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REVIEW

Trans-Compartmental Regulation of Tight Junction Barrier Function

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ABSTRACT

Tight junctions (TJs) are the most apical components of junctional complexes in epithelial and endothelial cells. Barrier function is one of the major functions of TJ, which restricts the ions and small water-soluble molecules from passing through the paracellular pathway. Adherens junctions (AJs) play an important role in cell–cell adhesion and cell signaling. Gap junctions (GJs) are intercellular channels regulating electrical and metabolic signals between cells. It is well known that TJ integral membrane proteins, such as claudins and occludins, are the molecular building blocks responsible for TJ barrier function. However, recent studies demonstrate that proteins of other junctional complexes can influence and regulate TJ barrier function. Therefore, the crosstalk between different cell junctions represents a common means to modulate cellular activities. In this review, we will discuss the interactions among TJ, AJ, and GJ by focusing on how AJ and GJ proteins regulate TJ barrier function in different biological systems.

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Introduction

Epithelial cells comprise several types of junctions, each with their unique function to maintain homeostasis. Tight junctions (TJs) – containing claudins, occludins, and junctional adhesion molecules (JAMs) – are the most apical component regulating ion and solute diffusion through the paracellular pathway as well as controlling movements of proteins and lipids between apical and basolateral surfaces.[1–3] TJs form a seal between cells and only allow the passage of certain ions and small molecules through TJ channels.[4,5] Leaky TJs are characterized by low transepithelial electrical resistance (TER) and high solute permeability.[6,7] Underneath TJs are the adherens junctions (AJs), made up of cadherins, catenins, and other associated proteins.[8,9] AJs have been shown to initiate cell–cell contacts and promote assembly, maturation, and maintenance of TJs.[10] In addition to TJs and AJs, cells also form gap junctions (GJs), which mediate cell-to-cell communication via the creation of channels consisting of connexins.[11–14]

The functional properties of epithelial barriers are heavily influenced by TJ composition.[15] Dysregulation of TJ proteins has been shown to be involved in inflammation, cancer progression, and metastasis through epithelial–mesenchymal transition (EMT), gastrointestinal diseases, central nervous system (CNS) disorders, and retinal diseases.[10,16–19] Many studies focus on upregulation or downregulation of TJ proteins affecting barrier function and cell homeostasis; however, the crosstalk between these junctions should also be considered when investigating TJ functions. While other junctions exist – such as desmosomes, focal adhesions, and hemidesmosomes – AJ and GJ proteins may interact more commonly with TJ proteins to modulate barrier function, as they share many cytoplasmic partners such as the scaffolding proteins ZO-1, afadin 6, and anillin.[20–22]

In this review, we discuss studies demonstrating how epithelial barriers are regulated by AJ and GJ proteins, as well as the formation of a novel hybrid TJ–AJ structure within the retina.

Regulation of epithelial barriers by adherens junction proteins

AJs lie below TJs, initiate cell–cell adhesion, and connect to the underlying actin cytoskeleton.[23] They are made up of classical cadherins, which bind to one another homotypically on opposing

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cell surfaces and then interact with the catenin family that attaches to actin filaments to strengthen adhesion between cells.[23,24] Here, we review how different AJ proteins such as p120^{ctn}, cadherins, β-catenin, and α-catenin, among others, regulate TJ protein organization, as well as TJ structure, integrity, and barrier function.

P120 catenin

p120^{ctn} is a prototypical member of a subclass of armadillo repeat proteins that include δ-catenin /NPRAP/Neurojungin, ARVCF, and p0071.[25,26] p120^{ctn} is a well-known AJ-associated protein and binds directly to the juxta-membrane domain of classical cadherins. p120^{ctn} functions in stabilizing cadherins at the cell–cell membrane to promote AJ and cell–cell adhesion strength.[27,28] In addition, p120^{ctn} and its related family members can bind small GTPases as a guanine-nucleotide dissociation inhibitor (GDI) (e.g. for RhoA) or associate indirectly via guanine nucleotide exchange factor (GEFs), GTPase activating proteins (GAPs), or other small GTPase effector proteins to regulate the cytoskeleton.[29]

On the other hand, p120^{ctn} has been shown to control many TJ-related functions including regulating the alveolar epithelial barrier, preventing ventilator-induced lung injury, and contributing to cell–cell junction integrity in endothelial cells.[8,30,31] Gu et al. demonstrated that loss of p120^{ctn} led to degradation and endocytosis of E-cadherin in AJs, reduced occludin expression levels in TJs, and altered the association of occludin with ZO-1.[31] When p120^{ctn} was overexpressed, these changes in E-cadherin, ZO-1, and occludin were all reversed, ultimately reestablishing barrier function, demonstrating the regulatory effects of p120^{ctn} on both AJs and TJs in lung tissue.[31] Under pathologic conditions such as ventilator-induced lung injury, oxidation of phospholipids occurs, which contributes to inflammation; however, there are some by-products of phospholipid oxidation that exhibit barrier-protective and anti-inflammatory effects.[24,32,33] 1-Palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine (OxPAPC) production has been demonstrated to induce translocation of TJ and AJ proteins including VE-cadherin, occludin, JAM-A, p120^{ctn}, α-catenin, and β-catenin to the cell membrane region to strengthen TJ complexes.[24] OxPAPC also induced co-localization of p120^{ctn} and ZO-1 at the cell–cell junction and interaction of VE-cadherin with ZO-1 to enhance endothelial barrier function.[24] These studies further illustrate the interactions between TJ and AJ proteins within the respiratory system to regulate barrier function.

p120^{ctn} also plays an essential role in maintaining the barrier function and intestinal homeostasis within the digestive system.[34] p120^{ctn}-deficient mice exhibited major cell adhesion defects and increased immune response and infiltration causing inflammation, which later led to mucosal erosion, terminal bleeding, and death within 21 d.[34] In culture, p120^{ctn}-deficient HCA-7 colonic adenocarcinoma cells displayed significantly reduced TER, demonstrating disruption of the intestinal barrier function. This study highlights the essential role of p120^{ctn} in maintaining TJ barrier function and intestinal homeostasis.[34] Recently, our group has also shown the crosstalk between TJ protein claudin-7 and AJ protein p120^{ctn} as claudin-7 knockout intestinal tissues exhibited altered p120^{ctn} localization at the cell–cell junction and disrupted p120^{ctn} topographical interaction with β-catenin as viewed at the nanoscale level utilizing super-resolution microscopy.[35] Interestingly, some studies showed that AJ proteins co-localized with TJ proteins to form a novel hybrid TJ structure with AJ organization.[36] In ear outer hair cells, claudins were found to partition into various subdomains where AJ proteins co-localized with claudin proteins to create a cytoskeletal network.[36] Specifically, α-catenin, β-catenin, and p120^{ctn} co-localized with claudin-9/6 forming a novel type of TJ highlighting the interdependencies between TJ and AJ proteins and the ability to form a "mix-and-match" type of complex.[36] Through super-resolution microscopy, p120^{ctn} was found to localize more toward the TJ side as p120^{ctn} was localized apical to β-catenin in healthy epithelial cells when viewed three-dimensionally.[35]

Cadherins

Specific positioning and assembly of TJs is vital for TJ barrier function; this process was found to be regulated by AJ protein E-cadherin.[37] For example, in mouse epidermis, E-cadherin regulates EGFR activity and tension-bearing AJ organization to

inhibit the formation of premature TJ complexes in lower layers of the skin.[37] This stimulates TJ stability and tension to form functional TJs in granular layer 2, therefore promoting a strong epithelial barrier.[37] Loss of E-cadherin in the epidermis was associated with the absence of claudin-1 staining in the granular layer of the epidermis, as well as altered distribution of ZO-1 at the cell surface.[38] Additionally, conditional knockout of E-cadherin and P-cadherin in the epidermis led to functionally compromised TJs, resulting in defective epidermal barrier.[39] E-cadherin regulation of TJ assembly and positioning has also been demonstrated in Madin-Darby canine kidney cells (MDCK).[40–42] Utilizing MDCK cells, Nita-Lazar et al. showed that hypoglycosylated E-cadherin coordinated AJ maturity and TJ assembly through protein phosphatase 2A to enhance TER and barrier function.[40] In Ras-transformed MDCK cells, E-cadherin expression was greatly reduced and TJ proteins such as occludin, ZO-1, and claudin-1 were mis-localized to the cytoplasm, rather than the cell–cell contact region.[41] Treatment with PD98059, a mitogen-activated protein kinase kinase inhibitor, restored recruitment of occludin, ZO-1, and claudin-1 to the cell membrane where TJ proteins assembled, and E-cadherin expression was induced.[41] Furthermore, Severson et al. showed glycogen synthase kinase 3 (GSK-3) regulation of barrier function through claudin-1, E-cadherin, and occludin in MDCK cells.[42] The above studies emphasized E-cadherin regulation of TJ assembly and positioning; however, Chen et al. demonstrated the specific sequence of events in that E-cadherin expression at the cell–cell contact occurred after recruitment of occludin to the cell–cell membrane.[41] These studies together emphasize the crosstalk between TJ and AJ and introduce the possibility that the role of E-cadherin in TJ positioning may be tissue-dependent.

Within the CNS, two barriers – endothelial blood–brain barrier (BBB) and epithelial blood–cerebrospinal fluid barrier (BCSFB) – are formed to regulate paracellular diffusion in the brain.[10] A review by Tietz and Engelhardt highlights the importance of studying the interactions between TJ and AJ proteins to understand brain barrier function.[10] BBB in endothelial cells is characterized by high levels of occludin and claudin-5, as well as low levels of VE-cadherin.[10] Throughout brain angiogenesis, cadherin-10 and N-cadherin are abundantly expressed, where they regulate expression of VE-cadherin to contribute to AJ maturation, and eventually activation of claudin-5 and TJ formation.[43–46]

β-Catenin and Sonic hedgehog

Both Wnt/β-catenin and Sonic hedgehog (Shh) signaling pathways have been shown to regulate angiogenesis and BBB maturation.[10] Through Wnt/β-catenin signaling, AJ protein β-catenin induced transcription of claudin-3, ZO-1, and claudin-5, which all contributed to the formation of properly functioning TJs for the BBB.[47–49] Additionally, the loss of the endothelial receptor Unc5B led to dysregulated Wnt/β-catenin signaling and impaired TJ integrity in which the BBB was leaky with decreased claudin-5 expression.[50] Interestingly, β-catenin activation has been demonstrated to induce EMT by altering cell–cell junctions.[51] Specifically, mutated β-catenin in HCT116 cells, a human colon cancer cell line, led to downregulation of both claudin-7 and E-cadherin through the transcription factor ZEB1.[51] This altered expression caused impairment of the TJ, increased cell motility, EMT progression, and loss of AJs, underlining the important role of β-catenin in regulating the maintenance of TJ and AJs.[51] β-Catenin level has also been shown to be strongly and positively correlated with claudin-1 expression in gastric cancer patients and gastric cancer cell lines.[52] These studies emphasize many roles of β-catenin in regulating barrier integrity.

Shh regulation of $p120^{ctn}$ also plays an important role in regulating the maturation of CNS endothelial TJs and AJs as Shh induces increased expression of occludin, claudin-3, claudin-5, and JAM-A.[53] Another study investigated the role of Shh signaling in maintaining epithelial barrier function through various proteins including ectodysplasin A, which regulated ZO-1 and claudin-1.[54] Additionally, the Shh pathway has been revealed to mediate protective effects in BBB disruption following ischemic stroke as it regulated Tongxinluo capsule (a Chinese medication for treating ischemic cerebrovascular diseases)-induced upregulation of TJ proteins such as occludin, claudin-5, and ZO-1.[55]

Overall, the crosstalk between TJ and AJs influences the stability and function of these junctions at both the structural and transcriptional levels. Dysfunction of these junctions can disrupt CNS homeostasis and may cause neurological disorders such as multiple sclerosis and stroke.[10]

α-Catenin and tricellular junctions

Aside from regulating the traditional TJ structure, AJ proteins have also been shown to function in the regulation of tricellular junctions (TCJs) to modulate barrier function.[56,57] TCJs exist where the vertices of three cells join and contribute to epithelial barrier function and mechanical integrity in epithelial cells.[57–59] Ikenouchi et al. identified tricellulin as a vital protein for TCJ composition and function, as it was found to be predominantly localized to tricellular contacts and was demonstrated to influence epithelial permeability.[59] Utilizing RNA interference, reduced tricellulin expression led to compromised epithelial barrier function as well as disorganized TCJs and traditional TJ structures.[59] While this study provided a novel finding for the molecular makeup of TCJs, little is known about the mechanisms through which tricellulin regulates barrier function at TCJs. Recently, Cho et al. further investigated a CRISPR-Cas9 tricellulin knockout model in which they demonstrated disrupted TCJ morphology, the increase in gaps at TCJs, and compromised barrier function in tricellulin knockout cells.[56] Additionally, gaps formed at the tricellular vertices in knockout cells as shown by a biotin tracer assay.[56] Furthermore, they found that two junctional proteins, α-catenin of AJ and vinculin of focal adhesion, localized to TCJs in a tricellulin-dependent manner to interact with actomyosin and closed the gap at tricellular TJs and regulated barrier function, highlighting a novel role for α-catenin in TCJs.[56]

Regulation of epithelial barriers by gap junction proteins

Gap junctions (GJs) are intercellular channels consisting of connexins (Cx) regulating diffusion of ions and small molecules less than 1 kDa in size between adjacent cells.[60,61] Connexins associate with both TJs and AJs and play a vital role in the differentiation of epithelial cells.[13] Specifically, GJ plaques have been shown to associate with TJ strands in vascular endothelial cells.[62] Here, we examine the regulation of TJ composition and barrier function by GJ proteins.

Calu-3 cells, a human airway epithelial cell line which inherently lacks Cx26, were treated with the Na^+/K^+-ATPase inhibitor ouabain, leading to disruption of both the barrier and fence functions of TJs, as well as dysregulation of TJ protein expression.[12] Occludin, JAM-1, claudin-2, and claudin-4 were downregulated, while ZO-1 and claudin-14 were found to be upregulated.[12] Interestingly, when these cells were transfected first with Cx26 and then treated with ouabain, they exhibited well-developed TJ strands, proper TJ function, and normal expression of TJ proteins, indicating that Cx26 expression can regulate the TJ barrier and fence functions in Calu-3 cells.[12] Cx26 also plays an influential role in maintaining barrier function in intestinal epithelial cells.[11] Caco-2, human colorectal adenocarcinoma cells, exhibited a gradual increase in Cx26 expression toward confluency.[11] Morita et al. showed that overexpression of Cx26 led to improved TJ formation, decreased mannitol flux, and increased claudin-4 expression, emphasizing connexin regulation of TJ barrier function in intestinal epithelial cells.[11]

It is known that Cx40 and Cx43 associate with TJ proteins such as occludin, ZO-1, and claudin-5 at the cell boundary of porcine BBB endothelium.[60] Further investigation into TJ function by TER measurement and treatment with GJ blockers 18β-glycyrrhetinic acid (18β-GA) and olemide (OA) highlighted the role of GJs in promoting the barrier function of TJs in BBB in endothelial cells.[60] TER was decreased and paracellular permeability was increased after cells were treated with 18β-GA or OA, demonstrating the crosstalk between GJ and TJ to influence TJ barrier function.[60] Another study investigating familial cerebral cavernous malformations (ccm) – caused by loss-of-function mutations in *ccm3* – revealed the functional interaction of Cx43 with ZO-1 and claudin-5.[63] The siRNA-mediated knockdown of *ccm3* in brain endothelial cells led to increased Cx43 expression and increased GJ plaque size and barrier permeability, in addition to fragmented ZO-1 and claudin-5 staining at TJs.[63] Inhibition of Cx43 restored ZO-1 expression at TJs,

reduced plaque accumulation at GJs, and increased claudin-5–claudin-5 trans-interaction, suggesting a vital role for Cx43 in regulating barrier permeability through TJ proteins.[63]

Interestingly, when Cx32 was introduced into Cx32-deficient mouse hepatocytes, expression of ZO-1, occludin, and claudin-1 was significantly increased, resulting in enhanced TJ barrier and fence function.[64] Murata et al. further investigated this interaction using a microarray approach.[65] They revealed that Cx32 induction of TJs occurred through modulation of TJ protein MAGI-1, which was found to co-localize with occludin, ZO-1, F-actin, and claudin-2 to modulate the formation and assembly of TJs.[65] Taken together, these studies illuminate the potential mechanisms by which GJ proteins influence and regulate TJ composition and barrier function.

A unique hybrid tight and adherens junction in the retina

Endothelial junctions, consisting of TJs, AJs, and GJs, are vital in maintaining the inner blood–retinal barrier (BRB), which regulates fluid entry into the retina.[66] These junctions are interdependent as the expression of AJ proteins induces expression of many TJ proteins. For example, VE-cadherin at the AJ upregulated the expression of claudin-5 in the TJ through the release of FoxO1 and the Tcf-4-β-catenin transcriptional repressor complex.[46] Control of the retinal microenvironment by endothelial junction proteins is highly important as disturbances may disrupt the structure as well as neural function of the macular region.[19,67] Disruption of the BRB function is a hallmark of retinal diseases including macular edema, diabetic retinopathy, and macular degeneration.[19,67] This disruption is often caused by dysregulation of TJ and AJ proteins. For example, loss of claudin-5 in murine models of diabetes was associated with increased vascular permeability in the BRB, leading to diabetic retinopathy.[19,68]

Interestingly, Paffenholz et al. characterized a novel hybrid TJ and AJ junction within the retina outer limiting zone (OLZ) region.[69] Within the OLZ, photoreceptors and glial cells are connected by plaque-bearing junctions with attached bundles of actin filaments.[69] Utilizing immuno-localization methods, it was determined that these plaques contain AJ, TJ, and desmosomal proteins including N-cadherin, δ-catenin/NPRAP/neurojungin, α-catenin, β-catenin, $p120^{ctn}$, vinculin, ZO-1, symplekin, and plakophilin 2.[69] With such diversified protein expression, these OLZ junctions demonstrate the formation of novel hybrid AJs containing proteins that are traditionally present in both TJs and desmosomes. Altered expression and/or localization of these proteins affect the functioning of junctions in the OLZ, leading to disturbances in the retinal microenvironment. These studies underline the importance of regulating TJ protein expression to ensure proper barrier function, as well as provide new insights into how the BRB is formed and the significance of hybrid AJs within the retina.

Conclusion

The integrity of cell junctions is vital for maintaining tissue homeostasis, as the disruption of barrier function is directly linked to inflammation, cancers, retinal disorders, and many other pathologic conditions.[17,18,66] Barrier function largely depends on the integrity and functioning of TJs. While most studies focus on how TJ proteins affect TJ functions, it is also important to recognize that AJ and/or GJ proteins elicit trans-compartmental regulation of barrier function. By studying the interactions among different types of cell junctions, we can better understand the roles of barrier dysfunction related to inflammatory bowel disease, cancer progression, macular edema, etc. Summarized from the above discussion, we have explored the complex crosstalk among TJs, AJs, and GJs to modulate barrier function and tissue homeostasis. Future studies in this area will help gain further insights into the mechanisms of pathologic conditions involving barrier dysfunction and the development of novel therapies.

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