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Phosphatase regulation of intercellular junctions

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Keywords: claudins, cadherins, occludin, permeability, adherens junction, tight junction, phosphorylation

Abbreviations: AJ, adherens junction; aPKC, atypical protein kinase C; BBB, blood-brain barrier; BTB, blood-testis barrier; CagA, cytotoxin-associated gene A; DEPI, density-enhanced protein tyrosine phosphatase 1; DSS, dextran sulfate sodium; DUSP, dual specificity phosphatases; ECL, extracellular loop; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; eNOS, endothelial nitric oxide synthase; FAK, focal adhesion kinase; FGF, fibroblast growth factor; IFN- γ , interferon-gamma; iNOS, inducible nitric oxide synthase, JAM, junctional adhesion molecule; LPS, lipopolysaccharide; MAGUK, membrane-associated guanylate kinase; MAPK, mitogen-activated protein kinase; MDCK, Madin-Darby canine kidney; MLC, myosin light chain; MYPT, myosin phosphatase targeting proteins; PAN, puromycin aminonucleoside nephrosis; PEP, PEST-domain-enriched tyrosine phosphatase; PLC, phospholipase C; PPI, protein phosphatase 1; PP2A, protein phosphatase 2A; PPM, metal-dependent protein phosphatases; PPP, phosphoprotein phosphatases; PSP, protein serine/threonine phosphatases; PTP, protein tyrosine phosphatase; PTPN2, protein tyrosine phosphatase non-receptor type 2; PTPRS, receptor protein-tyrosine phosphatase sigma; RTK, receptor tyrosine kinase; ROS, reactive oxygen species; SHP, Src homology-2 (SH2) domain-containing phosphatases; STAT, signal transducers and activators of transcription; TJ, tight junction; TAMPs, tight junction-associated marvel proteins; TCPTP, T-cell protein tyrosine phosphatase; TER, transepithelial electrical resistance; TIMAP, TGF- β 1-inhibited, membrane-associated protein; VE-PTP, vascular endothelial receptor tyrosine phosphatase; ZO, zonula occludens

Intercellular junctions represent the key contact points and sites of communication between neighboring cells. Assembly of these junctions is absolutely essential for the structural integrity of cell monolayers, tissues and organs. Disruption of junctions can have severe consequences such as diarrhea, edema and sepsis, and contribute to the development of chronic inflammatory diseases. Cell junctions are not static structures, but rather they represent highly dynamic microdomains that respond to signals

Introduction

The apical junctional complex that plays a pivotal role in cell-cell adhesion and regulation of barrier function, is comprised of tight junctions (TJ) and adherens junctions (AJ) (Fig. 1). Permeability defects arising from altered junctional composition are associated with many pathologic states including infection, chronic inflammatory diseases, edema, epilepsy and metabolic disease.^{1,2} Tight junctions are the major determinants of paracellular permeability as they restrict solute flux between cells. Consequently, tight junctions are the rate-limiting step in transepithelial transport.³ Tight junctions operate as selectively permeable barriers through two functionally distinct pathways. First, there is a high-capacity, charge-selective pore pathway that allows passage of small ions and uncharged molecules. Second,

a low-capacity leak pathway exists that allows the flux of larger ions and molecules, independent of charge.⁴ Tight junctions are comprised of a branching network of sealing strands consisting of integral membrane-spanning proteins such as members of the claudin family, occludin and the junctional adhesion molecules (JAM) that are members of the immunoglobulin superfamily.⁴

Occludin was the first identified transmembrane spanning tight junction protein and contains four transmembrane domains, two extracellular loops and one intracellular loop.⁵ The gene for human occludin is encoded on chromosome 5q13.1 and generates a protein of 522 amino acids.⁶ Four splice variants have been identified at the mRNA level and they appear to exhibit altered subcellular distribution.⁷ Antibodies against occludin detect multiple bands between 62–82 kDa that are products of alternative splicing or represent proteins with post-translational modifications, including phosphorylation.⁸ Occludin has a first extracellular loop enriched with tyrosine and glycine residues and a second loop enriched with tyrosines. Occludin is a major structural component of TJ filaments and is one of the tight junction-associated marvel proteins (TAMPs), that also includes tricellulin, and marvelD3.⁹ Although occludin overexpression or mutations severely affect paracellular movement of electrolytes as determined by measuring transepithelial electrical resistance (TER), a clear understanding of the role(s) of occludin in barrier function is yet to be determined and this is complicated by studies showing that occludin knockout mice are both viable and also exhibit tight junctions with an apparent normal morphology.^{10,11} Occludin is a substrate for a number of phosphatases and occludin regulation by phosphatases will be discussed in detail below. Perhaps the most critical of the transmembrane proteins are members of the claudin family. These proteins define various aspects of tight junction permeability in a tissue-specific

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manner. The great variety of claudin family members lends great flexibility to the composition of the tight junctions and their overall influence on tight junction function.⁴ Claudin isoforms are expressed in a tissue- and/or developmental stage-dependent manner. Claudins are 20–34 kDa proteins, containing four transmembrane domains, N- and C-terminal cytoplasmic domains and two extracellular loops (ECL).¹² The C-terminal tail of claudins is essential for their stability and intracellular transport to the TJ.¹³ For some claudins, this domain can be phosphorylated to regulate barrier function, and its phosphorylation has been linked to either increases or decreases in TJ assembly and function.¹⁴

A variety of other tight junction proteins including integral membrane, peripheral membrane tight junction proteins, and signaling proteins, such as a number of kinases involved in tight junction regulation, have also been identified (reviewed in 15).¹⁵ The TJ-associated scaffolding proteins, Zonula occludens-1 (ZO-1) is a Ser phosphoprotein and was the first identified protein specifically associated with the tight junction.¹⁶ ZO-1, ZO-2 and ZO-3 proteins are members of the membrane-associated guanylate kinase (MAGUK) homolog family of proteins. ZO proteins are required for the integration of transmembrane proteins, such as claudins, into TJ strands and direct the incorporation of these strands into the apical junctional complex. The ability of ZO proteins to direct junctional assembly is also dependent on their capacity to bind to and regulate components of the cortical actin cytoskeleton and to promote cadherin-mediated cell–cell adhesion.¹⁷

Adherens junctions are formed through interactions between a family of cadherin transmembrane proteins i.e., E-cadherin, that form strong interactions with molecules on adjacent cells such as p120 catenin and β -catenin. These molecules in turn regulate local actin assembly and perijunctional actomyosin ring development.³ Adherens junctions are required for assembly of the tight junction, which seals the paracellular space. The cadherin family of calcium-dependent cell adhesion molecules are transmembrane proteins concentrated at adherens junctions.¹⁸ The cadherins possess an extracellular segment rich in calcium-binding motifs.¹⁹ The highly conserved intracellular segment is the site of interaction with catenin proteins (α -, β -, and γ -catenin).²⁰ The cadherin cytoplasmic segment binds directly with β -catenin and γ -catenin/plakoglobin, which are related to the product of the segment polarity gene *armadillo*.²⁰ In contrast, α -catenin, which is related to the cytoskeleton-associated protein vinculin, binds indirectly to cadherins by interacting with β/γ catenin and functions to link the complex to the actin cytoskeleton.²⁰ The intracellular region of the cadherins is essential for adhesion. Mutations in this catenin-binding segment can result in a breakdown of adhesion even if an intact extracellular segment is present.^{21,22} Consequently, an intact cadherin-catenin complex is fundamentally required for appropriate cell adhesion and association with the actin cytoskeleton. The integrity of cadherin-catenin complexes, and by extension the stability of adherens junctions, is dynamic and can be regulated by reversible tyrosine residue phosphorylation status.²³⁻²⁵

The establishment of apical-basal polarity and the formation of tight junctions rely, at least in part, on the assembly and asymmetric distribution of polarity proteins, including the Par family of Ser/Thr kinase proteins and the signaling complex they form with atypical PKC enzymes (aPKC).^{26,27} Par-1 plays a key role in determining the spatial restriction of the Par/aPKC complex to the apical domain. In order to preserve apical membrane polarity, Par-1 needs to be excluded from the tight junction to maintain apical membrane polarity. This is in contrast to the active role of Par-1 in basolateral membrane polarization. The aPKC-mediated phosphorylation of Par-1 at the tight junction induces dissociation of Par-1 from the membrane and thereby prevents the incursion of Par-1 to the apical membrane.²⁸⁻³⁰ Basolateral Par-1 activity phosphorylates Par-3 and disrupts the Par/aPKC complex. This in turn creates docking sites for 14–3–3 proteins on Par-3, and facilitates release of the complex from the basolateral cell membrane to the apical membrane.³¹ Therefore, polarity proteins form an essential component of the machinery necessary for junction assembly. The third site of cell–cell connection is the desmosome. Desmosomes are specialized anchoring junctions that connect cytoskeletal elements to the plasma membrane at cell–cell or cell–substrate adhesions. While desmosomes will not be featured in this article, the reader is referred to a recent review on desmosome assembly and regulation.³²

Phosphorylation Dynamics of the Apical Junctional Complex

Tight and adherens junctions are dynamic structures that feature the rapid activation and deactivation of component proteins and their downstream signaling pathways. Moreover, proteins can translocate into and out of these intercellular junctions and the apicolateral domain of the cell in response to various stimuli.^{3,15,33,34} Junction dynamics are frequently regulated by transient shifts in protein phosphorylation or dephosphorylation under the control of specific protein kinases and phosphatases. Therefore, kinases and phosphatases act as strategically important regulators to control the extent, rate and duration of a signaling response, while the balance between their opposing activities can determine the composition and functional integrity of the tight junction.^{35,36} Modification of proteins via phosphorylation mainly occurs on the hydroxyl-group containing amino acid residues, namely serine (Ser), threonine (Thr) and tyrosine (Tyr). Protein phosphatases dephosphorylate these amino acids via nucleophilic attack of the phosphate group for catalysis in the presence of a water molecule.³⁷

While the human genome encodes ~500 protein kinases, approximately two thirds of which are serine/threonine kinases, the four distinct families of protein phosphatases, comprise only ~150 members.³⁷⁻³⁹ Phosphatases are categorized into two major classes, protein tyrosine phosphatases (PTPs) and protein serine/threonine phosphatases (PSPs).⁴⁰ The structural composition of phosphatases shows some degree of variety as they can be found as active monomers consisting solely

Table 1. Summary of phosphatase regulation of intercellular junction proteins and the consequences of substrate dephosphorylation for junctional integrity

Phosphatase	Substrate	Effect	Citation
PP1	Occludin	Dephosphorylates Serine residues	49
	Par-3	Regulates PKC- ζ and 14-3-3 binding	50, 51
	MLC	Dephosphorylation of MLC reduces permeability	53, 54
PP2A	ZO-1, claudin-1	Restricts accumulation at tight junction and TJ assembly	49,63
	Occludin	Dephosphorylates Ser residues, restricts TJ localization	8,63
	aPKC	Regulates aPKC activity and distribution in TJ formation	63,64
	E-cadherin	Sequesters PP2A at AJ to facilitate TJ assembly	76
	VE-cadherin	Prevents Ser phosphorylation and vascular junction disassembly	79, 82
SHP2	β -catenin, VE-cadherin	Prevents β -catenin phosphorylation and disruption of VE-cadherin endothelial AJ complexes	94–97
	P190RhoGAP	Modulates RhoA activation	100–103
	Src, FAK	Indirectly upregulates ERK1/2 activity, decreased FAK phosphorylation, AJ and TJ proteins internalized	104
	CagA	Forms complex with CagA and Par1; loss of polarity	30
PTP1B	E-cadherin, β -catenin	Dephosphorylates and stabilizes E-cadherin: β -catenin complex at AJ	120,121,123
	VEGFR	VEGFR dephosphorylation stabilizes cell-cell contacts	122
	Nephrin	Possible actin disruption; increased glomerular permeability	126
TCPTP	STAT1, STAT3	Restricts claudin-2 expression and epithelial permeability by IFN- γ	147,151
PTP-PEST	Cas, Paxillin, Pyk-2	Possible disruption of Cas localization at focal adhesions to facilitate cell disaggregation/migration	154, 155, 158
	Fyn	Reduces nephrin phosphorylation, increases podocyte permeability	126
	RhoA, Rac1	Promotes RhoA and limits Rac1 activity to enhance AJ assembly; Prevents aberrant epithelial cell motility	157
VE-PTP	VE-cadherin, Plakoglobin	Preserves VE-cadherin complexes in endothelial adherens junctions	162–164
DEP-1	VEGFR2	Attenuates VEGFR2 and MAPK activity; preserves endothelial barrier; cadherin-mediated contact inhibition	170–176
	Occludin, ZO-1	Preserves occludin:ZO-1 interactions and epithelial TJ integrity	177
RPTP μ	RACK1	Recruits RACK1 to cell-cell contacts; Links cell adhesion with intracellular signaling	179–182
	Cadherins	Dephosphorylates cadherins; stabilizes intercellular contacts	94, 165, 180
PTP σ	E-cadherin, β -catenin	Dephosphorylation, prevents their removal from AJ	192

of a catalytic subunit alone, as active dimers of catalytic and regulatory subunits, or as an active holoenzyme complex of catalytic, regulatory and scaffold subunits. Individual subunits can also have multiple isoforms and this facilitates increased diversity among phosphatases as subunit isoforms for a single phosphatase can form complexes in many possible combinations with isoforms of other subunits. The variety in subunit composition contributes to the specificity of phosphatases toward particular substrates while also explaining how an individual phosphatase can regulate the activity of a number of substrates. The following sections will discuss key Ser/Thr phosphatases, as well as non-transmembrane and receptor-like protein tyrosine phosphatases, that are involved in regulating intercellular adherens and tight junction proteins (Table 1).

Ser/Thr Phosphatases

While protein kinases are functionally derived from a common ancestor, by contrast, protein phosphatases have evolved in separate families that are structurally and mechanistically distinct.³⁵ The protein phosphatase super family can be broken down into two broad categories – protein serine/threonine phosphatases (PSPs) and phosphotyrosine phosphatase (PTPs).⁴¹ PSPs are further divided into three sub-groups. These are the phosphoprotein phosphatases (PPP), metal-dependent protein phosphatases (PPMs) and aspartate-based phosphatases.⁴² The PPP sequences are sufficiently distinctive to separate them into subtypes. However, an apparent consistent trait is that one of the major PPP, protein phosphatase-1 (PP1) binds its subunits

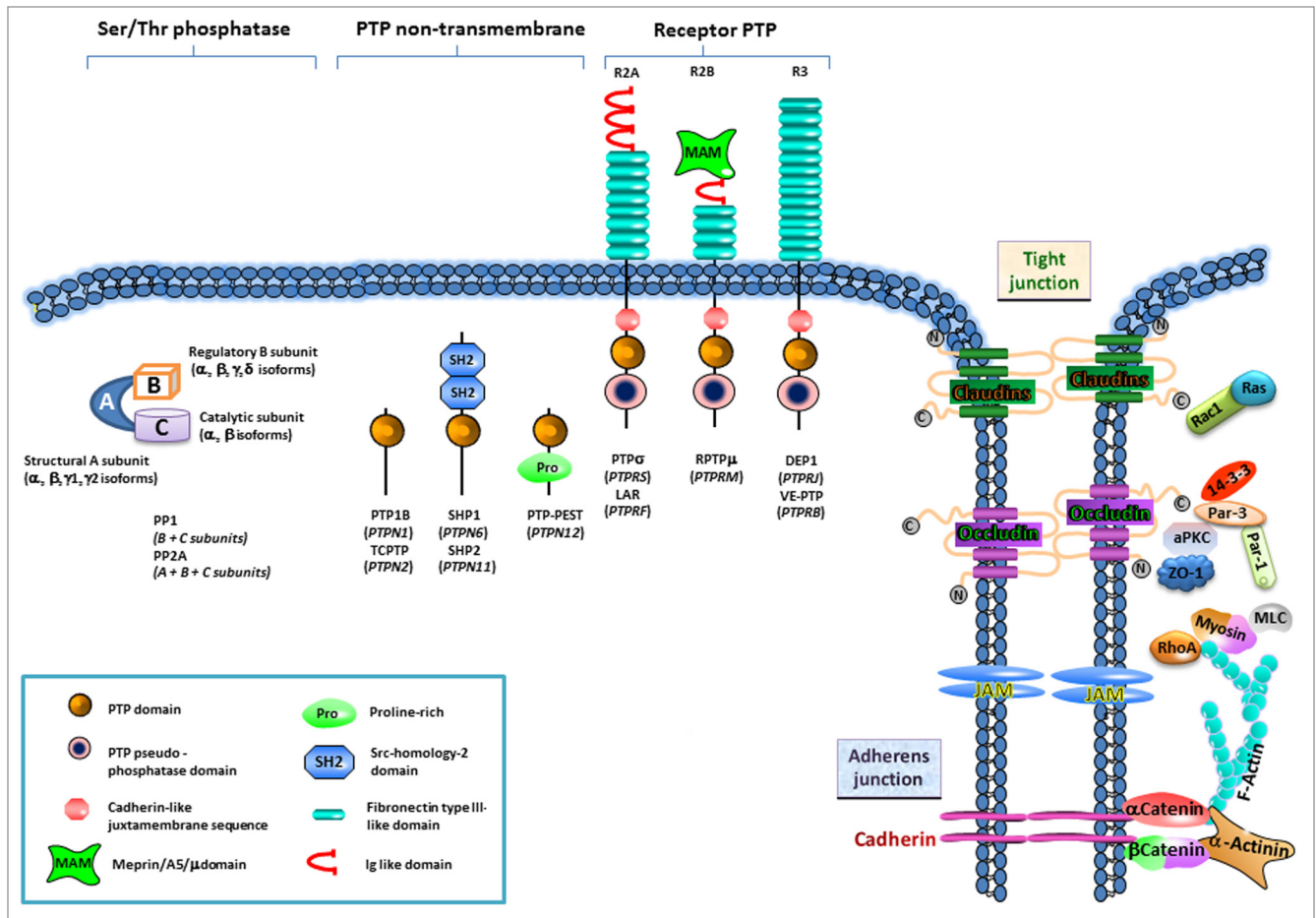


Figure 1. Phosphatases involved in regulation of tight and adherens junctions. 1. The major Ser/Thr phosphatases involved in regulation of junctional proteins are PP1 and PP2A. These are comprised of a catalytic subunit, one or more regulatory ‘B’ subunits, and in the case of PP2A, a structural ‘A’ subunit. Each subunit is present in different isoforms that can impart degrees of variation in enzyme activity, cellular localization, and distribution. 2. The classical protein tyrosine phosphatases (PTPs) involved in regulation of junction proteins are members of the receptor-like or non-transmembrane proteins (gene names in parentheses). The RPTP sub-families i.e., type IIa are listed as R2A, R2B and R3 respectively. The various functional domains of the PTPs represented are identified in the box. While the non-transmembrane PTPs contain a single PTP domain, the receptor-like PTPs contain a catalytically-active, membrane proximal, PTP domain and a membrane-distal PTP domain (PTP pseudo-phosphatase domain) that has residual activity. 3. Tight junction and adherens junction proteins including transmembrane proteins such as the claudins, occludin and cadherins, as well as accessory proteins and cytoskeletal elements that are direct or indirect targets of the described phosphatases, are also represented. For the sake of clarity, specific signaling interactions between the various phosphatases and junctional proteins are not shown.

directly using the RVxF motif common to regulatory subunits, and other sequences, whereas PPP such as PP2A, PP4 and PP6 use scaffold subunits to indirectly bridge together catalytic and regulatory subunits in heterotrimeric complexes.⁴³ PP1 and PP2A are among the most studied of protein phosphatases and prominent roles have been identified for them in the regulation of intercellular proteins (Fig. 1).

PP1

The mammalian genome encodes four protein phosphatase 1 (PP1) isoforms, PP1 α , PP1 β/δ , PP1 γ_1 , and PP1 γ_2 , with the latter two arising through alternative splicing.³⁹ The PP1 protein is approximately 38.5 kD in size and is tightly regulated by its interaction with over 200 known targeting proteins that both localize PP1 to distinct regions of the cell, but also modulate its

substrate specificity.⁴⁴ The PP1 catalytic subunit (PP1c) can form complexes with over 50 regulatory (bona fide or putative) subunits in a mutually exclusive manner.³⁹ Mammalian PP1c isoforms display differential tissue distribution and subcellular localization that is believed to be governed by regulatory subunits.^{45,46} One of the four different isoforms, α , β , γ_1 , or γ_2 , of the catalytic subunit (PP1c) binds to one, or possibly two, proteins from a pool of regulatory subunits to create a holoenzyme. As mentioned above, a common structural element of regulatory proteins is a short, conserved PP1c binding motif, (R/K)VXF.^{39,47} The composition of the holoenzyme in turn regulates PP1c substrate specificity through selective targeting. This allows PP1c to dephosphorylate only those substrates in the vicinity of the targeted complex.⁴⁸

With respect to regulation of junctional proteins, PP1 was identified as a negative regulator of Serine phosphorylation status on the transmembrane protein, occludin.⁴⁹ However,

the significance of this regulation with respect to calcium-induced tight junction (TJ) re-assembly was not conclusively elucidated. One hypothesis was that Ser phosphorylation of occludin may stabilize the TJ once it is assembled. Alternatively, it was suggested that PP1 interacts with occludin but its primary dephosphorylation target is an additional tight junction protein.⁴⁹ One possible mechanism through which PP1 may contribute to TJ stability is through effects on cell polarity. Traweger et al. identified that PP1, in particular the PP1 α isoform, is a functional component of the Par-3 scaffold and plays an important role in countering the effects of aPKC and Par-1 ser/thr kinases in the low resistance Madin-Darby canine kidney (MDCK) II cell subclone.⁵⁰ PP1 α can associate with multiple sites on Par-3 while retaining its phosphatase activity and specifically dephosphorylates Ser-144 and Ser-824 of mouse Par-3. In addition, PP1 α regulates the binding of 14-3-3 proteins and PKC zeta to Par-3, while expression of catalytically inactive PP1 α delays TJ formation, thus indicating a positive role for PP1 α in TJ formation.⁵⁰ The authors concluded that Par-3 functions as a scaffold capable of coordinating both serine/threonine kinases and the PP1 α phosphatase. This allows for dynamic control of the phosphorylation events involved in regulating the Par-3/aPKC complex. In contrast to data with PP2A (discussed below), and data generated with the PP1 and PP2A inhibitor calyculin A in intestinal epithelial cells, these data indicate a positive role for PP1 in TJ assembly thus emphasizing the need for caution in extrapolating specific functions for broadly acting phosphatases between different cell types.⁴⁹ Clinically relevant evidence for a role for PP1 in regulating TJ assembly came from studies of intestinal tissues isolated from celiac disease patients. Compared with control subjects, tissues from celiac disease patients exhibited increased PP1 expression, increased localization of Par-3 to the basolateral membrane, and an altered degree of expression of claudin proteins consistent with a more permeable intestinal barrier.⁵¹ The authors suggested that the altered assembly of TJs in celiac disease was due to upregulated PP1 expression and mislocalization of Par-3 to the basolateral, rather than to the apical, membrane of enterocytes.

Studies have also shed light on the roles of specific PP1c isoforms and their contributions to barrier regulation. The TGF- β 1-inhibited, membrane-associated protein (TIMAP) member of the myosin phosphatase targeting (MYPT) proteins appears to target PP1c β to the plasma membrane of endothelial cells where it serves to dephosphorylate proteins involved in regulation of the actin cytoskeleton and thereby enhance endothelial barrier function.⁵² Earlier work identified that PP1 appears to protect the endothelial barrier by dephosphorylating myosin light chain (MLC).⁵³ The protective role of PP1 in maintaining endothelial barrier function was underscored in studies investigating the mechanisms through which the *Pasteurella multocida* bacterium generates acute inflammatory symptoms of the skin, in particular, vascular edema. Exposure of HUVEC endothelial cells to the *P. multocida* toxin activated Rho/Rho kinase causing inactivation of PP1 and thus increased myosin light chain (MLC) phosphorylation. This resulted in endothelial cell retraction and increased endothelial permeability.⁵⁴ PP1 therefore appears to be

an integral protective factor in the maintenance of junctional integrity.

PP2A

Protein phosphatase 2A (PP2A) is another phosphoprotein phosphatase (PPP) member of the phosphoserine phosphatase family and plays an important role regulating many cellular functions including DNA replication, transcription and translation, signal transduction, cell proliferation, cytoskeleton dynamics and apoptosis. In addition, PP2A plays a role in cell metabolism by regulating the activity of enzymes involved in glycolysis, lipid metabolism, catecholamine synthesis, and cell transformation.^{41,55-57} PP2A is the major phosphatase responsible for dephosphorylation of Ser and Thr residues.⁴¹ The PP2A enzyme (~36 kDa) can be found in two structurally different complexes. The dimeric form, (PP2AD), is known as the core enzyme and is composed of the scaffold (PP2AA) and catalytic (PP2Ac) subunits.⁵⁸ PP2A also exists as a trimer, (PP2AT), and this is an active holoenzyme complex comprised of, scaffold, catalytic and regulatory 'B' subunits (PP2AB).^{59,60} Several families of regulatory B subunits have been identified and these serve a critical role in regulating PP2A enzymatic activity and substrate specificity.⁶¹ In addition, particular B subunits modulate PP2A targeting to specific intracellular domains and signaling complexes thus influencing the biological outcomes of PP2A activation.^{61,62} For example, the B α subunit is a major PP2A isoform involved in regulating cytoskeletal function and cell growth in a variety of cell types.⁶¹

PP2A was the first phosphatase identified to associate with tight junction complexes.⁶³ Using an MDCK (strain II D5 clone) epithelial cell line model, the authors observed that expression of the PP2A catalytic subunit restricted TJ assembly, while inhibition of PP2A by okadaic acid promoted the phosphorylation and recruitment of ZO-1, occludin, and claudin-1 to the TJ during junctional biogenesis following a calcium-switch assay. Negative regulation of TJ assembly by PP2A appeared to occur independently of F-actin organization or E-cadherin localization status, as they were not affected by PP2A overexpression. However, PP2A associated with and regulated the activity and distribution of aPKC during TJ formation, while inhibition of aPKC prevented the calcium- and serum-independent membrane redistribution of TJ proteins induced by okadaic acid. This study provided strong evidence for calcium-dependent targeting of PP2A in epithelial cells and a novel role for PP2A in the regulation of epithelial TJ assembly and barrier function. As regards specific junctional proteins targeted by PP2A subunits, the B α subunit was the predominant B subunit found in association with the scaffolding and catalytic subunits A and C in ZO-1, occludin, or claudin-1 immunoprecipitates.⁶³ The association of B α appeared to be specific as the B56 γ subunit found in PP2A holoenzymes, or any additional Ser/Thr phosphatase such as PP1, was not detected in TJ protein immunoprecipitates. The authors used immunogold-electron microscopy with anti-B α antibodies to examine AB α C localization in human colon, and identified a pool of TJ-associated PP2A. However, this contrasted with MDCK

cells where the AB α C form of PP2A was not detected at the apical membrane. This was interpreted as possibly representing a cell-type specific distribution of PP2A that may be more clearly delineated to the apical membrane in the more defined apical junctional complex present in intestinal epithelial cells.⁶³

PP2A regulation of ZO-1 phosphorylation was also confirmed in experiments showing that inhibition of PP2A by okadaic acid increased ZO-1 phosphorylation levels, while overexpression of the PP2A C subunit reduced ZO-1 phosphorylation and accumulation of ZO-1 and occludin at tight junctions during TJ formation.⁶³ Overall, this study indicated that inhibition of PP2A activity promoted the phosphorylation and association of ZO-1, claudin-1, and occludin with TJs. An important mechanism through which PP2A regulates TJ protein localization is through inhibition of the atypical PKC ζ isoform that plays an important role in phosphorylating TJ proteins through its protein kinase activity.⁶⁴ PP2A colocalizes with PKC ζ at the apical membrane of MDCK cells. Moreover, okadaic acid increases, but overexpression of the PP2A C subunit blocks, phosphorylation of PKC ζ on a critical Thr410 residue during TJ assembly. As with PKC ζ , PP2A also associates with and regulates the activity and distribution of another PKC isoform involved in TJ regulation, PKC λ .

Phosphorylation of occludin on Ser/Thr residues plays a crucial role in maintaining the integrity of epithelial TJ as indicated by hyperphosphorylation of occludin on Ser/Thr residues in intact epithelium and their dephosphorylation during TJ disassembly.^{8,65,66} However, the role of this phosphorylation in the assembly of the TJ is unclear. Seth et al. evaluated the influence of protein phosphatases PP2A and PP1 on the assembly of TJ and phosphorylation of occludin in Caco-2 intestinal epithelial cells.⁴⁹ Using pharmacologic and molecular approaches to inhibit protein phosphatase activity and reduce expression of PP2A-C α and PP1 α , they observed enhancement of a calcium-induced increase in TER and reduced permeability to inulin, a polyfructose molecule with a molecular weight of approximately 5 kD. This was coupled with enhanced junctional organization of occludin and ZO-1 during TJ assembly. Differential residue phosphorylation was observed as phosphorylation of occludin Thr, but not Ser, residues were dramatically reduced during TJ disassembly but gradually increased during reassembly. In contrast to earlier studies indicating a primary role for Ser phosphorylation in TJ assembly in high-resistance MDCK I cells, this study indicated that Thr phosphorylation is more important than Ser phosphorylation during the assembly of TJ in Caco-2 cells.⁸ This discrepancy may be due to complete vs. incomplete dissociation of occludin from ZO-1 and actin arising from different durations of Ca²⁺-depletion induced TJ disassembly, or it may suggest that cell-type specific roles for particular residues on TJ proteins may exist with respect to phospho-regulation of TJ protein function. In addition to observing a physical association of PP2A and PP1 with the C-terminal tail of occludin in co-immunoprecipitation and GST pull-down assays, the dynamics of this coupling with occludin were revealed as their association was reduced during TJ assembly. Furthermore, the authors uncovered specific roles for PP1 and PP2A as in vitro incubation studies with phospho-occludin indicated that PP1 dephosphorylates occludin on Ser

residues whereas PP2A dephosphorylates Thr residues. Overall, the study demonstrated direct physical interactions between PP2A and PP1 with occludin and their roles in negatively regulating the assembly of tight junctions through modification of the phosphorylation status of specific occludin residues.

Further work from the Rao group identified how inflammatory mediators can modulate barrier function and TJ composition through activation of PP2A. Hydrogen peroxide initiated disruption of tight junctions in Caco-2 cell monolayers by dephosphorylation of occludin Thr residues, but not Ser residues. This effect was mediated by translocation of PP2A to TJs that occurred in a Src kinase-dependent manner.⁶⁷ Intriguingly, activation of ERK mitogen-activated protein kinase mediated epidermal growth factor (EGF) protection against H₂O₂-induced barrier disruption in differentiated Caco-2 cells and reduced PP2A association with occludin.^{68,69} However, the opposite effect occurred in undifferentiated cells where ERK activation potentiated a drop in TER and did not modify PP2A-occludin interactions.⁶⁹ This demonstrated that distinct and opposing roles for the same signaling mediator were dictated by the differentiation status of the cell. The effects of H₂O₂ on barrier function do not occur in isolation through PP2A as it has also been shown to mediate its effects through specific PKC isoforms— δ and λ .⁷⁰⁻⁷² This example serves to further emphasize the integrated nature of kinase-phosphatase regulation of signaling events. Additional evidence for reactive oxygen species (ROS) regulation of PP2A was demonstrated by bacterial lipopolysaccharide (LPS) + interferon-gamma (IFN- γ) treatment of mouse skeletal muscle microvascular endothelial cell monolayers to produce inducible nitric oxide synthase (iNOS)-derived nitric oxide (NO) and NADPH oxidase-derived superoxide. This resulted in the formation of the highly reactive peroxynitrite that inhibited tyrosine residue phosphorylation of PP2Ac through nitration.⁷³ Tyrosine phosphorylation of PP2Ac inhibits catalytic activity and restricts the capacity of PP2A to compromise barrier function. In these studies, nitration of PP2Ac correlated with increased PP2A activation and an increase in endothelial barrier dysfunction. PP2A-induced dephosphorylation of occludin appears to mediate the effects of a number of agents known to disrupt barrier function including ethanol, along with its most potent metabolite, acetaldehyde. Disruption of Caco-2 barrier function and redistribution of occludin and ZO-1 from TJs by acetaldehyde was mitigated by siRNA knockdown of PP2A. Acetaldehyde also increased interaction of PP2A with occludin and dephosphorylation of occludin on threonine residues.⁷⁴ PP2A also mediated, in conjunction with PKC- ζ , alveolar barrier disruption and occludin internalization induced by hypoxia.⁷⁵ This indicates that PP2A can mediate junctional remodeling in response to oxygen deficiency in addition to an excess of reactive oxygen species.

The compartmentalization of PP2A within the cell also appears to play an important role in TJ assembly. Studies in MDCK cells showed that enhanced interaction of hypoglycosylated E-cadherin-containing adherens junctions with PP2A correlated with diminished binding of PP2A to ZO-1 and claudin-1, and with increased phosphorylation of Ser residues on ZO-1

and claudin-1. Increased ZO-1 was found in complexes with occludin and claudin-1, and this corresponded to enhanced physiological assembly of TJs as determined by increased TER. This study suggested that E-cadherin N-glycans coordinate the maturity of AJs with the assembly of TJs by modifying the association of PP2A with AJ and TJ complexes. Moreover, sequestration of PP2A by hypoglycosylated E-cadherin in adherens junctions appears to regulate tight junction assembly.⁷⁶ Broader roles for PP2A in the regulation of cell adhesion, polarity and cytoskeleton dynamics have also been identified. PP2A co-localizes with β 1-integrin and is an important regulator of the FAK (focal adhesion kinase) complex.⁷⁷ Moreover, inhibition of PP2A promotes disorganization of focal adhesion sites, loss of cell polarity, increased cell migration in endothelial cells through FAK/Src/paxillin hyperphosphorylation, and dissociation of PP2A from endothelial microtubules leading to destabilization of the microtubule network.^{78,79}

PP2A may also have a role in regulating angiogenesis. Studies in endothelial cells have shown that PP2A secures mature endothelial junctions against disruption of vascular integrity by preventing both serine phosphorylation and internalization of vascular endothelial (VE) cadherin. Conversely, Semaphorin 3A (S3A), one of the semaphorin guidance molecules that regulates endothelial cell migration and tumor angiogenesis by providing both repulsive and attractive signals, destabilizes the brain endothelial barrier by interrupting the continuous protective effect of PP2A on VE-cadherin.^{80,81} PP2A activation may also have clinical value as a modulator of retinal vasopermeability. Activation of PP2A by vasoinhibins, a family of peptides derived from the protein hormone, prolactin, dephosphorylated eNOS causing its inactivation. Inactivation of eNOS antagonized the proangiogenic effects of VEGF, a primary mediator of retinal vasopermeability that promotes eNOS activation. Vasoinhibins inhibited VEGF-induced vasopermeability in vitro and in vivo, and also blocked retinal vasopermeability in diabetic rats. Moreover, intravitreal injection of the PP2A inhibitor, okadaic acid, blocked the protective effect of vasoinhibin on endothelial cell permeability and retinal vasopermeability thus suggesting that enhancement of PP2A activity may have therapeutic value for diabetic retinopathy.⁸² Overall, these studies emphasize the importance of PP2A as a regulator of cell polarity and TJ assembly in a variety of cell types, but with cell-type specific effects regarding substrate targeting and positive or negative outcomes for overall barrier function following PP2A activation.

Tyrosine Phosphatases

There are approximately 100 human PTP superfamily genes, with additional diversity arising from the use of alternative promoters, alternative mRNA splicing and post-translational modifications. These genes encode enzymes that are divided into classical, phosphotyrosine (pTyr)-specific phosphatases and dual specificity phosphatases (DUSPs).^{42,55} The classical PTPs include transmembrane receptor like proteins (RPTPs) that can regulate signaling through ligand-controlled protein tyrosine dephosphorylation and non-transmembrane, cytoplasmic PTPs.

PTPs have the capacity to function both positively and negatively in the regulation of signal transduction and display high degrees of substrate, and functional, specificity in vivo.³⁵ PTPs specifically remove the phosphate group from post-translationally modified tyrosine residues. They were proposed to play an important role in the regulation of cell-cell contacts because treatment with sodium orthovanadate, a potent inhibitor of phosphatase activity, diminished normal cell contact inhibition in epithelial cells and led to increased tyrosine phosphorylation at adherens junctions.⁸³ Furthermore, many receptor-type PTPs display structural features of cell adhesion molecules and it was thought that RPTPs may play an important role in regulating phenomena associated with cell-cell contact, including contact inhibition of cell growth.^{84,85} As discussed below, many non-transmembrane and receptor-like PTPs play important roles in regulating the integrity and function of intercellular junctions (Fig. 1). The DUSPs are less well conserved than the classical PTPs. They share little sequence similarity with classical PTPs beyond the cysteine-containing signature motif, while they also contain smaller catalytic domains. Although they largely share the same catalytic mechanism as the classical PTPs, the structure of the DUSP active site allows them to target phosphorylated Ser/Thr residues in proteins as well as pTyr residues.³⁵ The DUSPs will not be discussed further as they do not, at the time of writing, appear to be prominent regulators of the apical junctional complex.

Non-Transmembrane PTPs

SHP2

The Src homology-2 (SH2) domain-containing phosphatases (Shps) comprise a sub-family of non-receptor protein-tyrosine phosphatases with two human members, SHP1 (encoded by *PTPN6*) and SHP2 (encoded by *PTPN11*). SHP1 expression is largely restricted to lympho-hematopoietic cells, whereas SHP2 is expressed ubiquitously.^{86,87} SHP2 is composed of two SH2 domains (N-SH2, C-SH2), a PTP domain, a C-terminal tail with tyrosine phosphorylation sites (Y542 and Y580) and a proline-rich motif.⁸⁸ A wide variety of genetic and biochemical evidence indicates that SHP2 plays a key role in receptor tyrosine kinase (RTK) signaling as it appears to be required for full activation of the RAS/ERK pathway by most RTKs and cytokine receptors.^{86,87,89,90} Furthermore, *PTPN11* mutations can give rise to autosomal recessive developmental disorders such as Noonan's syndrome and LEOPARD syndrome.^{86,88} The C-terminal tyrosines on SHP2 are phosphorylated upon activation of many receptors, and are involved in modulating downstream signaling pathways.⁹¹ In its basal state, SHP2 activity is suppressed by intramolecular interactions between residues in the N-SH2 domain and the catalytic surface of the PTP domain.^{92,93} Upon growth factor or cytokine stimulation, SHP2 is recruited, via its SH2 domains, to phosphorylated tyrosine residues on RTKs, cytokine receptors, and/or scaffolding adaptors, such as insulin receptor substrate, fibroblast growth factor receptor substrate, or GRB2-associated binder (GAB) proteins. Binding of substrate phosphorylated tyrosines to the N-SH2 domain of SHP2

disrupts the auto-inhibitory interface resulting in exposure of the PTP domain and catalytic activation.^{86,92,93}

The role of SHP2 in the regulation of junctional complexes and barrier function has perhaps been most extensively studied in endothelial cells. SHP2 has been identified as a key regulator of the endothelial specific cadherin, VE-cadherin, that localizes to adherens junctions.⁹⁴ Numerous studies support a link between increased protein tyrosine phosphorylation and vascular permeability, with SHP2 being a particular target for growth factors and cytokines that modify vascular permeability. One such example is the serine protease clotting factor, thrombin that increases vascular permeability via changes in endothelial cell adherens junctions. SHP2 associates selectively with β -catenin in VE-cadherin complexes in confluent, quiescent human umbilical vein endothelial cells, however thrombin induces SHP2 tyrosine phosphorylation and dissociation from VE-cadherin complexes.⁹⁵ SHP2 dissociation facilitates increased tyrosine phosphorylation of β -catenin, γ -catenin, and p120-catenin complexed with VE-cadherin. Increases in β -catenin and γ -catenin phosphorylation alter their interaction with α -catenin leading to diminished cytoskeletal association of VE-cadherin complexes.⁹⁵ This in turn promotes cell junction disassembly and intercellular gap formation detected in endothelial cell monolayers associated with thrombin treatment, and a subsequent increase in monolayer permeability.^{96,97} SHP2 also plays an important role in the recovery of endothelial barrier function after thrombin treatment by dephosphorylating VE-cadherin-associated β -catenin and promoting the mobility of VE-cadherin at the plasma membrane. Pharmacologic and molecular inhibition of SHP2 delayed recovery of endothelial barrier function after thrombin stimulation of HUVECs.⁹⁸ The role(s) of SHP2 in the maintenance of endothelial barrier function and VE-cadherin complex stability were also identified as being critical to the effects of fibroblast growth factor (FGF). FGF preserves vascular integrity by promoting the stability of VE-cadherin at adherens junctions. Suppression of FGF signaling reduced SHP2 expression levels and SHP2/VE-cadherin interaction due to accelerated SHP2 protein degradation. Inhibition of FGF signaling caused an increase in endothelial permeability that was rescued by SHP2 overexpression. Therefore, SHP2 is targeted by signaling pathways that exert positive or negative effects on endothelial junction integrity.⁹⁹

A major physiological consequence of disrupted cell-cell junctions between pulmonary endothelial cells is pulmonary edema. In addition to established effects of SHP2 in regulating endothelial cell barrier function in vitro, in vivo studies showed that SHP2 inhibition promoted edema formation in rat lungs. In addition, pulmonary endothelial cells demonstrated a decreased level of p190RhoGAP activity following inhibition of SHP2, and a concomitant increase in RhoA activity.¹⁰⁰ In endothelial barrier dysfunction RhoA activity is increased, and several studies have demonstrated that inhibition of RhoA or its downstream signaling molecule, Rho kinase, attenuates agonist-induced endothelial monolayer permeability through maintenance of adherens junctions, diminished cellular contraction and reduced stress fiber and intercellular gap formation.¹⁰¹ It has been proposed

that SHP2 modulates adherens junction formation both directly, through its interaction with VE-cadherin, as well as indirectly, through modulation of RhoA activation. p190RhoGAP has been shown to regulate RhoA activity and to be important in restoration of endothelial barrier function.^{102,103} Grinnell and colleagues showed that SHP2 inhibition in pulmonary endothelial cells attenuated the activity of p190RhoGAP, an effect that correlated with increased p190RhoGAP tyrosine phosphorylation.¹⁰⁰ Therefore, SHP2 appears to play a major role in supporting basal pulmonary endothelial adherens junction complex integrity and barrier function by coordinating the tyrosine phosphorylation levels of VE-cadherin, β -catenin, as well as p190RhoGAP and the activity of RhoA.

SHP2 regulation of cellular junctions has also been demonstrated to play an important role in maintaining the blood-testis barrier (BTB).¹⁰⁴ The BTB is a large junctional complex composed of tight junctions, adherens junctions, and gap junctions between adjacent Sertoli cells in the seminiferous tubules of the testis. Maintenance of the BTB as well as the controlled disruption and reformation of the barrier is essential for spermatogenesis and male fertility as breaches in the barrier can allow spermatozoa into the bloodstream and provoke an immune response. The adherens and tight junctions of the BTB are regulated by tyrosine phosphorylation. SHP2 is localized to Sertoli-Sertoli cell junctions in rat testis and its overexpression in primary rat Sertoli cells in vitro upregulated the BTB disruptor ERK1/2 via Src kinase activity. This also resulted in a reduction of tyrosine phosphorylation of focal adhesion kinase (FAK) leading to loss of AJs and TJs that was associated with internalization of N-cadherin, β -catenin, and ZO-1 coupled with actin cytoskeleton disruption.¹⁰⁴ These findings suggest that SHP2 is a negative regulator of BTB integrity and Sertoli cell support of spermatogenesis and fertility.

SHP2 is also a target for microbial manipulation of barrier function. *Helicobacter pylori* strains positive for the virulence factor, CagA (cytotoxin-associated gene A), are associated with gastritis, ulcerations and ultimately gastric adenocarcinoma. After attachment of *cagA*⁺ *H. pylori* to gastric epithelial cells, CagA can be directly injected into the epithelial cells via the bacterial type IV secretion system and undergoes tyrosine phosphorylation in the host cells.^{105,106} CagA induces a dramatic cell elongation of gastric epithelial cells referred to as the hummingbird phenotype.^{30,105} The hummingbird phenotype is caused by the specific interaction of tyrosine-phosphorylated CagA with SHP2 that is dependent on both increased SHP2 activity but also tethering of SHP2 at the membrane.^{106,107} In polarized epithelial cells, CagA disrupts tight junctions and induces loss of apical-basolateral polarity. Saadat et al. identified that CagA binds to the polarity protein, Par1, inhibits its kinase activity and blocks aPKC-mediated Par1 phosphorylation.³⁰ This causes dissociation of Par1 from the membrane, collectively causing junctional and polarity defects. A consequence of the multimeric nature of Par1 is that it also promotes CagA multimerization, thus stabilizing the CagA-SHP2 interaction and promoting induction of the hummingbird phenotype that also requires simultaneous inhibition of Par1 kinase activity by CagA. Although an exact role for SHP2 in

the polarity defects vs. the hummingbird phenotype has not yet been discerned, the fact that CagA, SHP2 and Par1 are capable of forming a biological complex suggests a possible role for SHP2 in the CagA-induced junctional defects.³⁰

PTP1B

PTP1B was the first member of the PTP family to be isolated and sequenced.¹⁰⁸⁻¹¹⁰ Encoded by the *PTPNI* gene, PTP1B contains an N-terminal PTP domain, followed by two tandem proline-rich motifs that may allow interaction with SH3 domain-containing proteins. PTP1B contains a C-terminal hydrophobic domain that targets the enzyme to its intracellular location on the cytoplasmic surface of the endoplasmic reticulum.^{111,112} PTP1B is a major regulator of metabolism, as demonstrated by the resistance to high fat diet-induced obesity and insulin hypersensitivity observed in PTP1B^{-/-} mice.¹¹³ PTP1B is also a major phosphatase involved in regulating the tyrosine phosphorylation status of the insulin receptor, and leptin receptors as well as growth factor receptors such as the epidermal growth factor (EGFR), in cultured cells.¹¹⁴⁻¹¹⁹

PTP1B regulation of junctional proteins was initially identified in studies on N-cadherin in neural cells.¹²⁰ PTP1B was first shown to play an important role in regulating epithelial AJs in studies by Sheth et al. who identified that acetaldehyde caused disruption of AJs in Caco-2 intestinal epithelial monolayers by reducing E-cadherin and β -catenin-associated PTPase activity and dissociating PTP1B from the E-cadherin- β -catenin complex.¹²¹ Furthermore, this effect was tyrosine kinase dependent and acetaldehyde increased tyrosine phosphorylation of E-cadherin and phosphorylation of β -catenin on Tyr-331, Tyr-333, Tyr-654 and Tyr-670. In endothelial cells, PTP1B acts similarly to other PTPs by negatively regulating VEGFR2 receptor activation and consequently reducing endothelial permeability. PTP1B further strengthens endothelial barrier properties by stabilizing cell-cell interactions through reducing tyrosine phosphorylation of VE-cadherin.¹²² Further studies in pulmonary endothelial cells and in mice expressing a catalytically inactive PTP1B, demonstrated a decrease in resting TER of endothelial cell cultures and increased edema in mouse lungs. In a model of sepsis-induced acute lung injury, administration of LPS to mice generated reactive oxygen species and PTP1B oxidation that inhibited phosphatase activity. This was associated with an increase in β -catenin tyrosine phosphorylation, dissociation of PTP1B and β -catenin and increased lung endothelial barrier dysfunction.¹²³ Therefore, PTP1B function appears to play a critical role in restricting barrier defects arising from sepsis-induced pulmonary vascular dysfunction. In addition, PTP1B protects against the effects of other signaling pathways utilized in inflammation including histamine H-1 receptor and PAR-2 receptor-induced disruption of transfected E-cadherin and β -catenin complexes in renal epithelial (MDCK) and enteroendocrine (L-cell) cell lines.¹²⁴

An additional role for PTP1B in the regulation of renal epithelial barrier integrity can be found in the maintenance of renal glomerular function. The barrier function of the kidney glomerulus is critical to overall renal function as a compromised barrier can lead to protein leakage into the urine

(proteinuria), a feature of many kidney diseases. Podocytes are the visceral epithelial cells inside Bowman's capsule that overlay the endothelial cells of the glomerulus. Podocytes are critical for the barrier integrity of the glomerulus and are involved in regulating glomerular filtration rate and nephrin is an important podocyte protein involved in regulation of the actin cytoskeleton via tyrosine phosphorylation of its cytoplasmic domain.¹²⁵ PTP1B directly binds to and dephosphorylates nephrin, and the authors determined that this may lead to disruption of the actin cytoskeleton and increased podocyte permeability. However, overexpression or inhibition of PTP1B disrupts the actin cytoskeleton in cultured mouse podocytes thus emphasizing the discreet level of control of phosphorylation levels that are required for appropriate podocyte function.¹²⁶ Cumulatively, these data emphasize the importance of PTP1B in modifying basal barrier function but also in restricting the effects of multiple inflammatory insults on intercellular junction integrity across multiple organs and cell types.

TCPTP

T-cell protein tyrosine phosphatase (TCPTP), shares 74% homology with PTP1B but has been demonstrated in a series of elegant studies to have non-overlapping roles in the regulation of dephosphorylation targets.¹²⁷⁻¹³¹ TCPTP is ubiquitously expressed with high expression in hematopoietic cells.¹²⁸ Two functional variants of TCPTP protein product are expressed that arise from alternative splicing of message from the encoding *PTPN2* gene. The 48 kD variant is restricted to the endoplasmic reticulum by a hydrophobic C-terminus that serves to mask a bipartite nuclear localization sequence. The 45 kD form is targeted to the nucleus by the nuclear localization sequence. In addition to its greater mobility within the cell that allows it to shuttle in and out of the nucleus in response to various stimuli, the 45 kD form also has the greater enzymatic activity.¹³²⁻¹³⁴ TCPTP substrates include: (a) receptor protein tyrosine kinases such as the EGFR and the insulin receptor; (b) non-receptor PTKs such as members of the Src family and JAK-1 and -3; and (c) PTK substrates such as p52Shc and signal transducers and activators of transcription (STAT)-1, -3, -5 and -6.^{131,135-139} In vivo, TCPTP appears to play a critical role in immune homeostasis as mice globally deficient for *Ptpn2* develop a systemic inflammation resulting in hematopoietic defects, increased levels of proinflammatory cytokines, splenomegaly and diarrhea. However, these effects were shown to be driven by loss of *Ptpn2* in the non-hematopoietic compartment as determined by bone marrow chimeric studies.¹⁴⁰ Although the severity and kinetics of inflammation in mice are strain-dependent, homozygous *Ptpn2*-deficient mice die soon after birth.¹⁴⁰⁻¹⁴² While heterozygous *Ptpn2*-deficient mice have no overt phenotype, they do exhibit increased sensitivity to chemically-induced colitis caused by dextran sulfate sodium (DSS) administration, suggesting that loss of *Ptpn2*/TCPTP increases susceptibility to barrier-disrupting agents.¹⁴³

TCPTP is of clinical significance as a number of SNPs in the *PTPN2* gene are associated with chronic inflammatory diseases including Crohn's disease, ulcerative colitis, celiac disease and Type 1 diabetes.¹⁴⁴⁻¹⁴⁶ A striking feature of the pathology of these four chronic inflammatory diseases, CD, UC, Type 1 diabetes

and celiac disease, is that they all feature increased intestinal permeability prior to the onset of inflammation.¹ Our group has previously identified that TCPTP plays a beneficial role in the regulation of epithelial barrier function. Using intestinal epithelial cell lines, we observed that TCPTP expression was increased following treatment with IFN- γ a pro-inflammatory cytokine involved in IBD and celiac disease pathogenesis.¹⁴⁷ Consistent with this, TCPTP levels were increased in intestinal epithelium in active CD.^{147,148} However, we also observed that knockdown of TCPTP resulted in an amplification of barrier defects following treatment with IFN- γ .¹⁴⁷ Loss of TCPTP was associated with a decrease in TER and elevated expression of the pore-forming protein, claudin-2, that forms a cation-selective pore. Increased claudin-2 expression permits increased paracellular passage of sodium ions and could therefore contribute to the loss of fluid that occurs in IBD.^{149,150} TCPTP-deficient cells were also more permeable to macromolecules following IFN- γ treatment as demonstrated by their increased apical-basolateral passage of FITC-dextran across epithelial monolayers.¹⁴⁷ As the claudin-2 pore is too narrow to allow FITC-dextran (10 kD) to pass through, this indicates that additional mechanisms responsible for a greater 'leak' barrier defect were also involved in the response to IFN- γ in TCPTP-deficient cells.¹⁵¹ Although TCPTP knockdown did not accentuate IFN- γ -induced decreases in expression of the tight junction proteins, occludin or ZO-1, a potential influence of TCPTP on localization of these proteins may contribute to this leak phenotype in TCPTP-deficient cells. These data suggest that TCPTP plays an important role in protecting intestinal epithelial barrier function. Even though TCPTP levels were increased in inflamed intestine and IFN- γ is capable of inducing expression of TCPTP in an apparent negative-feedback mechanism, clinically relevant loss-of-function mutations in the *PTPN2* gene may contribute to the etiopathogenesis of chronic inflammatory intestinal disease, at least in part, through dysregulation of epithelial barrier properties.

PTP-PEST

Encoded by the *PTPN12* gene, PTP-PEST is ubiquitously expressed with highest levels found in hematopoietic cells.¹⁵² PTP-PEST is an 88 kDa cytosolic PTP belonging to the PEST-domain-enriched tyrosine phosphatase (PEP) subfamily of non-receptor PTPases (Fig. 1).¹⁵³ Previous studies have shown that PTP-PEST can physically associate with several molecules involved in cell adhesion and signal transduction including focal adhesion proteins such as paxillin and Cas, the adaptor protein Shc, and the inhibitory tyrosine kinase Csk. These interactions occur via sequences outside of the PTP-PEST catalytic domain.^{154,155} Garton and Tonks showed that PKC and PKA are capable of phosphorylating PTP-PEST on Ser39 and Ser435, while further in vitro studies indicated that phosphorylation of Ser39 reduced PTP-PEST activity by decreasing its substrate affinity.¹⁵⁶ Therefore, signaling pathways mediated by the Ser/Thr kinases, PKA and PKC, can inhibit PTP-PEST function and thereby regulate cellular processes modified by PTP-PEST-dependent reversible tyrosine phosphorylation.

PTP-PEST has been shown to regulate elements of cell adhesion and barrier function. As described above, PTP1B plays an

important role in regulating renal glomerular podocyte function through modulation of the phosphorylation status of the nephrin protein. PTP-PEST also regulates nephrin phosphorylation albeit in a more indirect manner than PTP1B.¹²⁶ PTP-PEST is capable of binding to and dephosphorylating the Src family kinase member, Fyn, at Y418, thereby inhibiting its activity. Fyn is known to directly phosphorylate nephrin, therefore, PTP-PEST inhibition of Fyn in turn is likely to contribute to reduced phosphorylation of nephrin. Expression of PTP-PEST and PTP1B was increased in the puromycin aminonucleoside nephrosis (PAN) rat model of proteinuria. In contrast to the majority of studies where PTP activity is beneficial to the preservation of barrier function, the authors of this study concluded that upregulation of PTP-PEST and PTP1B contributes to decreased tyrosine phosphorylation of nephrin, that may in turn result in impaired cytoskeletal regulation in podocytes and development of proteinuria.¹²⁶

A pathologic consequence of loss of cell adhesion is increased metastatic and invasive potential of cells. PTP-PEST functions as a suppressor of colonic carcinoma epithelial cell motility by controlling Rho GTPase activity and the assembly of adherens junctions.¹⁵⁷ In the KM12C colonic epithelial cell line, PTP-PEST localized to adherens junctions while knockdown of PTP-PEST caused a disruption of cell-cell contacts due to a defect in AJ assembly, but with no effect on E-cadherin expression. As with other phosphatases, functional outcomes of PTP-PEST depletion can vary between different cell types. An elegant study utilizing primary endothelial cells from an inducible PTP-PEST-deficient mouse demonstrated that PTP-PEST was not essential for endothelial cell differentiation and proliferation or for the control of endothelial cell permeability.¹⁵⁸ However, it was required for integrin-mediated adhesion and migration of endothelial cells. PTP-PEST-deficient endothelial cells exhibited increased tyrosine phosphorylation of Cas, paxillin, and Pyk2 proteins that play important roles as mediators of integrin signaling and cell adhesion.¹⁵⁸ Therefore, PTP-PEST can function not only as a regulator of barrier properties but also exerts an influence on cell motility.

VE-PTP

Vascular endothelial receptor tyrosine phosphatase (VE-PTP), also known as PTPRB or PTPB, (VE-PTP) is the only known receptor type PTP specifically expressed in endothelial cells.¹⁵⁹⁻¹⁶¹ VE-PTP interacts with VE-cadherin via both intracellular, but mainly through extracellular, domains and is required for optimal adhesive function of VE-cadherin and for endothelial cell contact integrity.¹⁶²⁻¹⁶⁴ Major substrates of VE-PTP, with relevance to the adhesive function of VE-cadherin, are VE-cadherin itself and the catenin, plakoglobin.¹⁶³ Other tyrosine phosphatases that affect endothelial cell contact integrity and VE-cadherin-catenin phosphorylation are SHP2 (discussed above) and the receptor type tyrosine phosphatase RPTP μ .¹⁶⁵

Since VE-PTP strengthens the adhesive activity of VE-cadherin, dissociation of VE-PTP from VE-cadherin can be regarded as a prerequisite for the opening of endothelial junctions in response to stimuli that loosen endothelial cellular junctions and increase paracellular permeability. This has significant relevance for a number of physiological and pathophysiological

processes including leukocyte diapedesis. Evidence for a role for VE-PTP as a negative regulator of leukocyte migration was provided by a study demonstrating that docking of leukocytes to the apical surface of endothelial cells triggered rapid dissociation of VE-PTP from VE-cadherin.¹⁶³ It was demonstrated that both LPS-triggered neutrophil recruitment into the lung, or intravenous administration of VEGF, stimulated the dissociation of VE-PTP from VE-cadherin *in vivo*.¹⁶⁶ The necessity for dissociation of these proteins in leukocyte extravasation and the induction of vascular permeability was confirmed using knock-in mice that prevented dissociation of VE-PTP from VE-cadherin.¹⁶⁶ These studies demonstrated that tyrosine phosphorylation of the VE-cadherin–catenin complex, or of proteins associated with this complex, is necessary *in vivo* to disconnect endothelial junctions and that this process is restricted by VE-PTP.¹⁶⁴

Receptor-like PTPs

DEP-1

The receptor-type protein tyrosine phosphatase DEP-1 (density-enhanced protein tyrosine phosphatase-1), also known as CD148, PTP- η , or high cell density-enhanced PTP (HPTP- η), is a member of the type III family of protein tyrosine phosphatases (PTPs) (Fig. 1).³⁵ It is widely expressed in many cell types including epithelial cells, hematopoietic cells and fibroblasts, but is most abundantly expressed in endothelial cells.^{36,85} A tumor suppressor function was associated with DEP-1 in genetic studies and this is consistent with known substrates including c-Met, p120 catenin, c-Src, and PI3-K.¹⁶⁷ Initial studies of DEP-1 ablation in mice indicated that DEP-1 is critically important for blood vessel development during embryogenesis as ablation of DEP-1 in mice was embryonic lethal at E11.5 and was associated with elevated endothelial cell numbers and enlarged primitive vessels, indicative of a problem with vascular remodeling and branching.¹⁶⁸ However, DEP-1–deficient mice generated by other groups are viable and do not manifest any gross abnormalities.¹⁶⁹

In endothelial cells, DEP-1 tends to be localized at sites of cell-cell contact, and overlaps with VE-cadherin.¹⁷⁰ The expression level of DEP-1 is directly related to cell density, indicative of a regulatory role for this RPTP in cell contact–mediated growth inhibition.¹⁷¹ DEP-1 contributes to cadherin-mediated contact inhibition through dephosphorylation of VEGFR-2 and attenuation of the activation of mitogen-activated protein kinase (MAPK) signaling, suggesting that DEP-1 plays a positive role in the regulation of endothelial function.¹⁷² VEGFR2 is the main mediator of the mitogenic, chemotactic, permeability-inducing, and survival effects of VEGF, and it is also a potent activator of the angiogenic response.¹⁷³ Activated VEGFR2 localizes to VE-cadherin complexes and these are major sites of VEGF-dependent signaling in confluent cells.¹⁷⁴ Phosphorylation of Tyr and Ser residues on VE-cadherin is associated with increased vessel permeability. The roles of DEP-1 in the modulation of endothelial permeability and signaling by VEGF are complex. It has been proposed that DEP-1 has bivalent functions where moderate levels of DEP-1 activity support VEGF-dependent Src activation in actively growing and invading endothelial cells,

while increased DEP-1 expression in confluent cells, together with the recruitment of VEGFR2, reduces Src and VEGFR2 activity to promote vessel quiescence and stabilization.^{175,176}

DEP-1 also regulates phosphorylation profiles of tight junction proteins in epithelial cells. Sallee and BurrIDGE used a catalytically dead substrate-trapping mutant of DEP-1 to identify potential substrates of DEP-1 at cell-cell junctions.¹⁷⁷ The trapping mutant of DEP-1 physically associated with occludin and ZO-1 in a tyrosine phosphorylation-dependent manner, and binding occurred at the catalytic region of DEP-1. This interaction had some degree of specificity as PTP-PEST, SHP2, and PTP μ did not interact with either occludin or ZO-1. Moreover, occludin and ZO-1 were specifically dephosphorylated by DEP-1 but not the other phosphatases *in vitro*. DEP-1 appears to enhance epithelial barrier properties as overexpression of DEP-1 in MDCK-II epithelial cells increased barrier function as measured by an increase in TER, and a decrease in paracellular flux of FITC-dextran, following calcium switch. Furthermore, knockdown of DEP-1 in MCF10A mammary epithelial cells by siRNA prompted a small but statistically significant drop in TER indicating a decrease in barrier function. Increased tyrosine phosphorylation of occludin and ZO-1 disrupts their association with each other and their TJ localization, and results in reduced monolayer TER.¹⁷⁸ Therefore, dephosphorylation of tyrosine residues on occludin and ZO-1 by DEP-1 likely strengthens the integrity of the TJ and enhances barrier properties.

RPTP μ

Receptor protein tyrosine phosphatase mu (RPTP μ) is a member of the type IIB receptor protein tyrosine phosphatases (RPTPs). This sub-family of RPTPs can be considered bi-functional cell surface molecules as their ectodomains mediate stable, homophilic, cell-adhesive interactions, whereas the intracellular catalytic regions can modulate the phosphorylation state of cadherin complexes (Fig. 1).⁹⁴ RPTP μ -mediated cell adhesion is calcium independent and does not require a functional intracellular catalytic domain.¹⁷⁹ RPTP μ in mammalian cells is strictly localized to regions of intercellular contact, and it appears to function as a cell contact receptor mediating cell-cell signaling. Therefore, RPTP μ serves to link cell adhesion with intracellular signaling.¹⁸⁰ Interestingly, cell surface expression of RPTP μ increases in parallel with increased intercellular contacts, a consequence of increased cell density.¹⁷⁹ RPTP μ demonstrates a very cell density-dependent dynamic. In sparse *in vitro* cultures without intercellular contacts, RPTP μ is nonfunctional and its surface expression levels are low because of rapid internalization. In addition, a portion of RPTP μ molecules located on the cell surface shed their ectodomain into the medium. However, upon cell-cell contact, RPTP μ molecules on neighboring cells recognize and bind to each other in a homophilic manner, thus preventing RPTP μ from being internalized.¹⁸¹ The membrane-proximal catalytic domain of RPTP μ has also been shown to interact with the scaffolding protein RACK1 (receptor for activated protein C kinase) and the association of endogenous RPTP μ and RACK1 in a lung epithelial cell line was observed to be increased at high cell density.¹⁸² Furthermore, the recruitment of RACK1 to both the plasma membrane and cell-cell contact

sites is RPTP μ -dependent in these cells and its association with RACK1 is disrupted by the presence of constitutively active Src.¹⁸² Therefore, RPTP μ recruits RACK1 to points of cell-cell contact, and this may play an important role in RPTP μ regulation of cell-cell adhesion.

RPTP μ is widely distributed and has been found in the nervous system where it appears to perform functions related to axon guidance within the visual system (reviewed in^{183,184}), in cardiomyocytes and primarily in vascular beds where tight, continuous contacts between endothelial cells are extremely important.¹⁸³⁻¹⁸⁶ It has been shown that RPTP μ can interact with several members of the cadherin family of cell-adhesion molecules (N, E, R and VE cadherins).^{94,165,180} Functionally, it is thought that such an interaction localizes the phosphatase activity of RPTP μ near the cadherin-catenin complexes, maintaining them in a dephosphorylated state and thus stabilizing the intercellular contacts. Sui et al. showed that RPTP μ can bind directly to VE-cadherin and that overexpression of wild-type RPTP μ decreased tyrosine phosphorylation of VE-cadherin.¹⁶⁵ In immortalized human microvascular ECs, overexpression of wild-type RPTP μ itself resulted in enhanced barrier function. Therefore, RPTP μ is a critical regulator of both VE-cadherin phosphorylation status and endothelial barrier integrity.¹⁶⁵

PTP σ

PTPsigma (PTP σ) belongs to the type IIa subfamily of RPTPs that include the phosphatases LAR, PTP σ , and PTP δ (Fig. 1).^{35,187} The extracellular region of PTP σ comprises three immunoglobulin-like domains and four to nine fibronectin type III domains.¹⁸⁸ This region has structural similarity to cell adhesion molecules in its domain structure.¹⁸⁹ PTP σ has two intracellular catalytic domains but only one of these, D1, has PTP activity. The other domain, D2, has a regulatory function.¹⁹⁰ The type IIa RPTPs play a vital role in neural development and regeneration and mice lacking PTP σ show defects in neurological development.^{187,189,191} A role for PTP σ in cell junction regulation was identified by Muise and colleagues who showed that mice lacking the receptor protein-tyrosine phosphatase sigma (*PTPRS*) gene that encodes PTP σ , spontaneously develop mild colitis and exhibit a greatly exacerbated form of colitis following exposure to either a chemical inducer of colitis, DSS, or bacterial colitis caused by *Citrobacter rodentium*.¹⁹² They also showed that the adherens junction proteins, E-cadherin and β -catenin are substrates for PTP σ and that E-cadherin was hypertyrosine phosphorylated in the colons of the *Ptprs*-KO mice relative to sibling controls. Phosphorylation of E-cadherin leads to its cellular redistribution away from the adherens junction and cell disassociation resulting in disassembly of the adherens junction. The *PTPRS* gene is located in the inflammatory bowel disease (IBD)-associated IBD6 locus.^{193,194} Three SNPs (rs886936, rs17130, and rs8100586) that flank exon 8 in the human *PTPRS* gene were discovered to be associated with ulcerative colitis, one of the inflammatory bowel diseases. The SNPs were associated with a novel splicing that causes removal of the third Ig-like domain from the extracellular portion of PTP σ , possibly altering dimerization or ligand recognition.¹⁹² Therefore, polymorphisms in the human *PTPRS* gene encoding PTP σ could result in altered PTP σ regulation of

adherens junctions and thus contribute to the barrier function defects associated with the development of IBD. However, PTP σ regulation of epithelial integrity is not uniform in all organs. PTP σ is strongly expressed in fetal but not adult Clara cells and lung alveolar cells, yet knockout mice display no apparent structural abnormalities in airway or alveolar epithelium of the lung. This is in contrast to the loss of epithelial differentiation observed in the gastrointestinal tract as well as loss of pancreatic islet mass, and effects on pituitary neuroendocrine cells.¹⁹⁵

An additional member of the receptor transmembrane branch of PTPs, PTP-LAR, has been shown to localize to adherens junctions, dephosphorylate β -catenin, cause dissociation of β -catenin from E-cadherin and contribute to cell motility.¹⁹⁶ Although modulation of specific barrier function parameters by PTP-LAR does not appear to have been tested as yet, given the importance of other phosphatases in the regulation of cadherin-catenin complexes and the consequent impact on barrier function, it is likely that PTP-LAR activity also contributes to barrier function regulation.

Conclusion and Perspectives

Intercellular junctions, formed by tight or adherens junctions, are dynamic structures that play critical roles in maintaining cell polarity, barrier functions and overall cell homeostasis. The dynamism of these contacts is essential for a variety of outcomes. This includes transient changes in tight junction composition in response to physiologic or pathologic stimuli necessary to modify permeability to solutes, changes in cadherin/catenin-mediated cell-cell contacts during embryonic development or wound healing, and changes in adherens junctions assembly/reassembly required to aid cell motility.¹⁹⁷ Dissociation of junctional complexes can lead to separation of neighboring cells as occurs in epithelial-mesenchymal transition (EMT) of forming mesoderm and in the development of metastatic tumor cells.¹⁹⁸⁻²⁰⁰ Therefore, the regulation of the dynamics of junctional assembly and disassembly due to phosphorylation status is critical for the homeostasis of adherent cells (Table 1). The role of phosphatases as a counterbalance to kinase-induced phosphorylation is an essential component in maintaining the structural and functional integrity of multiple organ systems. One aspect that may seem surprising is why so many different phosphatases are involved in regulating the same protein, or cluster of proteins, for example cadherin-catenin complexes. The answer to this remains to be fully elucidated but may be due, in part, to allow discrimination between different stimuli of a particular protein as shown by the capacity of TCPTP to discern between direct ligand binding to the EGFR by EGF vs. indirect EGFR activation by the inflammatory cytokine, IFN- γ .²⁰¹ Moreover, the activity of different phosphatases may determine signaling outcomes of an individual junction protein responsible for barrier vs. cell motility vs. repair functions. Therefore, phosphatases appear to not only be required for switching off kinase-activated signals, but they exert a discreet level of control that permits amplification or narrowing of signaling outcomes arising from modifications of intercellular junction proteins phosphorylation

status. A major challenge that lies ahead rests on identifying the regulatory cues that determine phosphatase regulation of specific signaling outcomes and whether these can be subjected to external modification to enhance certain properties such as strengthening or repairing barrier properties of cellular junctions that would likely be of great benefit in alleviating or limiting specific pathologies.

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Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

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