Notably, the intrinsically disordered regions of CLDN9 and CLDN19 form a distinct evolutionary clade, while CLDN7 and CLDN18 cluster within a separate branch—a topological pattern completely absent in phylogenetic trees constructed using full-length protein sequences. This evolutionary divergence phenomenon may reflect potential mechanisms underlying functional diversification of CLDN proteins, though further functional experiments are required for verification. Further analytical investigations revealed a definitive correlation between the evolutionary relationships of domains and their three-dimensional structural similarities (Fig. 2E). Intriguingly, although the disordered sequences demonstrate substantial variability in length and primary structure across different family members, their spatial conformations maintain remarkably limited structural deviations. This compelling observation strongly suggests that the conservation patterns and functional diversification processes of these domains are intimately linked to the stability of their spatial architectures. These findings establish a critical theoretical framework and propose new research directions for elucidating the structure–function paradigm of the CLDN protein family.

While these findings provide insights into CLDN protein evolution and structure–function relationships, several limitations should be acknowledged: First, the phylogenetic analysis was confined to seven mammalian species, which may not fully capture the evolutionary diversity across the entire claudin protein family. Second, while bioinformatic predictions have identified potential functional motifs (particularly in disordered regions) (Abdelkader and Kim 2024; Zhu et al. 2023; Zou et al. 2023), these computational findings require experimental validation through protein–protein interaction studies to confirm their mechanistic roles. Third, the current classification of claudins into ‘classic’ and ‘non-classic’ subfamilies, while supported by our cross-species analysis, would benefit from additional validation through comprehensive expression profiling and functional characterization across a broader range of species. These limitations highlight important directions for future research to further refine our understanding of CLDN protein evolution and function.

The discovery of conserved sites and the analysis of their potential functions

InterPro analysis technology was able to identify and locate a functionally critical conserved site within the 48–64 amino acid region of the target protein. Visualization of the protein’s three-dimensional structure using PyMOL software revealed that this conserved site resides in the first extracellular loop (ECL1) of the CLDN protein. Comprising four β-strands (β1–β4) and an extracellular helix, this region forms an antiparallel β-sheet structure, which is highly conserved and essential for the formation of intercellular connections within the CLDN family (Marsch et al. 2024). The conserved site primarily consists of the β3 and β4 structures (Fig. 3A). These two β-sheets likely mediate protein–protein interactions or ligand binding directly, serving as the structural foundation for the functional regulation of CLDN proteins.

Extracellular loop 1 represents a key structural domain of tight junction proteins, such as claudins and occludins, playing multiple roles in cell–cell adhesion, barrier function, and ion channel regulation. Its unique structural features also contribute to maintaining the integrity of tight junctions (Krause et al. 2008; Powell 1981; Reviews 2013). ECL1 has a characteristic sequence (Gly-Leu-Trp-x-x-Cys-(8–10aa)-Cys) that is highly conserved and detected in a series of closely related proteins such as epithelial membrane proteins (EMPs, PMP22) (Koval 2006). The cysteines in this conserved sequence may form intramolecular disulfide bonds to stabilize the protein conformation (Fig. 3B, C)

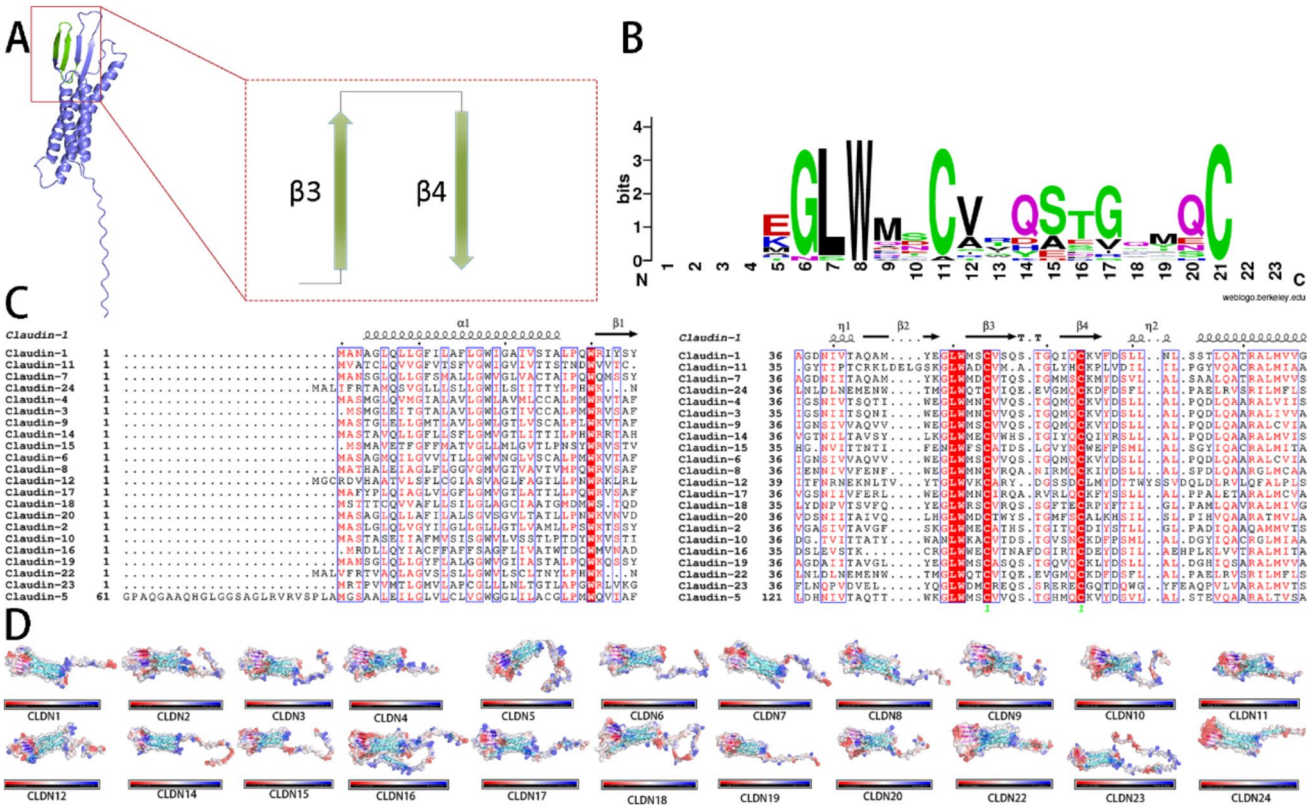


Fig. 3 Discovery of conserved sites and analysis of potential functions. **A** Topological map of the conserved site in CLDN proteins, shown in local magnification. **B** Web Logo diagram of the amino acid sequence of the conserved site in CLDN proteins. **C** The unique sequence of the conserved site containing 16 amino acids. **D** Electrostatic potential map of CLDN proteins, represented in combination with surface and ribbon views

and play a critical role in preserving the structural and functional integrity of tight junctions (Krause et al. 2008; Wen et al. 2004). Additionally, the unique distribution pattern of acidic and basic amino acids in ECL1 plays a pivotal role in modulating ion channel selectivity and permeability (Colegio et al. 2003, 2002b; Günzel et al. 2009; Yu et al. 2009). Molecular dynamics simulations reveal that these charged residues form a dynamic electrostatic network, enabling ion-selective filtering and pH-sensitive gating regulation (Rosenthal et al. 2017; Weber et al. 2015). For example, in CLDN4, the lysine 65 residue in the first extracellular loop is crucial for controlling paracellular permeability (Berselli et al. 2022). By employing PyMOL software, the spatial arrangement of these charged residues in CLDN proteins has been visualized (Fig. 3D), shedding light on how their electrostatic properties influence functional behavior. The analytical results demonstrate that Claudin-2, Claudin-15, and Claudin-22 are primarily involved in the formation of cation channels. This finding exhibits remarkable consistency with previous research observations, which demonstrate that substituting acidic residues with basic ones in the ECL1 of claudin-4 markedly enhances cation permeability. Similarly, in claudin-15, replacing acidic residues with basic residues in ECL1 inverts the charge selectivity of the paracellular pathway, transitioning it from a preference for cations to a preference for anions (Colegio et al. 2002a).

The selectivity and permeability of ion channels in ECL1 are also closely linked to the pathogenesis of various diseases. For example, mutations in claudin-16 or claudin-19 can lead to familial hypomagnesemia, where altered charge distribution disrupts selective permeability to Mg^{2+} (Hou et al. 2008). Furthermore, the high expression of claudin-2 strongly correlates with increased permeability to Na^{+} and water in the intestine, a factor particularly significant in the pathogenesis of diarrheal diseases (Rosenthal et al. 2010). These findings complement the current understanding of ECL1's functional mechanisms, and their structural characteristics may offer potential targets for future therapeutic research.

The interactions with the ZO protein family and their relationship with phosphorylation

CLDNs undergo dynamic regulation through C-terminal modifications. Kinases targeting serine, threonine, or tyrosine residues phosphorylate this domain to control CLDN

localization and functional states (Wang et al. 2023). Beyond phosphorylation, the C-terminus contains modification sites for SUMOylation, palmitoylation, and ubiquitination, each contributing to the spatiotemporal regulation of CLDNs in cellular contexts (Fig. 4) (Hashimoto and Oshima 2022; Itoh et al. 1999). Emerging studies demonstrate that tight junction (TJ) assembly and functionality are modulated by phosphorylation events (Findley and Koval 2009). Notably, protein kinase A-mediated phosphorylation of Thr-192 in the C-terminal cytoplasmic domain of CLDN3 has been shown to impair its oligomerization, leading to TJ destabilization in ovarian cancer cells. This molecular alteration correlates with loss of cellular polarity and enhanced invasive potential (D'Souza et al. 2005a). Additionally, this region contains typical PDZ-binding motifs (e.g., –K/R/H–X–Y–V), enabling specific interactions with scaffold proteins containing PDZ domains, such as ZO-1. This interaction facilitates the integration of claudin proteins into intracellular signaling networks and contributes to the regulation of cell polarity and the stability of intercellular junctions (Fanning and Anderson 2010; Itallie et al. 2014; Itoh et al. 1999; Riazuddin et al. 2006; Shen et al. 2011; Umeda et al. 2006).

To gain deeper insights into the molecular mechanisms of ZO protein-CLDN protein interactions, the structures of complexes involving CLDN1 and CLDN2 with the PDZ domain of ZO-1 were determined (Fig. 5A, B). Structural analyses have suggested that the C-terminal cytoplasmic domains of CLDN1 and CLDN2 may have a certain binding affinity for the PDZ domain of ZO-1. Notably, the C-terminal YV (Tyr-Val) sequences of CLDN1 and CLDN2 form a critical hydrogen bond network with the PDZ domain of ZO-1, a key interaction for complex stability. To be specific, the interaction between CLDN1 and CLDN2 and ZO—1 involves several key amino acid residues. These residues work together through different molecular forces such as hydrophobic interactions, hydrogen bonds and charge interactions to form a stable protein—protein complex. These interactions are crucial for the assembly and function of tight junctions.

To be specific, there are hydrophobic interactions between the residues Gly—207, Tyr—210 and Ser—205 of CLDN1 and the residues Ser—115, Tyr—119, and Lys—110 of ZO—1. These residues come close to each other through their hydrophobic side chains, reducing their contact area with water and thus increasing the stability of the complex. In addition to hydrophobic interactions, hydrogen bonds and charge interactions may also exist between these residues. For example, the hydroxyl group of Ser—205 may form a hydrogen bond with a charged residue on ZO—1. The residues Tyr—114, Glu—20, Thr—23 and Ser—98 of ZO-2 exhibit hydrophobic binding with the residues Phe—221, Lys—218 and Ser—208 of CLDN2. These residues come close to each other through their hydrophobic side chains, forming a hydrophobic core that helps stabilize the complex. Similar to CLDN1, hydrogen bonds and charge interactions may also exist between these residues. These structural data clarify the molecular basis of specific binding between ZO-1 and CLDN proteins, providing critical insights into the molecular mechanisms of tight junction assembly. Building on this understanding, the crystal structures of its interactions with ligands were further determined (Figs. 5C, D). In the structural complexes of CLDN1 with ligands 12P-A-201, ACT-A-202, and ACT-A-203, key amino acid residues—including Arg-74, His-46, Ser-39, Ile-54, and Arg-107—engage in direct binding with the ligands through hydrogen bonds and hydrophobic interactions, stabilizing the overall conformation of the complex. Similarly, studies on the interaction between CLDN2 and ligands FMT-A-201 and FMT-B-201 reveal that residues such as Thr-105, Lys-103, and Gly-80 play pivotal roles in ligand binding. The elucidated interaction mechanisms offer structural insights that could potentially guide the development of small-molecule modulators for experimental investigations.

The phosphorylation state of CLDN proteins was found to play a critical regulatory role in their interaction with ZO

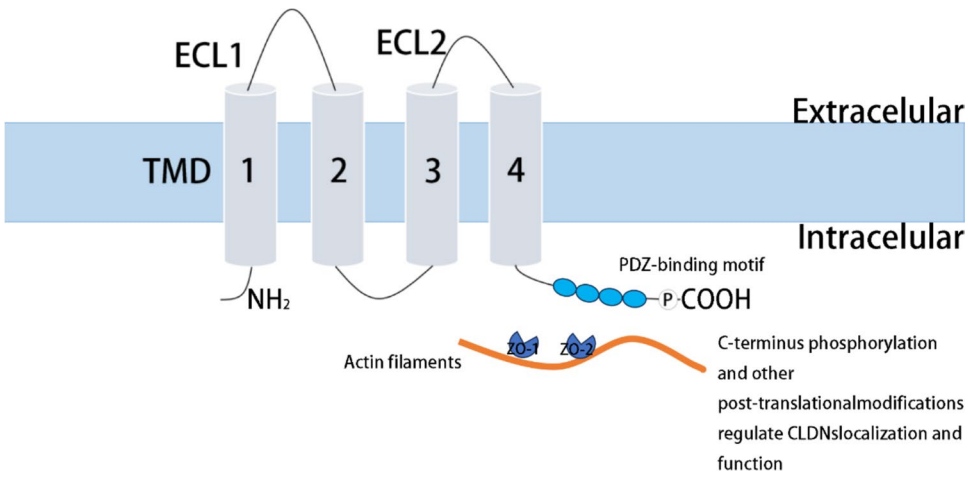
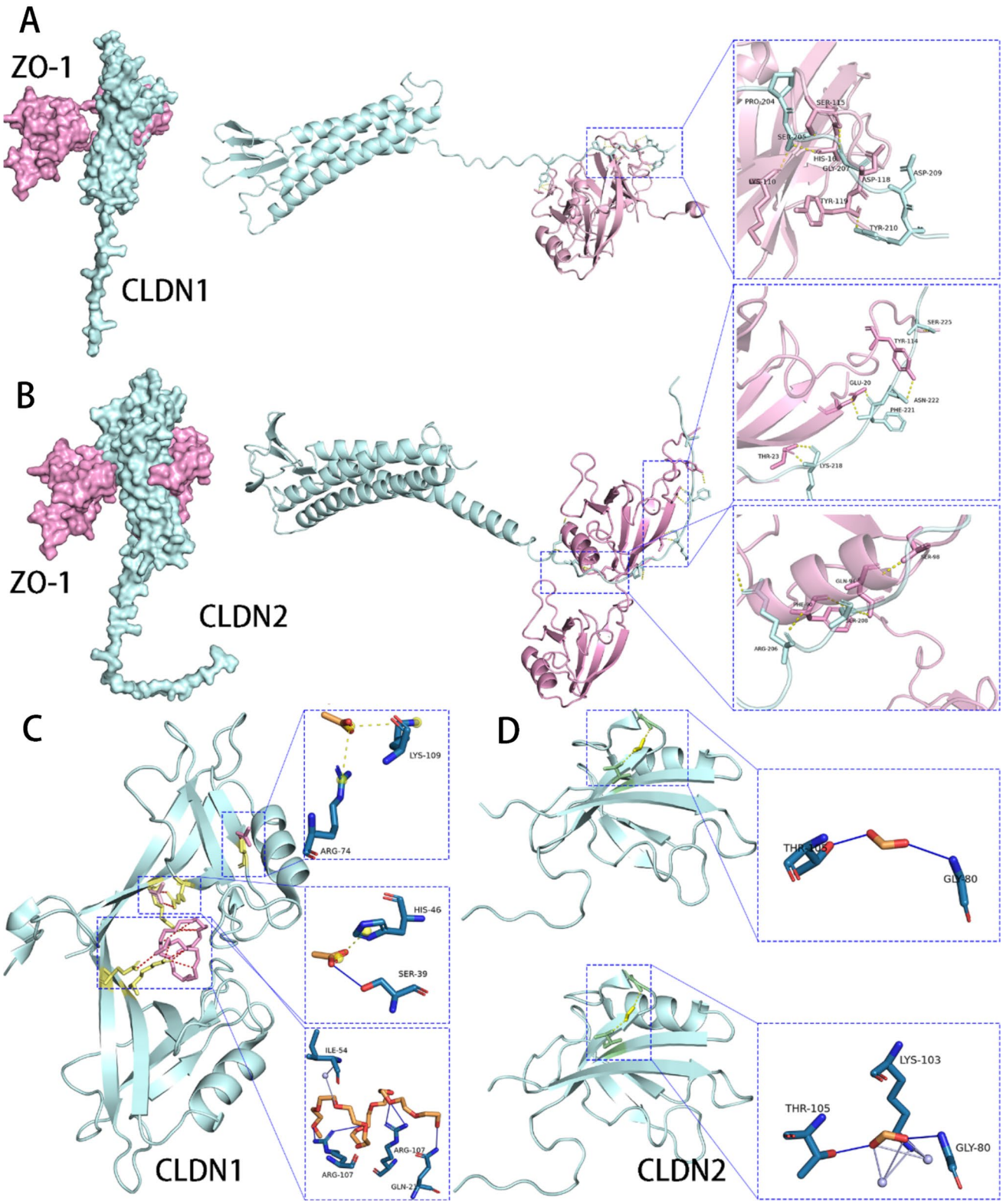


Fig. 4 Interactions with the ZO protein family and their relationship with phosphorylation. Structural diagram of the CLDN protein (monomer)



proteins, a mechanism pivotal in the development and progression of various diseases (Ahmad et al. 2011; D'Souza et al. 2005b). This conclusion is further supported by experimental results: in inflammatory bowel disease (IBD), the phosphorylation state of CLDN-2 significantly affects its binding ability to ZO-1, thereby regulating the permeability and function of the intestinal epithelial barrier (Molecules 2024); in diabetic nephropathy, the phosphorylation state of

Fig. 5 Interactions with the ZO protein family and their relationship with phosphorylation. **A** Fitting diagram of CLDN1 (AF-O95832-F1) protein and ZO-1 (AF-Q07157-F1) protein in surface representation. **B** Fitting diagram of CLDN2 (AF-P57739-F1) protein and ZO-1 protein in surface representation. **C** Overall and locally magnified diagrams of CLDN1 (PDB: 4OEP) protein interacting with ligands. Ligands include: 12P-A-201, ACT-A-202, ACT-A-203. **D** Overall and locally magnified diagrams of CLDN2 (PDB: 4YYX) protein interacting with ligands. Ligands include: FMT-A-201, FMT-B-201. All ligand structures are sourced from the PLIP database. In figure **A**, **B**: The fitting diagrams are represented in ribbon form and reveal the detailed interfaces between the binding sites. Key amino acid sites are marked, with yellow dashed lines indicating hydrogen bond interactions. In figure **C**, **D**: Key amino acid sites involved in ligand interactions are marked, with yellow dashed lines indicating hydrogen bond interactions

CLDN-1 directly influences the integrity of the glomerular filtration barrier by modulating its interaction with ZO-1. It is worth mentioning that this study offers a glimpse into the molecular mechanisms of CLDN-ZO protein interactions, shedding new light on the regulation of tight junctions. However, it is essential to highlight that the findings are mainly based on structural analyses. As such, their physiological significance needs further validation through experiments.

MAGUK family proteins, particularly the GK domain of MAGI2, can bind to phosphorylated peptides in a phosphorylation-dependent manner (Liu et al. 2024b; Zhang et al. 2023). As a subfamily of the MAGUK family, the ZO protein family also possesses the characteristic GK domain. Based on this, it is hypothesized that multiple phosphorylation sites at the C-terminus of CLDN proteins may play a critical role in their binding to ZO proteins.

CLDN signaling networks in physiology and pathology

The integrity and functionality of tight junctions largely depend on the expression and function of tight junction proteins. As illustrated, CLDN proteins interact with other proteins through various signaling pathways, influencing multiple physiological functions of cells (Fig. 6). These signaling pathways include cell polarity and proliferation, cell differentiation, cell survival, and intercellular permeability (Liu et al. 2021; Sugawara et al. 2025; Wang et al. 2024). For instance, CLDN proteins interact with ZO-1, ZO-2, and ZO-3 to affect cytoskeletal reorganization, thereby influencing cell polarity and proliferation; they interact with E-cadherin and β-catenin to regulate cell differentiation; their interaction with Bcl-2 family members (e.g., Bcl-2, Bcl-xL) may modulate mitochondrial apoptotic pathways, while interactions with Occludin and JAM coordinate tight junction strand assembly to regulate permeability (Raya-Sandino et al. 2023). Dysregulation of these interactions may contribute to the development of various diseases, such as cancer, inflammatory bowel disease, and neurodegenerative disorders.

Abnormal expression or dysfunction of CLDN proteins may lead to dysregulated cell proliferation, structural and functional impairments of tight junctions, and aberrant cell survival—pathological alterations that are closely associated with the development and progression of various diseases. For example, CLDN proteins interact with small GTPases like Rac1 and RhoA to influence cytoskeletal reorganization, thereby regulating cell proliferation (Inaba et al. 2021; Liu et al. 2022). Specifically, Rac1 and RhoA activate downstream signaling molecules such as PAKs and ROCK, which modulate cytoskeletal dynamics and thereby control cell morphology and motility. Disruption of this regulatory mechanism may lead to uncontrolled cell proliferation, increasing the risk of cancer. Additionally, CLDN proteins interact with Occludin and JAM to maintain the structure and function of tight junctions, which are critical for intercellular permeability (Nakamura et al. 2019; Otani et al. 2019). Dysregulation of these interactions may compromise tight junction integrity, contributing to the development of inflammatory bowel disease. Furthermore, CLDN proteins interact with Bcl-2 and Bcl-xL to regulate cell survival. The underlying mechanism involves Bcl-2 and Bcl-xL inhibiting apoptotic pathways, such as the activation of Caspase 3, thereby promoting cell survival (Ghai et al. 2024; Manjunath et al. 2024). Dysregulation of CLDN-Bcl-2/Bcl-xL interactions may impair apoptotic control, a process implicated in neurodegenerative models; however, further studies are needed to establish causality in human pathology. While we have managed to identify several key signaling pathways, such as those involved in cell polarity, proliferation, differentiation, survival, and intercellular permeability, the interactions among these pathways may be more intricate than currently understood. For instance, the interactions between Claudin proteins and Rac1 and RhoA may be modulated by other signaling molecules, the regulatory mechanisms of which have yet to be fully elucidated.

Claudin cis-stacking and trans-pairing architect tight junction barriers

Claudins, the primary sealing proteins of tight junctions, polymerize through homotypic and heterotypic interactions to form the structural scaffold of these intercellular complexes. The extracellular loops (ECL1 and ECL2) of CLDNs contain β -sheet and α -helix structures, which form stable multimers through hydrophobic interactions and hydrogen bonds (Hashimoto et al. 2023). The seminal work by Furuse et al. (1998a) demonstrated that claudins alone possess the intrinsic ability to assemble into functional tight junction strands, as evidenced by the formation

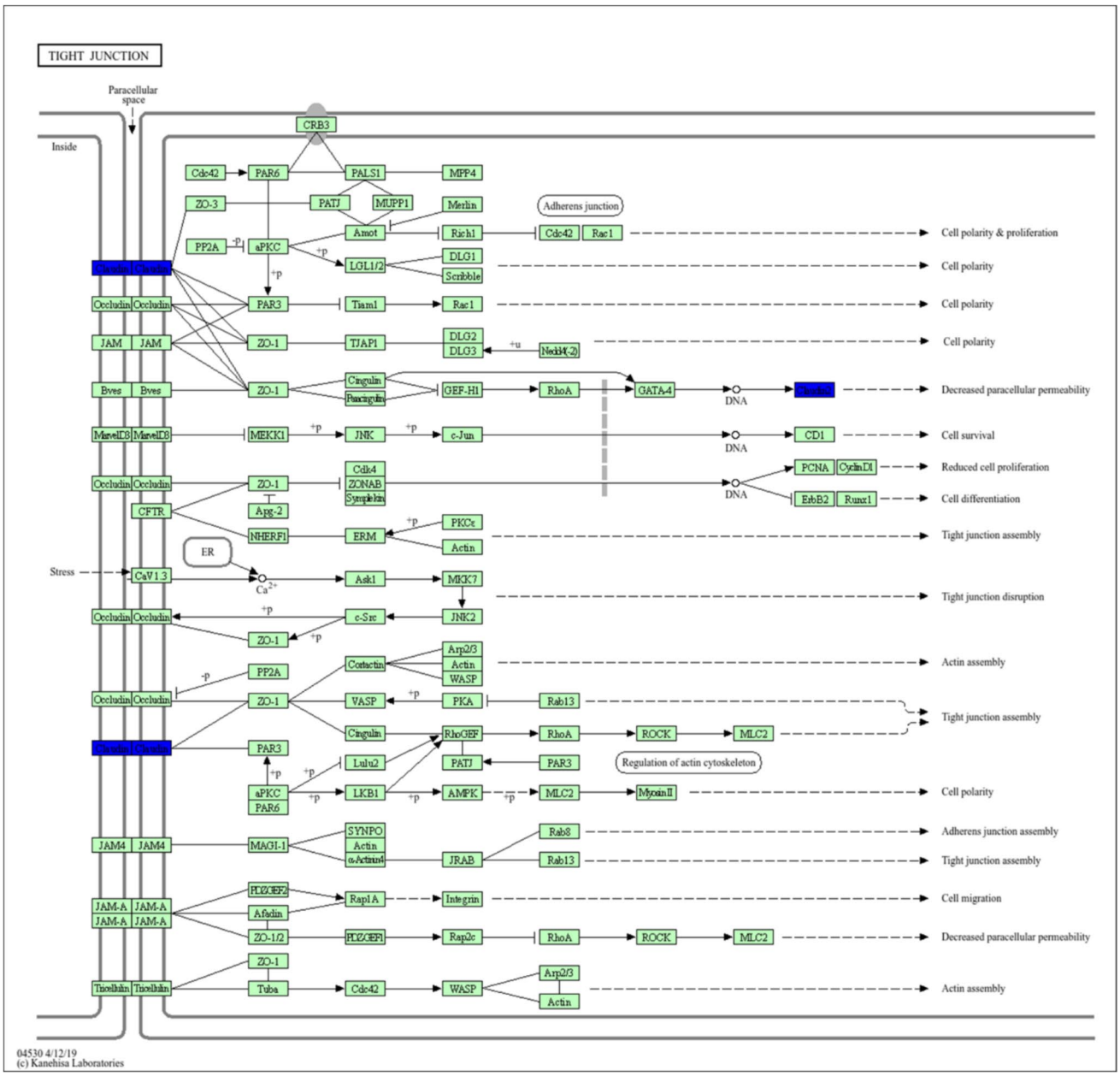


Fig. 6 Schematic representation of the role of CLDN proteins in tight junctions. The diagram shows the interaction network of CLDN proteins with other proteins such as Occludin and JAM, and how these interactions affect cellular functions through different signaling molecules, including PAR3, PAR6, aPKC, and Rac1. The CLDN protein indicated in blue (Figure source: https://www.kegg.jp/kegg/kegg1.html)

of characteristic freeze-fracture strands in claudin-1/-2-expressing fibroblasts (Furuse et al. 1998b). Within the same cell membrane, CLDN proteins engage in cis-interactions via their transmembrane domains and extracellular loops to form oligomers, a process confirmed by FRET studies that have revealed the existence of heteromeric complexes among CLDN1, CLDN2, CLDN3, and CLDN5. The heterotypic binding of different CLDNs is selective; for instance, CLDN3 can form trans-cellular associations with CLDN1, CLDN2, and CLDN5, whereas the binding between CLDN1 and CLDN5 is relatively weak (Daugherty et al. 2007). Moreover, specific pairs such as CLDN16 and CLDN19 necessitate heteromerization for proper targeting to tight junctions (Hou et al. 2009; Piontek et al. 2011). These intramembrane interactions are functionally significant, as their disruption can trigger occludin-dependent apoptosis (Beeman et al. 2012). Between adjacent cells, claudins engage in trans-interactions through their extracellular domains (Hashimoto et al. 2023), with homotypic pairing (e.g., claudin-1/-1) being predominant but selective

Table 1 Comparison of monomer analysis and polymer/TJ environment analysis in studying tight junction properties

Property	Monomer analysis	Polymer/TJ environment analysis
Barrier function	Cannot simulate pore or seal selectivity	Reflects true permeability (e.g., Claudin-2/15 synergy)
Signal recruitment	Only detects direct binding (e.g., PDZ)	Reveals scaffold-dependent signaling platforms
Conformational dynamics	Static structure (X-ray/NMR)	Force-sensitive/chemically induced allostery
Pathological relevance	May miss compensatory mechanisms (e.g., Claudin upregulation)	More closely mimics disease models (e.g., organoids/live imaging)

heterotypic combinations (e.g., claudin-1/-3 or renal claudin-16/-19) contributing to tissue-specific functions such as magnesium reabsorption—mutations in which cause familial hypomagnesemia (FHHNC) (Van Itallie and Anderson 2013). The assembly process begins with ER quality control but culminates in the Golgi apparatus, with cholesterol-rich membrane microdomains (e.g., those containing CD81) facilitating final multimerization (Koval 2013). This sophisticated polymerization mechanism underlies the dual functions of tight junctions: maintaining structural adhesion and regulating paracellular permeability.

However, the current overemphasis on monomeric CLDN protein studies limits our comprehensive understanding of their functional mechanisms, as these studies fail to reflect the true physiological context of CLDN polymer networks within intact tight junctions. Monomeric studies cannot replicate the cooperative barrier functions of claudin polymers in native tight junction environments (e.g., the synergistic permeability selectivity of claudin-2/15), the assembly of scaffold-dependent signaling platforms (e.g., ZO-1-mediated signalosome formation), or mechanically sensitive conformational changes. More critically, monomeric studies often overlook compensatory regulatory mechanisms among claudin subtypes, potentially leading to misinterpretations of disease pathogenesis. For example, while CLDN18.2 monomers exhibit weak signaling activity in vitro, in gastric cancer tissues, CLDN18.2 forms heteropolymers with HER2, significantly activating PI3K/AKT and S100A4-dependent metastatic pathways to promote tumor progression (Liu et al. 2024a). This mechanism is only demonstrable in TJ-like environments, whereas monomeric studies cannot reveal such interactions (Table 1).

Conclusion

The diverse biological functions of CLDN proteins are governed by the organization of specific sequence motifs, each encoding distinct functional properties. By summarizing the literature and data, we focus on these unique and functional motifs. Throughout the evolutionary history of CLDN proteins, their extracellular loop structures have retained conserved sites that confer intercellular adhesion, barrier functions, and the regulation of ion channel functions (Krause et al. 2008; Powell 1981). The CLDN protein regulates the function of ion channels based on the distribution of acidic and basic amino acids (Furuse and Biol 1999; Shin et al. 2022; Suzuki et al. 2014). When interacting with ZO proteins to maintain their function, the phosphorylated C-terminus may play a crucial role by exerting its effects through intermolecular interactions mediated by key amino acids. Recent research has found that CLDN proteins play a crucial role in various physiological and pathological processes by participating in key signaling pathways such as the establishment of cell polarity, cytoskeletal reorganization, and regulation of cell survival (Ling et al. 2024; Murakami-Nishimagi et al. 2023; Pan et al. 2024).

There remain several significant scientific issues in this field that require resolution: firstly, the functional domains of CLDN proteins and their dynamic regulatory mechanisms need to be more precisely defined; secondly, the collaborative regulatory relationship between protein interaction networks and post-translational modifications, such as phosphorylation, remains to be elucidated (Basith et al. 2022; Pham et al. 2024); lastly, CLDN proteins may initiate different signaling cascades in specific physiological states by conformationally dependent exposure of their functional domains. Targeted intervention strategies based on the CLDN signaling network still needs further optimization. The resolution of these issues will promote a deeper understanding of the functions of CLDN proteins and provide new ideas for the treatment of related diseases.

Acknowledgements This research was funded by the National Natural Scientific Foundation of China (62171241), The Group Project of Developing Inner Mongolia through Talents (2025TEL25), the China Postdoctoral Science Foundation under Grant Number (2024MD763987), the Central Guidance Fund for Local Science and Technology Development (2024ZY0168) and Natural Science Foundation of Inner
Mongolia Autonomous Region (2023LHMS08017).

Author contributions Conceptualization, Y.C.Z. and W.H.Z.; Visualization, formal analysis and writing—original draft, L.L.B. and S.Q.Y.; Writing—review & editing, S.Q.Y. All authors have read and agreed to the published version of the manuscript.

Funding This research was funded by the National Natural Scientific Foundation of China (62571279, 62171241), The Group Project of De-

veloping Inner Mongolia through Talents (2025TEL25), Hohhot City Basic Research and Applied Basic Research Project (2024GJ18), the Central Guidance Fund for Local Science and Technology Development (2024ZY0168) and Natural Science Foundation of Inner Mongolia Autonomous Region (2023LHMS08017).

Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

References

Abdelkader GA, Kim JD (2024) Advances in protein-ligand binding affinity prediction via deep learning: a comprehensive study of datasets, data preprocessing techniques, and model architectures. Curr Drug Targets 25(15):1041–1065

Ahmad W, Shabbiri K, Ijaz B, Asad S, Hassan SJVJ (2011) Claudin-1 required for HCV virus entry has high potential for phosphorylation and o-glycosylation. Virol J. https://doi.org/10.1186/1743-422X-8-229

Angelow S, Ahlstrom R, Yu A (2008) Biology of claudins. Am J Physiol Renal Physiol 295(4):867

Bakir B, Chiarella AM, Pitarresi JR, Rustgi AKJ (2020) Emt, met, plasticity, and tumor metastasis. Trends Cell Biol 30(10):764–776

Basith S, Lee G, Manavalan B (2022) Stallion: a stacking-based ensemble learning framework for prokaryotic lysine acetylation site prediction. Brief Bioinform. https://doi.org/10.1093/bib/bbab376

Beeman N, Webb PG, Baumgartner HK (2012) Occludin is required for apoptosis when claudin-claudin interactions are disrupted. Cell Death Dis 3(2):e273

Berselli A, Alberini G, Benfenati F, Maragliano L (2022) Computational study of ion permeation through claudin-4 paracellular channels. Ann N Y Acad Sci 1516(1):162–174

Brunner N, Stein L, Amasheh S (2023) Cellular distribution pattern of TJP1 (ZO-1) in *Xenopus laevis* oocytes heterologously expressing claudins. J Membr Biol 256(1):51–61

Colegio OR, Van Itallie CM, Mccrea HJ, Rahner C, Anderson J (2002a) Claudins create charge-selective channels in the paracellular pathway between epithelial cells. Am J Physiol Cell Physiol 283(1):142

Colegio OR, Van Itallie CM, McCrea HJ, Rahner C, Anderson JM (2002b) Claudins create charge-selective channels in the paracellular pathway between epithelial cells. Am J Physiol Cell Physiol 283(1):C142-147

Colegio OR, Van Itallie C, Rahner C, Anderson JM (2003) Claudin extracellular domains determine paracellular charge selectivity and resistance but not tight junction fibril architecture. Am J Physiol Cell Physiol 284(6):C1346-1354

Daugherty BL, Ward C, Smith T, Ritzenthaler JD, Koval M (2007) Regulation of heterotypic claudin compatibility. J Biol Chem 282(41):30005–30013

D'Souza T, Agarwal R, Morin PJ (2005) Phosphorylation of claudin-3 at threonine 192 by camp-dependent protein kinase regulates tight junction barrier function in ovarian cancer cells. J Biol Chem 280(28):26233–26240

Fanning AS, Anderson J (2010) Zonula occludens-1 and -2 are cytosolic scaffolds that regulate the assembly of cellular junctions. Ann N Y Acad Sci 1165:113–120

Findley MK, Koval M (2009) Regulation and roles for claudin-family tight junction proteins. IUBMB Life 61(4):431–437

Furuse BM (1999) Manner of interaction of heterogeneous claudin species within and between tight junction strands. J Cell Biol 147(4):891–903

Furuse M, Fujita K, Hiiragi T, Fujimoto K, Tsukita S (1998a) Claudin-1 and -2: Novel integral membrane proteins localizing at tight junctions with no sequence. J Cell Biol 141(7):1539–1539

Furuse M, Sasaki H, Fujimoto K, Tsukita S (1998b) A single gene product, claudin-1 or -2, reconstitutes tight junction strands and recruits occludin in fibroblasts. J Cell Biol 143(2):391–401

Ghai S, Shrestha R, Su KH (2024) Hsf1 at the crossroads of chemoresistance: from current insights to future horizons in cell death mechanisms. Front Cell Dev Biol 12:1500880

Günzel D, Yu AS (2013) Claudins and the modulation of tight junction permeability. Physiol Rev 93(2):525–569

Günzel D, Stuiver M, Kausalya PJ, Haisch L, Krug SM, Rosenthal R, Meij IC, Hunziker W, Fromm M, Müller D (2009) Claudin-10 exists in six alternatively spliced isoforms that exhibit distinct localization and function. J Cell Sci 122(Pt 10):1507–1517

Hashimoto I, Oshima T (2022) Claudins and gastric cancer: an overview. Cancers. https://doi.org/10.3390/cancers14020290

Hashimoto Y, Greene C, Munnich A, Campbell M (2023) The *cldn5* gene at the blood-brain barrier in health and disease. Fluids Barriers CNS 20(1):22

Hou J, Renigunta A, Konrad M, Gomes AS, Goodenough D (2008) Claudin-16 and claudin-19 interact and form a cation-selective tight junction complex. J Clin Invest 118(2):619–628

Hou J, Renigunta A, Gomes AS, Hou M, Paul DL, Waldegger S, Goodenough DA (2009) Claudin-16 and claudin-19 interaction is required for their assembly into tight junctions and for renal reabsorption of magnesium. Proc Natl Acad Sci U S A 106(36):15350–15355

Hou J, Rajagopal M, Yu A (2012) Claudins and the kidney. Annu Rev Physiol 75(1):479–502

Inaba H, Miao Q, Nakata T (2021) Optogenetic control of small gtpases reveals rhoa mediates intracellular calcium signaling. J Biol Chem 296:100290

Itallie CMV, Anderson J (2014) Architecture of tight junctions and principles of molecular composition. Semin Cell Dev Biol 36:157–165

Itoh M, Furuse M, Morita K, Kubota K, Tsukita S (1999) Direct binding of three tight junction-associated maguks, zo-1, zo-2, and zo-3, with the cooh termini of claudins. J Cell Biol. https://doi.org/10.1083/jcb.147.6.1351

Jeansonne B, Lu Q, Goodenough DA, Chen Y (2003) Claudin-8 interacts with multi-pdz domain protein 1 (mupp1) and reduces paracellular conductance in epithelial cells. Cell Mol Biol 49(1):13–21

Kay Y (2017) Epithelial-mesenchymal transition in tumor metastasis. Annu Rev Pathol. https://doi.org/10.1146/annurev-pathol-020117-043854

Koval M (2006) Claudins–key pieces in the tight junction puzzle. Cell Commun Adhes 13(3):127–138

Koval M (2013) Differential pathways of claudin oligomerization and integration into tight junctions. Tissue Barriers 1(3):e24518

Krause G, Winkler L, Mueller SL, Haseloff RF, Piontek J, Blasig I (2008) Structure and function of claudins. Biochim Biophys Acta 1778(3):631–645

Ling Y, Kang X, Yi Y, Feng S, Ma G, Qu H (2024) Cldn5: from structure and regulation to roles in tumors and other diseases beyond cns disorders. Pharmacol Res 200:107075

Liu Q, Shen H, Naguib A, Weiss RM, Martin DT (2021) Knocking down claudin receptors leads to a decrease in prostate cancer cell migration, cell growth, cell viability and clonogenic cell survival. Mol Biomed 2(1):31

Liu H, Zhang Z, Zhou S, Liu X, Li G, Song B, Xu W (2022) Claudin-1/4 as directly target gene of hif-1α can feedback regulating hif-1α by pi3k-akt-mtor and impact the proliferation of esophageal squamous cell though rho gtpase and p-jnk pathway. Cancer Gene Ther 29(6):665–682

Liu S, Zhang Z, Jiang L, Zhang M, Zhang C, Shen L (2024a) Claudin-18.2 mediated interaction of gastric cancer cells and cancer-associated fibroblasts drives tumor progression. Cell Commun Signal 22(1):27

Liu T, Qiao H, Wang Z, Yang X, Pan X, Yang Y, Ye X, Sakurai T, Lin H, Zhang Y (2024b) Codlncscape provides a self-enriching framework for the systematic collection and exploration of coding lncrnas. Adv Sci 11(22):2400009

Manjunath M, Ravindran F, Sharma S, Siddiqua H, Raghavan SC, Choudhary B (2024) Disarib, a specific bcl2 inhibitor, induces apoptosis in triple-negative breast cancer cells and impedes tumour progression in xenografts by altering mitochondria-associated processes. Int J Mol Sci. https://doi.org/10.3390/ijms25126485

Marsch P, Rajagopal N, Nangia SJBJ (2024) Biophysics of claudin proteins in tight junction architecture: three decades of progress. Biophys J 123(16):2363–2378

Mineta K, Yamamoto Y, Yamazaki Y, Tanaka H, Tada Y, Saito K, Tamura A, Igarashi M, Endo T, Takeuchi K, Tsukita S (2011) Predicted expansion of the claudin multigene family. FEBS Lett 585(4):606–612

Molecules KK (2024) Biochemical modulators of tight junctions (tjs): Occludin, claudin-2 and zonulin as biomarkers of intestinal barrier leakage in the diagnosis and assessment of inflammatory bowel disease progression. Molecules 29(19):4577

Morin PJ (2005) Claudin proteins in human cancer: promising new targets for diagnosis and therapy. Cancer Res 65(21):9603–9606

Morin ML (2009) The claudins. Genome Biol 10(8):235

Murakami-Nishimagi Y, Sugimoto K, Kobayashi M, Tachibana K, Kojima M, Okano M, Hashimoto Y, Saji S, Ohtake T, Chiba H (2023) Claudin-4-adhesion signaling drives breast cancer metabolism and progression via liver x receptor β. Breast Cancer Res 25(1):41

Nakamura S, Irie K, Tanaka H, Nishikawa K, Suzuki H, Saitoh Y, Tamura A, Tsukita S, Fujiyoshi Y (2019) Morphologic determinant of tight junctions revealed by claudin-3 structures. Nat Commun 10(1):816

Ohta S, Misawa A, Fukaya R, Inoue S, Kanemura Y, Okano H, Kawakami Y, Toda MJ (2012) Macrophage migration inhibitory factor (mif) promotes cell survival and proliferation of neural stem/progenitor cells. J Cell Sci 125(13):3210–3220

Otani T, Nguyen TP, Tokuda S, Sugihara K, Sugawara T, Furuse K, Miura T, Ebnet K, Furuse M (2019) Claudins and Jam-A coordinately regulate tight junction formation and epithelial polarity. J Cell Biol 218(10):3372–3396

Pan X, Ren L, Yang Y, Xu Y, Ning L, Zhang Y, Luo H, Zou Q, Zhang Y (2024) Mcsdb, a database of proteins residing in membrane contact sites. Sci Data 11(1):281

Pham NT, Zhang Y, Rakkiyappan R, Manavalan B (2024) Hotgpred: enhancing human o-linked threonine glycosylation prediction using integrated pretrained protein language model-based features and multi-stage feature selection approach. Comput Biol Med 179:108859

Piontek J, Winkler L, Wolburg H, Müller SL, Blasig I (2008) Formation of tight junction: Determinants of homophilic interaction between classic claudins. FASEB J 22(1):146–158

Piontek J, Fritzsche S, Cording J, Richter S, Hartwig J, Walter M, Yu D, Turner JR, Gehring C, Rahn HP, Wolburg H, Blasig IE (2011) Elucidating the principles of the molecular organization of heteropolymeric tight junction strands. Cell Mol Life Sci 68(23):3903–3918

Powell DW (1981) Barrier function of epithelia. Am J Physiol 241(4):275–288

Raya-Sandino A, Lozada-Soto KM, Rajagopal N, Garcia-Hernandez V, Luissint AC, Brazil JC, Cui G, Koval M, Parkos CA, Nangia S, Nusrat A (2023) Claudin-23 reshapes epithelial tight junction architecture to regulate barrier function. Nat Commun 14(1):6214

Reviews AS (2013) Claudins and the modulation of tight junction permeability. Physiol Rev 93(2):525–569

Riazuddin S, Ahmed ZM, Fanning AS, Lagziel A, Kitajiri SI, Ramzan K, Khan SN, Chattaraj P, Friedman PL, Anderson JM (2006) Tricellulin is a tight-junction protein necessary for hearing. Am J Hum Genet 79(6):1040–1051

Rosenthal R, Milatz S, Krug SM, Oelrich B, Schulzke JD, Amasheh S, Gunzel D, Fromm MJ (2010) Claudin-2, a component of the tight junction, forms a paracellular water channel. J Cell Sci 123(11):1913–1921 (**JoCS**)

Rosenthal R, Günzel D, Krug SM, Schulzke JD, Fromm M, Yu AS (2017) Claudin-2-mediated cation and water transport share a common pore. Acta Physiol (Oxf) 219(2):521–536

Shen L, Weber CR, Raleigh DR, Yu D, Turner JRJ, ARoP (2011) Tight junction pore and leak pathways: a dynamic duo. Annu Rev Physiol 73(1):283

Shin A, Sugiura K, Masuike Y, Suzuki K, Lengner CJ, Rustgi AJCR (2022) Abstract b007: Lin28b promotes collective cell invasion and colorectal cancer metastasis via a novel cldn1 and notch3 axis. JCI Insight. https://doi.org/10.1172/jci.insight.167310

Sugawara T, Sonoda K, Chompusri N, Noguchi K, Okada S, Furuse M, Wakayama T (2025) Claudin-11 regulates immunological barrier formation and spermatogonial proliferation through stem cell factor. Commun Biol 8(1):148

Suzuki H, Nishizawa T, Tani K, Yamazaki Y, Fujiyoshi YJS (2014) Crystal structure of a claudin provides insight into the architecture of tight junctions. Science 344(6181):304–307

Taylor A, Warner M, Mendoza C, Memmott C, LeCheminant T, Bailey S, Christensen C, Keller J, Suli A, Mizrachi D (2021) Chimeric claudins: a new tool to study tight junction structure and function. Int J Mol Sci. https://doi.org/10.3390/ijms22094947

Tsukita S, Furuse M, Itoh M (2001) Multifunctional strands in tight junctions. Nat Rev Mol Cell Biol 2(4):285–293

Tsukita S, Tanaka H, Tamura A (2019) The claudins: from tight junctions to biological systems. Trends Biochem Sci 44(2):141–152

Umeda K, Ikenouchi J, Katahira-Tayama S, Furuse K, Sasaki H, Nakayama M, Matsui T, Tsukita S, Furuse M, Tsukita SJ (2006) Zo-1 and zo-2 independently determine where claudins are polymerized in tight-junction strand formation. Cell 126(4):741–754

Van Itallie CM, Anderson JM (2013) Claudin interactions in and out of the tight junction. Tissue Barriers 1(3):e25247

Van Itallie C, Fanning A, Anderson JJ (2003) Reversal of charge selectivity in cation or anion-selective epithelial lines by expression of different claudins. Bosn J Basic Med Sci 285(6):F1078–F1084

Villagomez FR, Lang J, Nunez-Avellaneda D, Behbakht K, Dimmick HL, Webb PG, Nephew KP, Neville M, Woodruff ER, Bitler BG (2025) Claudin-4 stabilizes the genome via nuclear and cell-cycle remodeling to support ovarian cancer cell survival. Cancer Res Commun 5(1):39–53

Wang C, Wu N, Pei B, Ma X, Yang W (2023) Claudin and pancreatic cancer. Front Oncol 13:1136227

Wang K, Liu Y, Li H, Liang X, Hao M, Yuan D, Ding LJCD (2024) Claudin-7 is essential for the maintenance of colonic stem cell homoeostasis via the modulation of wnt/notch signalling. Cell Death Dis. https://doi.org/10.1038/s41419-024-06658-x

Weber CR, Liang GH, Wang Y, Das S, Shen L, Yu AS, Nelson DJ, Turner JR (2015) Claudin-2-dependent paracellular channels are dynamically gated. Elife 4:e09906

Wen H, Watry DD, Marcondes MCG, Fox H (2004) Selective decrease in paracellular conductance of tight junctions: role of the first extracellular domain of claudin-5. Mol Cell Biol 24(19):8408–8417

Yu AS, Cheng MH, Angelow S, Günzel D, Kanzawa SA, Schneeberger EE, Fromm M, Coalson RD (2009) Molecular basis for cation selectivity in claudin-2-based paracellular pores: identification of an electrostatic interaction site. J Gen Physiol 133(1):111–127

Zhang M, Cao A, Lin L, Chen Y, Shang Y, Wang C, Zhang M, Zhu J (2023) Phosphorylation-dependent recognition of diverse protein targets by the cryptic gk domain of magi maguks. Sci Adv 9(19):eadf3295

Zhang Y, Yang Y, Ren L, Zhan M, Sun T, Zou Q, Zhang Y (2024) Predicting intercellular communication based on metabolite-related ligand-receptor interactions with mrclinkdb. BMC Biol 22(1):152

Zhu W, Yuan SS, Li J, Huang CB, Lin H, Liao B (2023) A first computational frame for recognizing heparin-binding protein. Diagnostics. https://doi.org/10.3390/diagnostics13142465

Zou X, Ren L, Cai P, Zhang Y, Ding H, Deng K, Yu X, Lin H, Huang C (2023) Accurately identifying hemagglutinin using sequence information and machine learning methods. Front Med Lausanne 10:1281880