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## **Claudins in viral infection: From entry to spread**

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## **Abstract**

Tight junctions are critically important for many physiological functions, including the maintenance of cell polarity, regulation of paracellular permeability and involvement in signal transduction pathways to regulate integral cellular processes. Furthermore, tight junctions enable epithelial cells to form physical barriers, which act as an innate immune mechanism that can impede viral infection. Viruses, in turn, have evolved mechanisms to exploit tight junction proteins to gain access to cells or spread through tissues in an infected host. Claudin family proteins are integral components of tight junctions, and are thought to play crucial roles in regulating their permeability. Claudins have been implicated in the infection process of several medically important human pathogens, including hepatitis C virus, dengue virus, West Nile virus and human immunodeficiency virus, among others. In this review, we summarize the role of claudins in viral infections, and discuss their potential as novel antiviral targets. A better understanding of claudins during viral infection may provide insight into physiological roles of claudins and uncover novel therapeutic antiviral strategies.

## Introduction

Tight junctions are highly specialized membrane domains that regulate paracellular permeability by forming intercellular barriers between epithelial cells. They also provide a physical barrier between apical and basolateral membrane domains of polarized epithelial cells, thus regulating compartmentalization of membrane molecules. As such, tight junctions maintain cell polarity [84] and have also been implicated in signal transduction pathways [36].

Integral membrane tight junction proteins include occludin (OCLN) [32], claudins (CLDNs) [31] and junctional adhesion molecule-1 (JAM-1) [63]. The claudin family is thought to be the most crucial for mediating formation and permeability of tight junctions. Structurally, claudins are 25-27 kDa proteins comprised of intracellular N-terminal and C-terminal tails, four transmembrane helices, two extracellular loops (large ECL1 and small ECL2) and one cytoplasmic loop (**Figure 1**). Typically, claudins have a signature sequence within ECL1 and a conserved C-terminal motif for binding to PDZ (PSD95, postsynaptic density protein; Dlg1, Drosophila disc large tumor suppressor; ZO-1, zonula occludens-1 protein) domains, enabling interaction with tight junction-associated scaffolding and adaptor proteins [49]. Homophilic and heterophilic interactions between different claudins as well as other TJ members mediate paracellular tightening at tight junctions, thus dictating permeability.

The mammalian claudin family is comprised of 27 different members to date, although only 26 of these are found in humans [39]. Splice variants have been reported for some of these claudins, resulting in different protein isoforms with distinct expression patterns and function. Claudins are expressed in all epithelial tissues, although claudin family members have differential expression in different

tissues [39]. Although claudins are typically found in tight junctions, non-junctional localization of some claudins has been reported [37, 48, 78]. For example, CLDN1 associates with tetraspanins on the hepatocyte cell surface to form tetraspanin enriched microdomain (TEM) [78]. Furthermore, CLDN1 directly associates with tetraspanin CD9 on Madin-Darby canine kidney cells and various carcinoma cells, and these CLDN1-CD9 complexes did not reside in tight junctions [52]. However, the physiological role of non-junctional claudin complexes remains to be identified.

Tight junctions enable epithelial cells to form tight physical barriers that help to defend against infection. Some viruses counter this by infecting epithelial cells via receptors on the apical surface. Other viruses have evolved mechanisms to bypass epithelial cell barriers, either by using tight junction proteins as entry factors or by opening the tight junctions to facilitate their entry and dissemination. Indeed, tight junctions have been implicated in the infection process of several viruses (**Table 1**). In this review, we discuss the role of integral tight junction components, claudins, in viral infection and pathogenesis, and explore the potential of claudins as a target for antiviral therapy. Further studies into the role of claudins and tight junctions during viral infection will be important to better understand the mechanisms involved and to identify novel antiviral targets.

## **Claudins and viral entry**

### *Hepatitis C virus*

Claudins were first recognized to play a role in viral entry in 2007, when CLDN1 was identified as a host factor for the hepatitis C virus (HCV) [25]. HCV, a positive sense single stranded RNA virus belonging to the *Flaviviridae* family, chronically infects approximately 130 million people worldwide. These individuals are at increased risk

for severe liver disease, such as cirrhosis and hepatocellular carcinoma. As an RNA virus, HCV exists as a highly variable population of quasispecies and is classified into seven major genotypes. HCV infects hepatocytes via a complex, multi-step process involving several host proteins, including glycosaminoglycans [8, 9, 57, 83], low density lipoprotein receptor [2], very-low-density lipoprotein receptor [95], tetraspanins CD81 [76] and CD63 [74], scavenger receptor class B type 1 [82, 103], tight junction proteins CLDN1 [25] and occludin [77], E-cadherin [58], receptor tyrosine kinases such as epidermal growth factor receptor (EGFR) [59, 106], serum response factor binding protein 1 [35], cholesterol transporter Niemann-Pick C1-like 1 [80] and transferrin receptor 1 [62]. Following virion internalization [26, 68], fusion is triggered by low pH in the endosome [56]. The 9.6-kilobase genome is translated into a polyprotein of approximately 3000 amino acids [18], which then undergoes cleavage by cellular and viral proteases to generate 3 structural and 7 non-structural viral proteins.

CLDN1 plays a central role in the HCV entry process [25]. It was identified as an HCV entry factor using an iterative expression cloning approach in which non-hepatic 293T cells were transfected with a cDNA library derived from Huh7.5 hepatoma cells [25]. CLDN1 was later shown to be important for cell-to-cell transmission of HCV [12], as well as cell-free entry. Mechanistically, CLDN1 is thought to form a co-receptor complex with CD81, an interaction that likely occurs on the basolateral hepatocyte surface and involves non-TJ CLDN1 [43, 44]. The CD81-CLDN1 interaction involves the N-terminal portion of the ECL1 of CLDN1 [25]. Nine residues within the ECL1 of CLDN1 (W<sub>30</sub>-I<sub>32</sub>-D<sub>38</sub>-EGLW<sub>51</sub>-C<sub>54</sub>-C<sub>64</sub>) contributed to HCV entry [19, 25, 101]. Interestingly, these residues include W-GLW-C-C, the signature sequence shared by the majority of claudin family members [40]. In

particular, residues W<sub>30</sub>-I<sub>32</sub>-D<sub>38</sub>-EG<sub>49</sub>-W<sub>51</sub> interacted with CD81 to promote HCV entry [20]. Formation of the CD81-CLDN1 co-receptor complex is regulated by EGFR [59], which recruits the GTPase Harvey rat sarcoma viral oncogene homolog (HRas) to mediate co-receptor interaction and downstream MAPK signaling [106].

CLDN1 may also contribute to HCV entry by direct interaction with the HCV particle. HCV envelope glycoproteins E1 and E2 coimmunoprecipitate with CLDN1 [101], and the E1E2 heterodimer was shown to recognize CLDN1 [23]. Furthermore, a genetic interaction between E1 and CLDN family members was recently described [47]. Given that HCV E2 interacts with CD81 [46, 75] [51], both HCV envelope proteins may mediate binding to the co-receptor complex.

CLDN6 and CLDN9 show high sequence homology to CLDN1 in the CD81-interacting region, and have been proposed to function as complementary HCV co-receptors [67] [104]. Although CLDN6 and CLDN9 are predominantly expressed in non-hepatic epithelial tissue during embryonic or neonate development [1, 69, 70, 87, 94], their expression could be detected in human hepatoma cell lines, primary human hepatocytes and liver tissue by qPCR approaches [67, 104]. Expression of CLDN6 and CLDN9 in CLDN-deficient 293T cells facilitated entry of HCV pseudoparticles (HCVpp) and cell culture-derived HCV (HCVcc) [67, 104]. Furthermore, CLDN9 expression in CLDN1-deficient Bel7402 human hepatoma cells permitted HCV entry [104]. However, CLDN receptor usage appears to be genotype-dependent [41]. Genotypes 2, 5 and 7 were restricted to CLDN1, whereas other genotypes were able to efficiently use CLDN1 or CLDN6 for entry, as was shown in a CLDN-deficient cell line [41]. Interestingly, strong selection pressure led to a single amino acid substitution in the E1 protein of a CLDN1-dependent strain of HCV (genotype 2), conferring the ability to enter hepatocytes via CLDN6 [47].

As the CD81-CLDN1 co-receptor complex is essential for HCV entry, but lacks any known physiological (or pathological) function, therapies directed towards CLDN1 show great promise in preclinical models. Peptides derived from CLDN1 sequences inhibit HCV entry in cell culture models [85]. Monoclonal antibodies that target CLDN1 interfere with the formation of the co-receptor complex [54]. These antibodies pan-genotypically inhibit cell-free infection and cell-to-cell transmission of HCV in human hepatoma cells [27, 54, 100]. Strikingly, anti-CLDN1 antibodies prevent HCV infection of human liver chimeric mice [30, 60] and were even able to cure chronically HCV-infected liver chimeric mice [60] without any detectable toxicity.

One possible limitation for CLDN1-directed therapies is escape via CLDN6 or CLDN9 on hepatocytes. Indeed, CLDN1-specific antibodies only partially inhibited infection by HCV strains with broad CLDN tropism in CLDN6-expressing Huh7-derived hepatoma cell lines [41]. However, the functional relevance of these findings is not clear. CLDN6 and CLDN9 expression could not be detected at the protein level in primary human hepatocytes [67], and CLDN6 protein expression could not be detected in liver sections [28]. Furthermore, anti-CLDN6 and anti-CLDN9 antibodies did not inhibit HCV infection of hepatoma cells or primary hepatocytes [28]. Most importantly, treatment with an anti-CLDN1 monoclonal antibody cured chronically infected human liver chimeric mice, without escape [60]. Overall, these findings suggest that low expression levels of CLDN6 and CLDN9 likely precludes their use as HCV entry factors, at least in the majority of patients.

### *Dengue virus*

Like HCV, Dengue virus (DENV) is a positive sense single stranded RNA virus in the *Flaviviridae* family. The DENV genome is ~10.7-kb in length, encoding for 3



structural proteins (capsid, C; premembrane, prM; envelope, E) and 7 non-structural proteins [34]. Although DENV does not cause chronic infection, it is nonetheless a serious cause of morbidity and mortality around the world, particularly as it is a mosquito-borne virus endemic in over 100 countries [10]. In some patients, dengue virus infection leads to severe dengue hemorrhagic fever and shock syndrome (DHF/DSS) [55]. No specific antiviral therapy or vaccine is yet available.

The molecular mechanisms of DENV entry into human cells remain unclear. Several host proteins have been proposed as DENV entry factors, including glycosaminoglycans, lectins, glycosphingolipids and laminin-binding proteins [45]. Among these potential factors, CLDN1 was shown to be involved in DENV entry [17, 33]. CLDN1 knockout studies and RNAi-mediated gene silencing in hepatoma cells inhibited DENV infection. The DENV prM protein binds to CLDN1 residues I<sub>32</sub>, C<sub>54</sub> and C<sub>64</sub>, which interestingly are also implicated in HCV infection [17]. Further studies are needed to elucidate the mechanistic role of CLDN1 during DENV entry and potential roles of other CLDN family members.

### **Claudins and viral spread**

Viral infection and dissemination within a host is limited by epithelial cells, which line surfaces of organs and tissues to form a physical barrier enforced by tight junctions. Therefore, disruption of tight junctions in epithelial and endothelial barriers facilitates viral dissemination within the infected host. Several viruses, therefore, modulate expression of tight junction proteins such as claudins to enhance their dissemination.

### *West Nile virus*

Like HCV and DENV, West Nile virus is classified in the *Flaviviridae* family and has a single-stranded positive sense RNA genome of ~11 kb [13]. WNV is a mosquito-borne virus capable of infecting the central nervous system, resulting in neurological disease in a minority of infected patients. Following mosquito transmission, the virus crosses several polarized cell layers, requiring a disruption of tight junctions by mechanisms that are not completely understood. One study in kidney tubules reported that WNV capsid protein induced the degradation of CLDN1, CLDN2, CLDN3 and CLDN4 by lysosomal proteases [66]. In endothelial cells, the disruption of tight junctions was found to be an indirect result of WNV infection, by secretion of matrix metalloproteases from infected astrocytes [96, 97]. Furthermore, matrix metalloprotease 9 was found to be involved in WNV infection of the brain by disrupting the blood brain barrier [98]. More recently, Xu and colleagues reported that CLDN1 and other tight junction proteins undergo endocytosis in WNV-infected endothelial and epithelial cells, resulting in the lysosomal degradation of tight junction proteins [99]. Interestingly, CLDN1 degradation was also observed in endothelial and epithelial cells infected with Japanese encephalitis virus (a related neurotropic flavivirus) [3], but not DENV [99]. For WNV, multiple mechanisms of tight junction disruption appear to be involved, ranging from WNV-induced endocytosis and degradation of tight junction proteins to immune cell-mediated production of matrix metalloproteases and proinflammatory cytokines.

### *Human immunodeficiency virus*

Human immunodeficiency virus 1 (HIV-1) belongs to the *Retroviridae* family. HIV-1 has a single stranded positive sense RNA genome, which undergoes reverse transcription into double stranded DNA that is integrated into the host genome. Thus,

HIV establishes a persistent, life-long infection. HIV-1 is transmitted via sexual routes, which requires the virus to cross genital or intestinal epithelial cell layers. HIV-1 typically infects CD4<sup>+</sup> T cells, via interaction between viral gp120 and CD4 [65]. Interestingly, one study reported that HIV-1 is capable of using CLDN7 as an entry factor in CD4-negative T cells independently of gp120 [105], although the physiological relevance remains unclear. To facilitate viral dissemination, HIV-1 has been shown to alter the expression of tight junction claudins in intestinal cell lines and primary genital epithelial cells [24, 72, 93]. HIV-1 infection can also lead to neuropathogenesis [11], following invasion of the central nervous system. Indeed, HIV-1 disrupts the tight junctions of the blood brain barrier [89], at least in part by downregulating CLDN5 expression [16], which may be the result of virus-induced post-translational modifications of CLDN5 [7]. This effect may be mediated by the viral Tat protein, which was shown to alter CLDN1 and CLDN5 expression in brain endothelial cells and in the brains of mice [4, 5]. In colonic cell lines and primary genital epithelial cells, gp120 was shown to disrupt CLDN1, CLDN2 and CLDN4 expression and increase permeability [72]. Other tight junction proteins were also implicated [4]. Interestingly, disruption of tight junctions by HIV proteins was found to facilitate the paracellular spread of herpes simplex virus type 1 and type 2 [86].

### *Respiratory viruses*

Human rhinovirus (HRV), a single stranded positive sense RNA virus in the *Picornaviridae* family, is the main cause of the common cold and as such is one of the most common viral infections in humans [50]. Respiratory syncytial virus (RSV) is a single stranded negative sense RNA virus in the *Paramyxoviridae* family. It is a common cause of lower respiratory tract infections, particularly in children and immunocompromised individuals [42]. To establish infection, these viruses must

bypass the airway epithelium, a well-developed barrier regulated by tight junctions. Therefore, respiratory viruses have evolved mechanisms to disrupt or alter tight junctions. In primary human nasal epithelial cells, HRV was shown to decrease expression of CLDN1 and other tight junction components, thus increasing permeability [102]. Similarly, RSV decreased expression of CLDN1 in primary human nasal epithelial cells [64]. Conversely, however, RSV infection induced expression of CLDN4 and other tight junction components, which was suggested to facilitate viral assembly and budding at the apical membrane by promoting cell polarity [64].

#### *Gastrointestinal viruses*

Rotavirus (RV), a double stranded RNA virus in the *Reoviridae* family, infects the gastrointestinal tract and is a major causative agent of diarrhea in children [21]. RV infection of intestinal epithelial cell lines altered the distribution of CLDN1 and CLDN3, thus disrupting tight junctions and resulting in decreased permeability [22, 71]. This effect was mediated at least in part by viral protein VP8 [71]. Given that RV uses integrins for cell entry [38], this disruption of the tight junctions was proposed to open paracellular spaces, allowing access to the receptors. This likely contributes to pathogenesis by disrupting the intestinal lining.

Norovirus (NV), a single stranded positive sense RNA virus in the *Caliciviridae* family, is the most common cause of viral gastroenteritis [79]. As for RV, infection with NV leads to a reduction in expression of tight junction proteins, including CLDN4 and CLDN5 [92]. The resulting epithelial barrier dysfunction contributes to pathogenic effects of infection, such as diarrhea.

### **Beyond claudins: Tight junctions and viral infection**

Although claudins are key players in tight junction physiology, other proteins from different families contribute to tight junction structure and function. The Junctional Adhesion Molecules (JAM-A, JAM-B and JAM-C) as well as the Coxsackievirus and Adenovirus Receptor (CAR) [29] are part of the immunoglobulin superfamily. CAR was the first tight junction protein shown to be involved in viral entry, and mediates the entry of both adenoviruses and coxsackieviruses, by different mechanisms [15]. JAM-A, another tight junction component, is important for the entry and internalization of reoviruses [14], such as RV [91], as well as feline calicivirus [61]. Indeed, viruses from several different families use tight junction proteins either for entry, dissemination or egress [90]. Further research into tight junctions with respect to viral infection will allow for a better understanding of viral replication/dissemination strategies and may provide targets for novel therapeutic strategies.

### **Conclusions and perspectives**

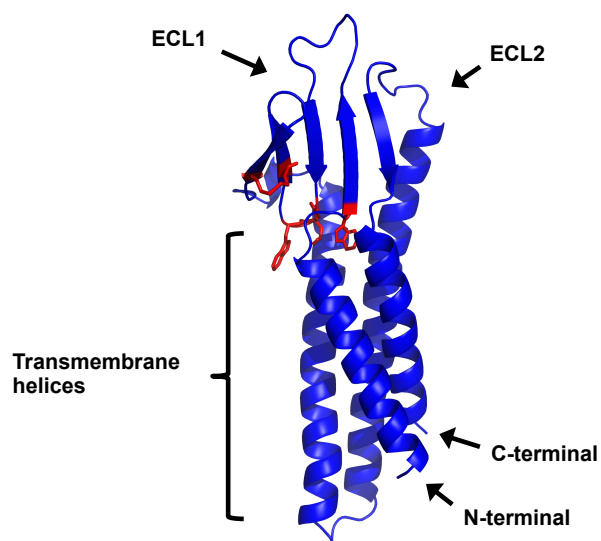
As key components of tight junctions, claudins are critical for the regulation of tight junction structure and function. Given that claudins regulate paracellular permeability and form barriers between epithelial cells, several viruses evolved mechanisms to use claudins during their replication cycle or to disseminate within the host. As such, claudins are attractive antiviral targets. Indeed, antibodies and peptides targeting CLDN1 have been shown to be highly effective against HCV [27, 30, 54, 60, 73, 85, 100]. These antibodies are thought to block formation of the nonphysiological CLDN1-CD81 co-receptor complex during HCV entry, and thus lack any obvious toxic effects for the host. The potential of claudins as antiviral targets in the context of

other viral infections remains to be established. Furthermore, claudins are implicated in the pathology of several diseases. Further research into the roles of claudins in viral infection will provide insight into their physiological roles, opening avenues for novel antiviral and therapeutic strategies.

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**Table 1.** Claudin usage by different viruses.

<b>Virus</b>	<b>Claudin member</b>	<b>Function</b>	<b>Reference(s)</b>
<b>Hepatitis C virus</b>	CLDN1, CLDN6, CLDN9	Viral entry into hepatocytes, cell-to-cell transmission	[19, 25, 26, 41, 67, 104]
<b>Dengue virus</b>	CLDN1	Viral entry	[17, 33]
<b>West Nile virus</b>	CLDN1, CLDN2, CLDN3, CLDN4	Degradation of claudins facilitates viral dissemination into the brain	[66, 96, 97, 99]
<b>Japanese encephalitis virus</b>	CLDN1	Degradation of CLDN1 likely facilitates viral dissemination	[3]
<b>Human immunodeficiency virus</b>	CLDN7 CLDN1, CLDN2, CLDN4, CLDN5	Viral entry into CD4(-) T cells in gp120-independent manner Degradation of claudins facilitates viral dissemination	[105] [4, 5, 7, 16, 24, 72, 93]
<b>Human rhinovirus</b>	CLDN1	Degradation of CLDN1 facilitates viral access to receptors	[102]
<b>Respiratory syncytial virus</b>	CLDN1 CLDN4	Degradation of CLDN1 facilitates viral access to receptors Induction of CLDN4 expression facilitates viral budding at apical membrane	[64] [64]
<b>Rotavirus</b>	CLDN1, CLDN3	Disruption of claudin localization facilitates viral access to receptors	[22, 71]
<b>Norovirus</b>	CLDN4, CLDN5	Reduction in claudin expression may enhance viral infection/dissemination	[92]



**Figure 1.** Homology model showing the general structure of CLDN1 as a representative claudin. Claudin signature sequence residues within ECL1 (W-GLW-C-C) are shown in red with side chains. The homology model was generated using the crystal structure of murine CLDN19 [81] as a template in SWISS-MODEL [6]. CLDN19 is closely related to CLDN1 [53]. The structure was rendered in PyMol [88]. ECL1, extracellular loop 1; ECL2, extracellular loop 2.



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