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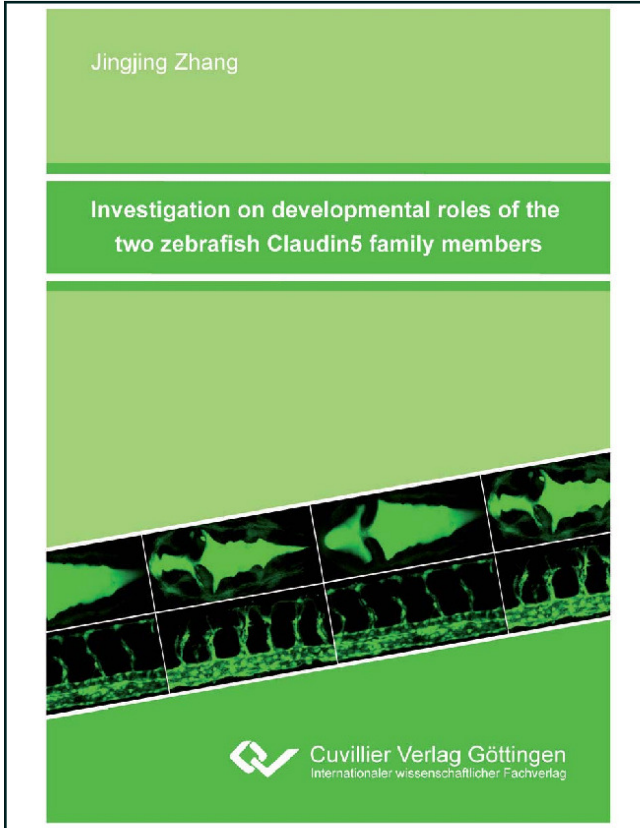
Investigation on developmental roles of the two zebrafish Claudin5 family members



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1. Introduction

1.1. Claudins as structural and functional components of tight junctions

Tight junctions (TJs) are located at the most apical part of lateral plasma membranes, in epithelial or endothelial cells, where they form tight seals between adjacent cells. Within the cell membrane, TJs act as fences that block lateral diffusion of membrane proteins and lipids between the apical and basolateral surfaces, thereby maintaining apical-basal cell polarity (Gonzalez-Mariscal et al., 2003; Matter and Balda, 2003; Turksen and Troy, 2004). Between adjacent endothelial or epithelial cells, TJs function as gates, which control the passage of ions and molecules through the paracellular pathway and create borders which separate external from internal milieus throughout the body (Fig. 1.1). By these divergent functions, TJs are essential components of tissue barriers that are involved in the proper function of different organs including the brain, kidney, intestine or vasculature.

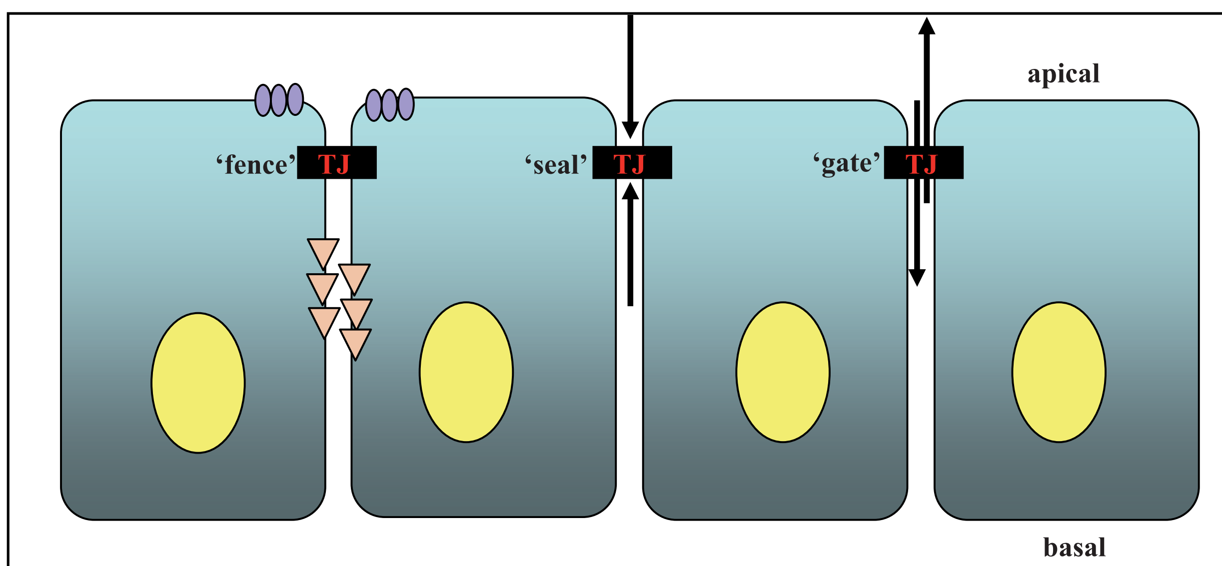

Fig. 1.1. Schematic diagram of tight junction fence and gate functions. TJs act as 'fences' to prevent the mixing of apical and basolateral membrane components (left). TJs can form a tight seal between epithelial/endothelial cells that blocks the movement of ions through the paracellular space (middle pair of cells). Alternatively, as shown on the right, some TJs function as 'gate' and are permissive or 'leaky' which allows the movement of water and ions through the paracellular space. (Figure modified after Gupta and Ryan, 2010)

1.1.1. Structure and classes of Claudins

Claudins (Cldns) are critical structural and functional components of TJs. In mammals, 24 Cldn family members have been reported. They are range in size from 22 to 27 kDa and contain four hydrophobic transmembrane domains, two extracellular loops (ECLs), a short intracellular loop and N- and C-termini extending into the cytoplasm (Fig. 1.2; Krause et al., 2008; Lal-Nag and Morin, 2009).

It has been suggested that the first ECL domain (ECL1) is critical for determining paracellular tightness and selective paracellular ion permeability (Van Itallie and Anderson, 2006; Colegio et al., 2002). Pore formation or tightness is supported by the spatial encounter of a surplus of repulsing or attracting charged amino acids at ECL1. A pore is likely opened by repulsion of equally charged residues, while an encounter of unequally charged residues leads to tight interaction (Amasheh et al., 2002; Hou et al., 2005; Colegio et al., 2003; Alexandre et al., 2007; Van Itallie et al., 2006; Krause et al., 2009).

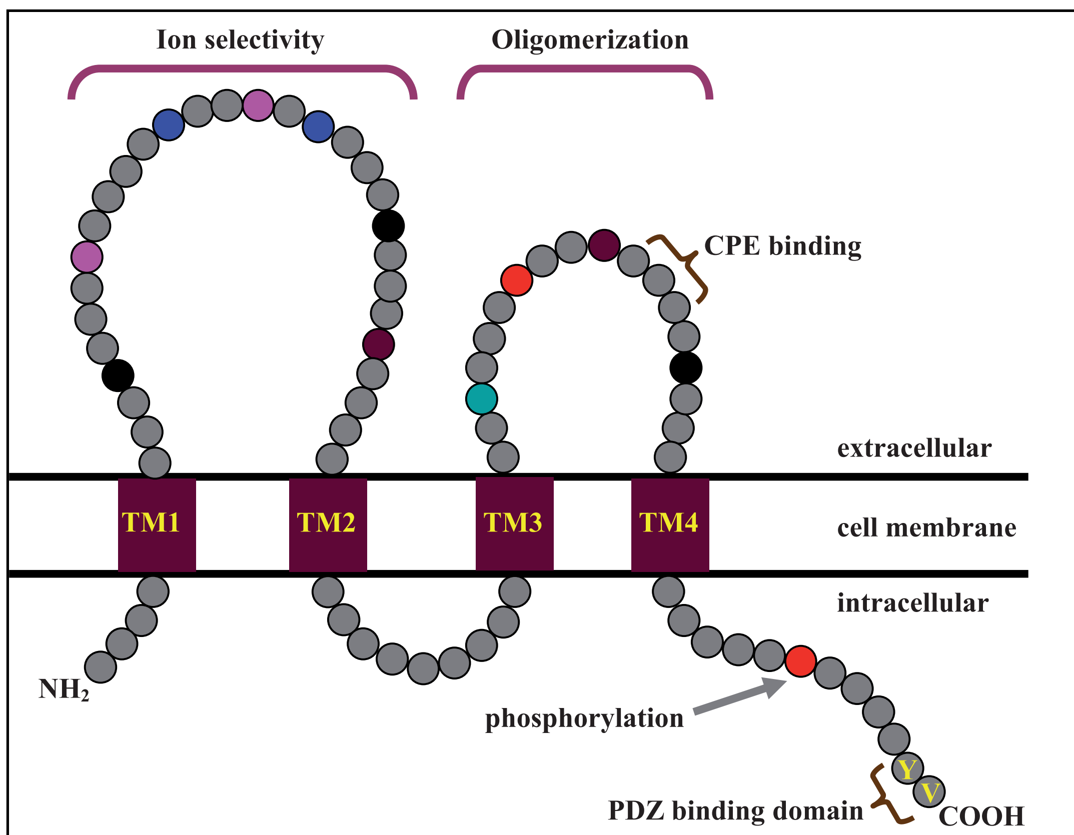

Fig. 1.2. Structure of Claudins. Cldns contain four transmembrane domains (TM1–4), two ECLs and a C-terminal cytoplasmic tail. The ECL1 domain contains several basic (blue) and acidic (pink) amino acid residues that regulate ion selectivity of the TJ, whereas ECL2 participates in binding interactions with other Cldn family members and in some family members contains a binding site for the CPE. The C-terminal cytoplasmic tail contains phosphorylation consensus sites (red circle) and a binding domain for PDZ-domain containing proteins, such as Zonula Occludens-1 (ZO-1). (Figure modified after Gupta and Ryan, 2010)

Within different Cldns, ECL2 domains are comprised of 16 to 33 amino acids and participate in side-to-side oligomerization of Cldns, which is required for the TJ strands formation between cells (Coyne et al., 2003) as well as head-to-head interactions of Cldn molecules between opposing cells (Blasig et al., 2006; Daugherty et al., 2007). Moreover, Cldn ECL2 has been reported as a receptor for *Clostridium perfringens* enterotoxin (CPE) (Fig. 1.2; Van Itallie et al., 2008). Direct binding of CPE to Cldn4 in Madin-Darby canine kidney (MDCK) cells inhibits barrier functions (Sonoda et al., 1999).

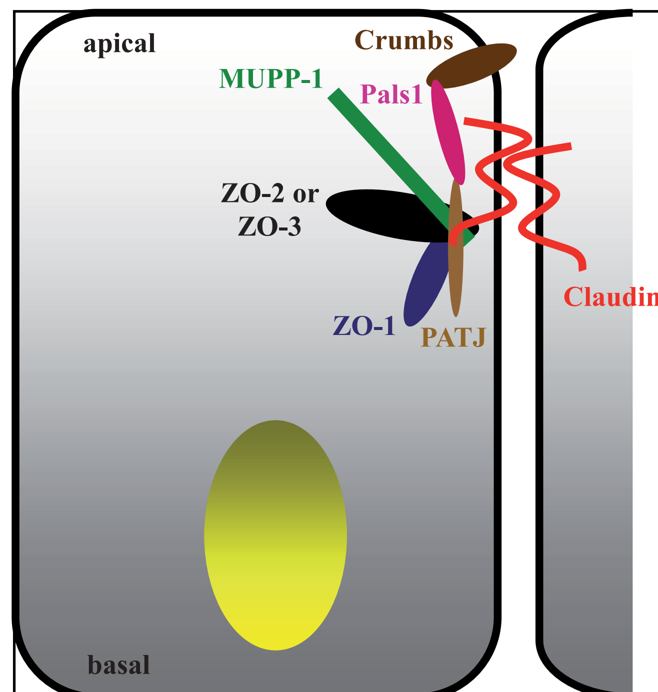

Fig. 1.3. Schematic representation of Claudin and interacting molecules at the tight junction. The C-terminal tail interacts with PDZ domain adaptor proteins such as ZO-1 and MUPP1. These adaptors link the TJ to the cytoskeleton. Several transcriptional regulators are known to interact with proteins at the TJ. (Figure modified after Turksen and Troy, 2004)

The region that shows the most sequence and size heterogeneity among different Cldns is the C-terminal tail (Fig. 1.2) which contains a conserved PDZ-domain-binding motif that allows Cldns to interact with other TJ scaffolding proteins, such as multiple PDZ domain containing proteins-1 (MUPP1) (Hamazaki et al., 2002), PALS1-associated TJ protein (PATJ) (Roh et al., 2002), Zonula Occludens-1 (ZO-1), ZO-2 and ZO-3, and other membrane-associated guanylate kinases (MAGUKs) (Fig. 1.3). This motif has been shown to be required for the interaction between murine Cldn1-8 with the PDZ domains of ZO-1, ZO-2 and ZO-3 *in vitro* (Fig. 1.2; Itoh et al., 1999). Furthermore, the C-terminal tail upstream of the PDZ-binding motif is also involved in targeting the protein to the TJ complex (Ruffer and Gerke, 2004) and functions as a determinant of protein stability and function (Van Itallie and Anderson, 2006). Various post-translational modifications that can significantly alter Cldn localization and function, such as serine/threonine and tyrosine phosphorylation (Gonzalez-Mariscal et al., 2008) and palmitoylation (Van Itallie et al., 2005), target the C-terminal tail. Recent experimental evidence has shown that, Cldn5 phosphorylation by protein kinase C induces increased murine brain endothelial permeability (Stamatovic et al., 2006). There is also evidence suggesting that phosphorylation of a conserved tyrosine residue within the PDZ binding domain (Tyr208) of human Cldn4 by EphrinA2 causes the removal of this Cldn from the TJ and results in increased paracellular permeability (Tanaka et al., 2005).

Cldns have been subdivided into ‘classic’ (including Cldn1-10, 14, 15, 17, 19) or ‘non-classic’ (including Cldn11-13, 16, 18, 20-24) groups based on their sequence similarities (Fig. 1.4; Krause et al., 2009; Lal-Nag and Morin, 2009). Functionally, Cldns can be categorized either as barrier- or pore-forming (Amasheh et al., 2009): based on functional assays, Cldn2, 7, 10, 15 and 16 have been identified as paracellular pore-forming (Amasheh et al., 2002; Hou et al., 2005; Van Itallie et al., 2006; Alexandre et al., 2005; Van Itallie et al., 2003), whereas Cldn1, 3, 4, 5, 8, 11, 14 and 19 have been shown to be barrier-forming (Gow et al., 1999; Furuse, et al. 2002; Nitta et al. 2003; Ben-Yosef et al., 2003; D’Souza et al., 2005; Litkouhi et al. 2007; Boireau et al. 2007; Angelow et al., 2006; Angelow et al., 2007).