Tissue Barriers 2, e26713; 2013; © 2013 Landes Bioscience

Phosphatase regulation of intercellular junctions

Declan F McCole

Division of Biomedical Sciences; University of California, Riverside; Riverside, CA USA

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; DEP1, 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; PP1, 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-β1-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

Correspondence to: Declan F McCole; Email: declan.mccole@ucr.edu
Submitted: 08/25/13; Revised: 10/03/13; Accepted: 10/04/13
Citation: McCole DF. Phosphatase regulation of intercellular junctions. Tissue Barriers 2013; 1:e26713; http://dx.doi.org/10.4161/tisb.26713

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
RPTPμ	RACK1	Recruits RACK1 to cell-cell contacts; Links cell adhesion with intracellular signaling	179–182
	Cadherins	Dephosphorylates cadherins; stabilizes intercellular contacts	94, 165, 180
PTPσ	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

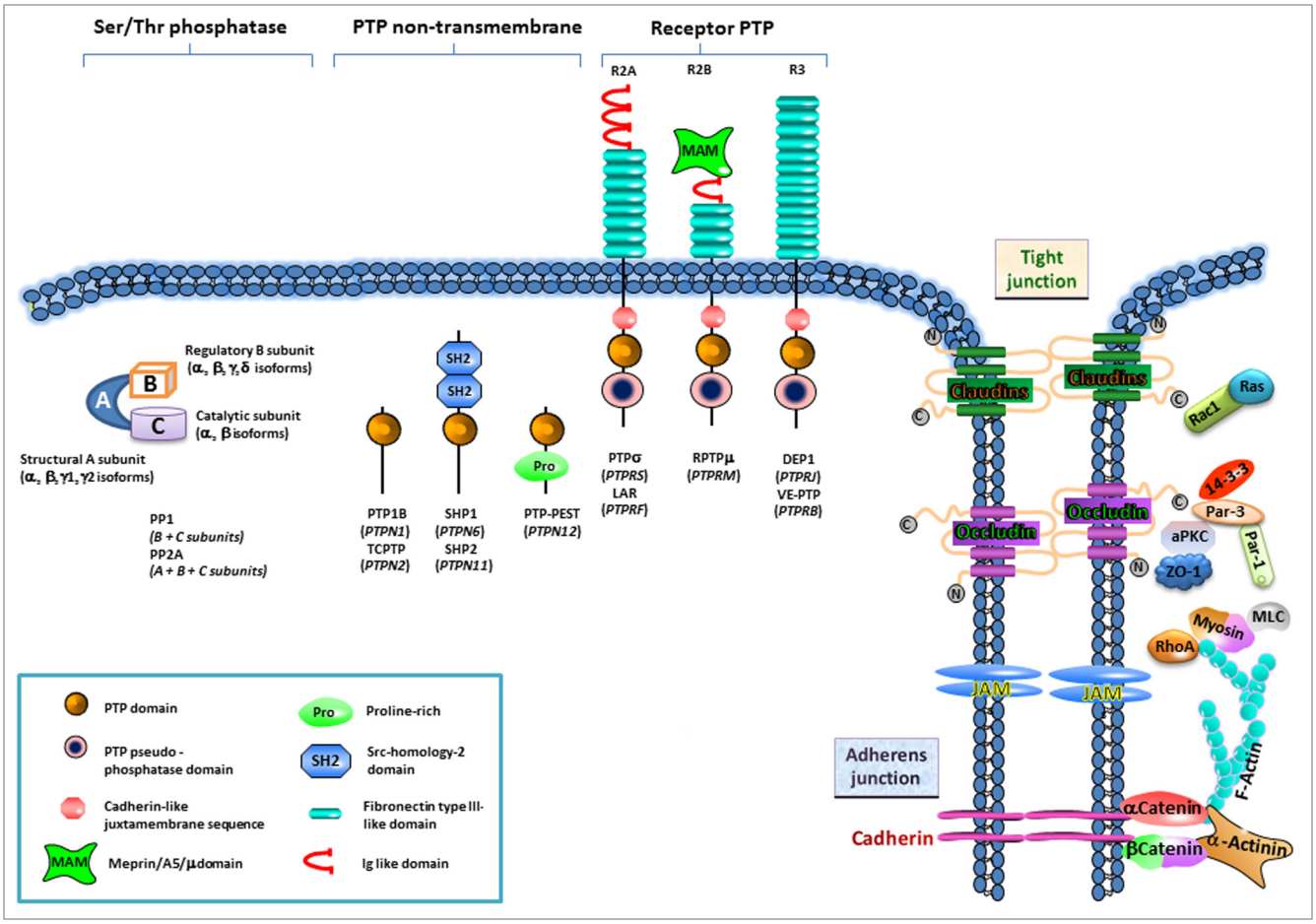

Figure 1. Phosphatases involved in regulation of tight and adherens junctions. 1. The major Ser/Thr phosphatases involved in regulation of junctional proteins are PP1 and PP2A. These are comprised of a catalytic subunit, one or more regulatory 'B' subunits, and in the case of PP2A, a structural 'A' subunit. 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 heterotrimers.[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, PP1α, PP1β/δ, PP1γ1, and PP1γ2, 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 PP1α 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] PP1α 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, PP1α regulates the binding of 14–3-3 proteins and PKC zeta to Par-3, while expression of catalytically inactive PP1α delays TJ formation, thus indicating a positive role for PP1α in TJ formation.[50] The authors concluded that Par-3 functions as a scaffold capable of coordinating both serine/threonine kinases and the PP1α 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-β1-inhibited, membrane-associated protein (TIMAP) member of the myosin phosphatase targeting (MYPT) proteins appears to target PP1cβ 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 Bα 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 Bα 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 Bα appeared to be specific as the B56γ 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-Bα antibodies to examine ABαC localization in human colon, and identified a pool of TJ-associated PP2A. However, this contrasted with MDCK

cells where the ABαC 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 phosporylation 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 PKCζ isoform that plays an important role in phosphorylating TJ proteins through its protein kinase activity.[64] PP2A colocalizes with PKCζ at the apical membrane of MDCK cells. Moreover, okadaic acid increases, but overexpression of the PP2A C subunit blocks, phosphorylation of PKCζ on a critical Thr410 residue during TJ assembly. As with PKCζ, PP2A also associates with and regulates the activity and distribution of another PKC isoform involved in TJ regulation, PKCλ.

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-Cα and PP1α, 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 Ca^{2+}- 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 H_2O_2-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 H_2O_2 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 β1-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, intravitreous 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 *PTPN1* 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 b-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 PTPβ, (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 RPTPμ.[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 PTPμ 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.

RPTPμ

Receptor protein tyrosine phosphatase mu (RPTPμ) 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] RPTPμ-mediated cell adhesion is calcium independent and does not require a functional intracellular catalytic domain.[179] RPTPμ 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, RPTPμ serves to link cell adhesion with intracellular signaling.[180] Interestingly, cell surface expression of RPTPμ increases in parallel with increased intercellular contacts, a consequence of increased cell density.[179] RPTPμ demonstrates a very cell density-dependent dynamic. In sparse in vitro cultures without intercellular contacts, RPTPμ is nonfunctional and its surface expression levels are low because of rapid internalization. In addition, a portion of RPTPμ molecules located on the cell surface shed their ectodomain into the medium. However, upon cell-cell contact, RPTPμ molecules on neighboring cells recognize and bind to each other in a homophilic manner, thus preventing RPTPμ from being internalized.[181] The membrane-proximal catalytic domain of RPTPμ has also been shown to interact with the scaffolding protein RACK1 (receptor for activated protein C kinase) and the association of endogenous RPTPμ 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 RPTPμ-dependent in these cells and its association with RACK1 is disrupted by the presence of constitutively active Src.[182] Therefore, RPTPμ recruits RACK1 to points of cell-cell contact, and this may play an important role in RPTPμ regulation of cell-cell adhesion.

RPTPμ 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 RPTPμ 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 RPTPμ near the cadherin–catenin complexes, maintaining them in a dephosphorylated state and thus stabilizing the intercellular contacts. Sui et al. showed that RPTPμ can bind directly to VE-cadherin and that overexpression of wild-type RPTPμ decreased tyrosine phosphorylation of VE-cadherin.[165] In immortalized human microvascular ECs, overexpression of wild-type RPTPμ itself resulted in enhanced barrier function. Therefore, RPTPμ is a critical regulator of both VE-cadherin phosphorylation status and endothelial barrier integrity.[165]

PTPσ

PTPsigma (PTPσ) belongs to the type IIa subfamily of RPTPs that include the phosphatases LAR, PTPσ, and PTPδ (**Fig. 1**).[35,187] The extracellular region of PTPσ 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] PTPσ 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 PTPσ show defects in neurological development.[187,189,191] A role for PTPσ 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 PTPσ, 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 PTPσ 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 PTPσ, possibly altering dimerization or ligand recognition.[192] Therefore, polymorphisms in the human *PTPRS* gene encoding PTPσ could result in altered PTPσ regulation of adherens junctions and thus contribute to the barrier function defects associated with the development of IBD. However, PTPσ regulation of epithelial integrity is not uniform in all organs. PTPσ 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.

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

Acknowledgments

This work was supported by the National Institute of Health grants DK091281 and AA019708 to DFM. Grateful thanks to Dr. Meera G Nair (UC Riverside) for helpful comments.

References

1. Arrieta MC, Bistritz L, Meddings JB. Alterations in intestinal permeability. Gut 2006; 55:1512-20; PMID:16966705; http://dx.doi.org/10.1136/gut.2005.085373
2. Abbott NJ, Friedman A. Overview and introduction: the blood-brain barrier in health and disease. Epilepsia 2012; 53(Suppl 6):1-6; PMID:23134489; http://dx.doi.org/10.1111/j.1528-1167.2012.03696.x
3. Turner JR. Intestinal mucosal barrier function in health and disease. Nat Rev Immunol 2009; 9:799-809; http://dx.doi.org/10.1038/nri2653; PMID:19855405
4. Shen L, Weber CR, Raleigh DR, Yu D, Turner JR. Tight junction pore and leak pathways: a dynamic duo. Annu Rev Physiol 2011; 73:283-309; http://dx.doi.org/10.1146/annurev-physiol-012110-142150; PMID:20936941
5. Furuse M, Hirase T, Itoh M, Nagafuchi A, Yonemura S, Tsukita S, Tsukita S. Occludin: a novel integral membrane protein localizing at tight junctions. J Cell Biol 1993; 123:1777-88; PMID:8276896; http://dx.doi.org/10.1083/jcb.123.6.1777
6. Saitou M, Ando-Akatsuka Y, Itoh M, Furuse M, Inazawa J, Fujimoto K, Tsukita S. Mammalian occludin in epithelial cells: its expression and subcellular distribution. Eur J Cell Biol 1997; 73:222-31; PMID:9243183
7. Mankertz J, Waller JS, Hillenbrand B, Tavalali S, Florian P, Schöneberg T, Fromm M, Schulzke JD. Gene expression of the tight junction protein occludin includes differential splicing and alternative promoter usage. Biochem Biophys Res Commun 2002; 298:657-66; PMID:12419305; http://dx.doi.org/10.1016/S0006-291X(02)02487-7
8. Sakakibara A, Furuse M, Saitou M, Ando-Akatsuka Y, Tsukita S. Possible involvement of phosphorylation of occludin in tight junction formation. J Cell Biol 1997; 137:1393-401; PMID:9182670; http://dx.doi.org/10.1083/jcb.137.6.1393
9. Balda MS, Flores-Maldonado C, Cereijido M, Matter K. Multiple domains of occludin are involved in the regulation of paracellular permeability. J Cell Biochem 2000; 78:85-96; PMID:10797568; http://dx.doi.org/10.1002/(SICI)1097-4644(20000701)78:1<85::AID-JCB8>3.0.CO;2-F
10. Saitou M, Furuse M, Sasaki H, Schulzke JD, Fromm M, Takano H, Noda T, Tsukita S. Complex phenotype of mice lacking occludin, a component of tight junction strands. Mol Biol Cell 2000; 11:4131-42; PMID:11102513; http://dx.doi.org/10.1091/mbc.11.12.4131
11. Schulzke JD, Gitter AH, Mankertz J, Spiegel S, Seidler U, Amasheh S, Saitou M, Tsukita S, Fromm M. Epithelial transport and barrier function in occludin-deficient mice. Biochim Biophys Acta 2005; 1669:34-42; PMID:15842997; http://dx.doi.org/10.1016/j.bbamem.2005.01.008
12. Furuse M, Fujita K, Hiiragi T, Fujimoto K, Tsukita S. Claudin-1 and -2: novel integral membrane proteins localizing at tight junctions with no sequence similarity to occludin. J Cell Biol 1998; 141:1539-50; PMID:9647647; http://dx.doi.org/10.1083/jcb.141.7.1539
13. Rüffer C, Gerke V. The C-terminal cytoplasmic tail of claudins 1 and 5 but not its PDZ-binding motif is required for apical localization at epithelial and endothelial tight junctions. Eur J Cell Biol 2004; 83:135-44; PMID:15260435; http://dx.doi.org/10.1078/0171-9335-00366
14. Gonçalves A, Ambrósio AF, Fernandes R. Regulation of claudins in blood-tissue barriers under physiological and pathological states. Tissue Barriers 2013; 1:e24782; http://dx.doi.org/10.4161/tisb.24782
15. Steed E, Balda MS, Matter K. Dynamics and functions of tight junctions. Trends Cell Biol 2010; 20:142-9; PMID:20061152; http://dx.doi.org/10.1016/j.tcb.2009.12.002
16. Anderson JM, Stevenson BR, Jesaitis LA, Goodenough DA, Mooseker MS. Characterization of ZO-1, a protein component of the tight junction from mouse liver and Madin-Darby canine kidney cells. J Cell Biol 1988; 106:1141-9; PMID:2452168; http://dx.doi.org/10.1083/jcb.106.4.1141
17. Fanning AS, Anderson JM. Zonula occludens-1 and -2 are cytosolic scaffolds that regulate the assembly of cellular junctions. Ann N Y Acad Sci 2009; 1165:113-20; http://dx.doi.org/10.1111/j.1749-6632.2009.04440.x; PMID:19538295
18. Gumbiner BM. Cell adhesion: the molecular basis of tissue architecture and morphogenesis. Cell 1996; 84:345-57; PMID:8608588; http://dx.doi.org/10.1016/S0092-8674(00)81279-9
19. Takeichi M. Morphogenetic roles of classic cadherins. Curr Opin Cell Biol 1995; 7:619-27; PMID:8573335; http://dx.doi.org/10.1016/0955-0674(95)80102-2
20. Gumbiner BM. Signal transduction of beta-catenin. Curr Opin Cell Biol 1995; 7:634-40; PMID:8573337; http://dx.doi.org/10.1016/0955-0674(95)80104-9
21. Nagafuchi A, Takeichi M. Cell binding function of E-cadherin is regulated by the cytoplasmic domain. EMBO J 1988; 7:3679-84; PMID:3061804
22. Ozawa M, Nuruki K, Toyoyama H, Ohi Y. Cloning of an alternative form of plakoglobin (gamma-catenin) lacking the fourth armadillo repeat. J Biochem 1995; 118:836-40; PMID:8576101
23. Volberg T, Geiger B, Dror R, Zick Y. Modulation of intercellular adherens-type junctions and tyrosine phosphorylation of their components in RSV-transformed cultured chick lens cells. Cell Regul 1991; 2:105-20; PMID:1650581
24. Birchmeier W, Behrens J. Cadherin expression in carcinomas: role in the formation of cell junctions and the prevention of invasiveness. Biochim Biophys Acta 1994; 1198:11-26; PMID:8199193
25. Brady-Kalnay SM, Rimm DL, Tonks NK. Receptor protein tyrosine phosphatase PTPmu associates with cadherins and catenins in vivo. J Cell Biol 1995; 130:977-86; PMID:7642713; http://dx.doi.org/10.1083/jcb.130.4.977
26. Goldstein B, Macara IG. The PAR proteins: fundamental players in animal cell polarization. Dev Cell 2007; 13:609-22; PMID:17981131; http://dx.doi.org/10.1016/j.devcel.2007.10.007
27. Ohno S. Intercellular junctions and cellular polarity: the PAR-aPKC complex, a conserved core cassette playing fundamental roles in cell polarity. Curr Opin Cell Biol 2001; 13:641-8; PMID:11544035; http://dx.doi.org/10.1016/S0955-0674(00)00264-7
28. Suzuki A, Hirata M, Kamimura K, Maniwa R, Yamanaka T, Mizuno K, Kishikawa M, Hirose H, Amano Y, Izumi N, et al. aPKC acts upstream of PAR-1b in both the establishment and maintenance of mammalian epithelial polarity. Curr Biol 2004; 14:1425-35; PMID:15324659; http://dx.doi.org/10.1016/j.cub.2004.08.021
29. Hurov JB, Watkins JL, Piwnica-Worms H. Atypical PKC phosphorylates PAR-1 kinases to regulate localization and activity. Curr Biol 2004; 14:736-41; PMID:15084291; http://dx.doi.org/10.1016/j.cub.2004.04.007
30. Saadat I, Higashi H, Obuse C, Umeda M, Murata-Kamiya N, Saito Y, Lu H, Ohnishi N, Azuma T, Suzuki A, et al. Helicobacter pylori CagA targets PAR1/MARK kinase to disrupt epithelial cell polarity. Nature 2007; 447:330-3; PMID:17507984; http://dx.doi.org/10.1038/nature05765
31. Benton R, St Johnston D. Drosophila PAR-1 and 14-3-3 inhibit Bazooka/PAR-3 to establish complementary cortical domains in polarized cells. Cell 2003; 115:691-704; PMID:14675534; http://dx.doi.org/10.1016/S0092-8674(03)00938-3
32. Nekrasova O, Green KJ. Desmosome assembly and dynamics. Trends Cell Biol 2013; PMID:23891292; http://dx.doi.org/10.1016/j.tcb.2013.06.004
33. Samarin S, Nusrat A. Regulation of epithelial apical junctional complex by Rho family GTPases. [Landmark Ed]. Front Biosci (Landmark Ed) 2009; 14:1129-42; PMID:19273120; http://dx.doi.org/10.2741/3298
34. Ivanov AI, Samarin SN, Bachar M, Parkos CA, Nusrat A. Protein kinase C activation disrupts epithelial apical junctions via ROCK-II dependent stimulation of actomyosin contractility. BMC Cell Biol 2009; 10:36; PMID:19422706; http://dx.doi.org/10.1186/1471-2121-10-36
35. Tonks NK. Protein tyrosine phosphatases: from genes, to function, to disease. Nat Rev Mol Cell Biol 2006; 7:833-46; PMID:17057753; http://dx.doi.org/10.1038/nrm2039
36. Dörfel MJ, Huber O. Modulation of tight junction structure and function by kinases and phosphatases targeting occludin. J Biomed Biotechnol 2012; 2012:807356; PMID:22315516; http://dx.doi.org/10.1155/2012/807356
37. Barford D. Molecular mechanisms of the protein serine/threonine phosphatases. Trends Biochem Sci 1996; 21:407-12; PMID:8987393; http://dx.doi.org/10.1016/S0968-0004(96)10060-8
38. Kobor MS, Archambault J, Lester W, Holstege FC, Gileadi O, Jansma DB, Jennings EG, Kouyoumdjian F, Davidson AR, Young RA, et al. An unusual eukaryotic protein phosphatase required for transcription by RNA polymerase II and CTD dephosphorylation in S. cerevisiae. Mol Cell 1999; 4:55-62; PMID:10445027; http://dx.doi.org/10.1016/S1097-2765(00)80187-2
39. Cohen PT. Protein phosphatase 1--targeted in many directions. J Cell Sci 2002; 115:241-56; PMID:11839776
40. Alonso A, Sasin J, Bottini N, Friedberg I, Friedberg I, Osterman A, Godzik A, Hunter T, Dixon J, Mustelin T. Protein tyrosine phosphatases in the human genome. Cell 2004; 117:699-711; PMID:15186772; http://dx.doi.org/10.1016/j.cell.2004.05.018

41. Seshacharyulu P, Pandey P, Datta K, Batra SK. Phosphatase: PP2A structural importance, regulation and its aberrant expression in cancer. Cancer Lett 2013; 335:9-18; http://dx.doi.org/10.1016/j.canlet.2013.02.036; PMID:23454242
42. Moorhead GB, De Wever V, Templeton G, Kerk D. Evolution of protein phosphatases in plants and animals. Biochem J 2009; 417:401-9; PMID:19099538; http://dx.doi.org/10.1042/BJ20081986
43. Brautigan DL. Protein Ser/Thr phosphatases--the ugly ducklings of cell signalling. FEBS J 2013; 280:324-45; PMID:22519956; http://dx.doi.org/10.1111/j.1742-4658.2012.08609.x
44. Peti W, Nairn AC, Page R. Structural basis for protein phosphatase 1 regulation and specificity. FEBS J 2013; 280:596-611; PMID:22284538; http://dx.doi.org/10.1111/j.1742-4658.2012.08509.x
45. Shima H, Hatano Y, Chun YS, Sugimura T, Zhang Z, Lee EY, Nagao M. Identification of PP1 catalytic subunit isotypes PP1 gamma 1, PP1 delta and PP1 alpha in various rat tissues. Biochem Biophys Res Commun 1993; 192:1289-96; PMID:7685164; http://dx.doi.org/10.1006/bbrc.1993.1556
46. da Cruz e Silva EF, Fox CA, Ouimet CC, Gustafson E, Watson SJ, Greengard P. Differential expression of protein phosphatase 1 isoforms in mammalian brain. J Neurosci 1995; 15:3375-89; PMID:7751917
47. Barford D, Das AK, Egloff MP. The structure and mechanism of protein phosphatases: insights into catalysis and regulation. Annu Rev Biophys Biomol Struct 1998; 27:133-64; PMID:9646865; http://dx.doi.org/10.1146/annurev.biophys.27.1.133
48. Cohen PT. The structure and regulation of protein phosphatases. Annu Rev Biochem 1989; 58:453-508; PMID:2549856; http://dx.doi.org/10.1146/annurev.bi.58.070189.002321
49. Seth A, Sheth P, Elias BC, Rao R. Protein phosphatases 2A and 1 interact with occludin and negatively regulate the assembly of tight junctions in the CACO-2 cell monolayer. J Biol Chem 2007; 282:11487-98; PMID:17298946; http://dx.doi.org/10.1074/jbc.M610597200
50. Traweger A, Wiggin G, Taylor L, Tate SA, Metalnikov P, Pawson T. Protein phosphatase 1 regulates the phosphorylation state of the polarity scaffold Par-3. Proc Natl Acad Sci U S A 2008; 105:10402-7; PMID:18641122; http://dx.doi.org/10.1073/pnas.0804102105
51. Schumann M, Günzel D, Buergel N, Richter JF, Troeger H, May C, Fromm A, Sorgenfrei D, Daum S, Bojarski C, et al. Cell polarity-determining proteins Par-3 and PP-1 are involved in epithelial tight junction defects in coeliac disease. Gut 2012; 61:220-8; http://dx.doi.org/10.1136/gutjnl-2011-300123; PMID:21865402
52. Csortos C, Czikora I, Bogatcheva NV, Adyshev DM, Poirier C, Olah G, Verin AD. TIMAP is a positive regulator of pulmonary endothelial barrier function. Am J Physiol Lung Cell Mol Physiol 2008; 295:L440-50; PMID:18586956; http://dx.doi.org/10.1152/ajplung.00325.2007
53. Verin AD, Patterson CE, Day MA, Garcia JG. Regulation of endothelial cell gap formation and barrier function by myosin-associated phosphatase activities. Am J Physiol 1995; 269:L99-108; PMID:7631821
54. Essler M, Hermann K, Amano M, Kaibuchi K, Heesemann J, Weber PC, Aepfelbacher M. Pasteurella multocida toxin increases endothelial permeability via Rho kinase and myosin light chain phosphatase. J Immunol 1998; 161:5640-6; PMID:9820544
55. Tung HY, Alemany S, Cohen P. The protein phosphatases involved in cellular regulation. 2. Purification, subunit structure and properties of protein phosphatases-2A0, 2A1, and 2A2 from rabbit skeletal muscle. Eur J Biochem 1985; 148:253-63; PMID:2985385; http://dx.doi.org/10.1111/j.1432-1033.1985.tb08833.x
56. Ronne H, Carlberg M, Hu GZ, Nehlin JO. Protein phosphatase 2A in Saccharomyces cerevisiae: effects on cell growth and bud morphogenesis. Mol Cell Biol 1991; 11:4876-84; PMID:1656215
57. Schönthal AH. Role of serine/threonine protein phosphatase 2A in cancer. Cancer Lett 2001; 170:1-13; PMID:11448528; http://dx.doi.org/10.1016/S0304-3835(01)00561-4
58. Cohen PT. Novel protein serine/threonine phosphatases: variety is the spice of life. Trends Biochem Sci 1997; 22:245-51; PMID:9255065; http://dx.doi.org/10.1016/S0968-0004(97)01060-8
59. Mayer-Jaekel RE, Hemmings BA. Protein phosphatase 2A--a ménage à trois. Trends Cell Biol 1994; 4:287-91; PMID:14731592; http://dx.doi.org/10.1016/0962-8924(94)90219-4
60. Kamibayashi C, Estes R, Lickteig RL, Yang SI, Craft C, Mumby MC. Comparison of heterotrimeric protein phosphatase 2A containing different B subunits. J Biol Chem 1994; 269:20139-48; PMID:8051102
61. Sontag E. Protein phosphatase 2A: the Trojan Horse of cellular signaling. Cell Signal 2001; 13:7-16; PMID:11257442; http://dx.doi.org/10.1016/S0898-6568(00)00123-6
62. Sim AT, Scott JD. Targeting of PKA, PKC and protein phosphatases to cellular microdomains. Cell Calcium 1999; 26:209-17; PMID:10643559; http://dx.doi.org/10.1054/ceca.1999.0072
63. Nunbhakdi-Craig V, Machleidt T, Ogris E, Bellotto D, White CL 3rd, Sontag E. Protein phosphatase 2A associates with and regulates atypical PKC and the epithelial tight junction complex. J Cell Biol 2002; 158:967-78; PMID:12196510; http://dx.doi.org/10.1083/jcb.200206114
64. Suzuki A, Yamanaka T, Hirose T, Manabe N, Mizuno K, Shimizu M, Akimoto K, Izumi Y, Ohnishi T, Ohno S. Atypical protein kinase C is involved in the evolutionarily conserved par protein complex and plays a critical role in establishing epithelia-specific junctional structures. J Cell Biol 2001; 152:1183-96; PMID:11257119; http://dx.doi.org/10.1083/jcb.152.6.1183
65. Farshori P, Kachar B. Redistribution and phosphorylation of occludin during opening and resealing of tight junctions in cultured epithelial cells. J Membr Biol 1999; 170:147-56; PMID:10430658; http://dx.doi.org/10.1007/s002329900544
66. Simonovic I, Rosenberg J, Koutsouris A, Hecht G. Enteropathogenic Escherichia coli dephosphorylates and dissociates occludin from intestinal epithelial tight junctions. Cell Microbiol 2000; 2:305-15; PMID:11207587; http://dx.doi.org/10.1046/j.1462-5822.2000.00055.x
67. Sheth P, Samak G, Shull JA, Seth A, Rao R. Protein phosphatase 2A plays a role in hydrogen peroxide-induced disruption of tight junctions in Caco-2 cell monolayers. Biochem J 2009; 421:59-70; PMID:19356149; http://dx.doi.org/10.1042/BJ20081951
68. Basuroy S, Seth A, Elias B, Naren AP, Rao R. MAPK interacts with occludin and mediates EGF-induced prevention of tight junction disruption by hydrogen peroxide. Biochem J 2006; 393:69-77; PMID:16134968; http://dx.doi.org/10.1042/BJ20050959
69. Aggarwal S, Suzuki T, Taylor WL, Bhargava A, Rao RK. Contrasting effects of ERK on tight junction integrity in differentiated and under-differentiated Caco-2 cell monolayers. Biochem J 2011; 433:51-63; PMID:20961289; http://dx.doi.org/10.1042/BJ20100249
70. Yamaya M, Sekizawa K, Masuda T, Morikawa M, Sawai T, Sasaki H. Oxidants affect permeability and repair of the cultured human tracheal epithelium. Am J Physiol 1995; 268:L284-93; PMID:7864148
71. Banan A, Fields JZ, Farhadi A, Talmage DA, Zhang L, Keshavarzian A. Activation of delta-isoform of protein kinase C is required for oxidant-induced disruption of both the microtubule cytoskeleton and permeability barrier of intestinal epithelia. J Pharmacol Exp Ther 2002; 303:17-28; PMID:12235228; http://dx.doi.org/10.1124/jpet.102.037218
72. Banan A, Zhang LJ, Farhadi A, Fields JZ, Shaikh M, Forsyth CB, Choudhary S, Keshavarzian A. Critical role of the atypical lambda isoform of protein kinase C (PKC-lambda) in oxidant-induced disruption of the microtubule cytoskeleton and barrier function of intestinal epithelium. J Pharmacol Exp Ther 2005; 312:458-71; PMID:15347733; http://dx.doi.org/10.1124/jpet.104.074591
73. Wu F, Wilson JX. Peroxynitrite-dependent activation of protein phosphatase type 2A mediates microvascular endothelial barrier dysfunction. Cardiovasc Res 2009; 81:38-45; http://dx.doi.org/10.1093/cvr/cvn246; PMID:18791203
74. Dunagan M, Chaudhry K, Samak G, Rao RK. Acetaldehyde disrupts tight junctions in Caco-2 cell monolayers by a protein phosphatase 2A-dependent mechanism. Am J Physiol Gastrointest Liver Physiol 2012; 303:G1356-64; PMID:23064762; http://dx.doi.org/10.1152/ajpgi.00526.2011
75. Caraballo JC, Yshii C, Butti ML, Westphal W, Borcherding JA, Allamargot C, Comellas AP. Hypoxia increases transepithelial electrical conductance and reduces occludin at the plasma membrane in alveolar epithelial cells via PKC-ζ and PP2A pathway. Am J Physiol Lung Cell Mol Physiol 2011; 300:L569-78; PMID:21257729; http://dx.doi.org/10.1152/ajplung.00109.2010
76. Nita-Lazar M, Rebustini I, Walker J, Kukuruzinska MA. Hypoglycosylated E-cadherin promotes the assembly of tight junctions through the recruitment of PP2A to adherens junctions. Exp Cell Res 2010; 316:1871-84; PMID:20156436; http://dx.doi.org/10.1016/j.yexcr.2010.02.008
77. Young MR, Liu SW, Meisinger J. Protein phosphatase-2A restricts migration of Lewis lung carcinoma cells by modulating the phosphorylation of focal adhesion proteins. Int J Cancer 2003; 103:38-44; PMID:12455051; http://dx.doi.org/10.1002/ijc.10772
78. Young MR, Kolesiak K, Meisinger J. Protein phosphatase-2A regulates endothelial cell motility and both the phosphorylation and the stability of focal adhesion complexes. Int J Cancer 2002; 100:276-82; PMID:12115541; http://dx.doi.org/10.1002/ijc.10491
79. Tar K, Birukova AA, Csortos C, Bakó E, Garcia JG, Verin AD. Phosphatase 2A is involved in endothelial cell microtubule remodeling and barrier regulation. J Cell Biochem 2004; 92:534-46; PMID:15156565; http://dx.doi.org/10.1002/jcb.20036
80. Serini G, Valdembri D, Zanivan S, Morterra G, Burkhardt C, Caccavari F, Zammataro L, Primo L, Tamagnone L, Logan M, et al. Class 3 semaphorins control vascular morphogenesis by inhibiting integrin function. Nature 2003; 424:391-7; PMID:12879061; http://dx.doi.org/10.1038/nature01784
81. Le Guelte A, Galan-Moya EM, Dwyer J, Treps L, Kettler G, Hebda JK, Dubois S, Auffray C, Chneiweiss H, Bidere N, et al. Semaphorin 3A elevates endothelial cell permeability through PP2A inactivation. J Cell Sci 2012; 125:4137-46; PMID:22685328; http://dx.doi.org/10.1242/jcs.108282
82. García C, Aranda J, Arnold E, Thébault S, Macotela Y, López-Casillas F, Mendoza V, Quiroz-Mercado H, Hernández-Montiel HL, Lin SH, et al. Vasoinhibins prevent retinal vasopermeability associated with diabetic retinopathy in rats via protein phosphatase 2A-dependent eNOS inactivation. J Clin Invest 2008; 118:2291-300; PMID:18497878

83. Volberg T, Zick Y, Dror R, Sabanay I, Gilon C, Levitzki A, Geiger B. The effect of tyrosine-specific protein phosphorylation on the assembly of adherens-type junctions. EMBO J 1992; 11:1733-42; PMID:1316270

84. de la Fuente-García MA, Nicolás JM, Freed JH, Palou E, Thomas AP, Vilella R, Vives J, Gayá A. CD148 is a membrane protein tyrosine phosphatase present in all hematopoietic lineages and is involved in signal transduction on lymphocytes. Blood 1998; 91:2800-9; PMID:9531590

85. Matozaki T, Murata Y, Mori M, Kotani T, Okazawa H, Ohnishi H. Expression, localization, and biological function of the R3 subtype of receptor-type protein tyrosine phosphatases in mammals. Cell Signal 2010; 22:1811-7; PMID:20633639; http://dx.doi.org/10.1016/j.cellsig.2010.07.001

86. Neel BG, Gu H, Pao L. The 'Shp'ing news: SH2 domain-containing tyrosine phosphatases in cell signaling. Trends Biochem Sci 2003; 28:284-93; PMID:12826400; http://dx.doi.org/10.1016/S0968-0004(03)00091-4

87. Feng GS. Shp-2 tyrosine phosphatase: signaling one cell or many. Exp Cell Res 1999; 253:47-54; PMID:10579910; http://dx.doi.org/10.1006/excr.1999.4668

88. Chan G, Kalaitzidis D, Neel BG. The tyrosine phosphatase Shp2 (PTPN11) in cancer. Cancer Metastasis Rev 2008; 27:179-92; PMID:18286234; http://dx.doi.org/10.1007/s10555-008-9126-y

89. Tonks NK, Neel BG. Combinatorial control of the specificity of protein tyrosine phosphatases. Curr Opin Cell Biol 2001; 13:182-95; PMID:11248552; http://dx.doi.org/10.1016/S0955-0674(00)00196-4

90. Van Vactor D, O'Reilly AM, Neel BG. Genetic analysis of protein tyrosine phosphatases. Curr Opin Genet Dev 1998; 8:112-26; PMID:9529614; http://dx.doi.org/10.1016/S0959-437X(98)80070-1

91. Araki T, Nawa H, Neel BG. Tyrosyl phosphorylation of Shp2 is required for normal ERK activation in response to some, but not all, growth factors. J Biol Chem 2003; 278:41677-84; PMID:12923167; http://dx.doi.org/10.1074/jbc.M306461200

92. Hof P, Pluskey S, Dhe-Paganon S, Eck MJ, Shoelson SE. Crystal structure of the tyrosine phosphatase SHP-2. Cell 1998; 92:441-50; PMID:9491886; http://dx.doi.org/10.1016/S0092-8674(00)80938-1

93. Barford D, Neel BG. Revealing mechanisms for SH2 domain mediated regulation of the protein tyrosine phosphatase SHP-2. Structure 1998; 6:249-54; PMID:9551546; http://dx.doi.org/10.1016/S0969-2126(98)00027-6

94. Brady-Kalnay SM, Mourton T, Nixon JP, Pietz GE, Kinch M, Chen H, Brackenbury R, Rimm DL, Del Vecchio RL, Tonks NK. Dynamic interaction of PTPmu with multiple cadherins in vivo. J Cell Biol 1998; 141:287-96; PMID:9531566; http://dx.doi.org/10.1083/jcb.141.1.287

95. Ukropec JA, Hollinger MK, Salva SM, Woolkalis MJ. SHP2 association with VE-cadherin complexes in human endothelial cells is regulated by thrombin. J Biol Chem 2000; 275:5983-6; PMID:10681592; http://dx.doi.org/10.1074/jbc.275.8.5983

96. Tsukatani Y, Suzuki K, Takahashi K. Loss of density-dependent growth inhibition and dissociation of alpha-catenin from E-cadherin. J Cell Physiol 1997; 173:54-63; PMID:9326449; http://dx.doi.org/10.1002/(SICI)1097-4652(199710)173:1<54::AID-JCP7>3.0.CO;2-I

97. Ozawa M, Kemler R. Altered cell adhesion activity by pervanadate due to the dissociation of alpha-catenin from the E-cadherin.catenin complex. J Biol Chem 1998; 273:6166-70; PMID:9497337; http://dx.doi.org/10.1074/jbc.273.11.6166

98. Timmerman I, Hoogenboezem M, Bennett AM, Geerts D, Hordijk PL, van Buul JD. The tyrosine phosphatase SHP2 regulates recovery of endothelial adherens junctions through control of β-catenin phosphorylation. Mol Biol Cell 2012; 23:4212-25; PMID:22956765; http://dx.doi.org/10.1091/mbc.E12-01-0038

99. Hatanaka K, Lanahan AA, Murakami M, Simons M. Fibroblast growth factor signaling potentiates VE-cadherin stability at adherens junctions by regulating SHP2. PLoS One 2012; 7:e37600; PMID:22629427; http://dx.doi.org/10.1371/journal.pone.0037600

100. Grinnell KL, Casserly B, Harrington EO. Role of protein tyrosine phosphatase SHP2 in barrier function of pulmonary endothelium. Am J Physiol Lung Cell Mol Physiol 2010; 298:L361-70; PMID:20023173; http://dx.doi.org/10.1152/ajplung.00374.2009

101. Adamson RH, Curry FE, Adamson G, Liu B, Jiang Y, Aktories K, Barth H, Daigeler A, Golenhofen N, Ness W, et al. Rho and rho kinase modulation of barrier properties: cultured endothelial cells and intact microvessels of rats and mice. J Physiol 2002; 539:295-308; PMID:11850521; http://dx.doi.org/10.1113/jphysiol.2001.013117

102. Arthur WT, Burridge K. RhoA inactivation by p190RhoGAP regulates cell spreading and migration by promoting membrane protrusion and polarity. Mol Biol Cell 2001; 12:2711-20; PMID:11553710; http://dx.doi.org/10.1091/mbc.12.9.2711

103. Holinstat M, Knezevic N, Broman M, Samarel AM, Malik AB, Mehta D. Suppression of RhoA activity by focal adhesion kinase-induced activation of p190RhoGAP: role in regulation of endothelial permeability. J Biol Chem 2006; 281:2296-305; PMID:16308318; http://dx.doi.org/10.1074/jbc.M511248200

104. Puri P, Walker WH. The tyrosine phosphatase SHP2 regulates Sertoli cell junction complexes. Biol Reprod 2013; 88:59; PMID:23325809; http://dx.doi.org/10.1095/biolreprod.112.104414

105. Segal ED, Cha J, Lo J, Falkow S, Tompkins LS. Altered states: involvement of phosphorylated CagA in the induction of host cellular growth changes by *Helicobacter pylori*. Proc Natl Acad Sci U S A 1999; 96:14559-64; PMID:10588744; http://dx.doi.org/10.1073/pnas.96.25.14559

106. Higashi H, Tsutsumi R, Muto S, Sugiyama T, Azuma T, Asaka M, Hatakeyama M. SHP-2 tyrosine phosphatase as an intracellular target of Helicobacter pylori Cag. Protein Sci 2002; 295:683-6

107. Higashi H, Tsutsumi R, Fujita A, Yamazaki S, Asaka M, Azuma T, Hatakeyama M. Biological activity of the Helicobacter pylori virulence factor CagA is determined by variation in the tyrosine phosphorylation sites. Proc Natl Acad Sci U S A 2002; 99:14428-33; PMID:12391297; http://dx.doi.org/10.1073/pnas.222375399

108. Tonks NK, Diltz CD, Fischer EH. Purification of the major protein-tyrosine-phosphatases of human placenta. J Biol Chem 1988; 263:6722-30; PMID:2834386

109. Tonks NK, Diltz CD, Fischer EH. Characterization of the major protein-tyrosine-phosphatases of human placenta. J Biol Chem 1988; 263:6731-7; PMID:2834387

110. Guan KL, Haun RS, Watson SJ, Geahlen RL, Dixon JE. Cloning and expression of a protein-tyrosine-phosphatase. Proc Natl Acad Sci U S A 1990; 87:1501-5; PMID:2154749; http://dx.doi.org/10.1073/pnas.87.4.1501

111. Frangioni JV, Beahm PH, Shifrin V, Jost CA, Neel BG. The nontransmembrane tyrosine phosphatase PTP-1B localizes to the endoplasmic reticulum via its 35 amino acid C-terminal sequence. Cell 1992; 68:545-60; PMID:1739967; http://dx.doi.org/10.1016/0092-8674(92)90190-N

112. Woodford-Thomas TA, Rhodes JD, Dixon JE. Expression of a protein tyrosine phosphatase in normal and v-src-transformed mouse 3T3 fibroblasts. J Cell Biol 1992; 117:401-14; PMID:1373143; http://dx.doi.org/10.1083/jcb.117.2.401

113. Elchebly M, Payette P, Michaliszyn E, Cromlish W, Collins S, Loy AL, Normandin D, Cheng A, Himms-Hagen J, Chan CC, et al. Increased insulin sensitivity and obesity resistance in mice lacking the protein tyrosine phosphatase-1B gene. Science 1999; 283:1544-8; PMID:10066179; http://dx.doi.org/10.1126/science.283.5407.1544

114. Elchebly M, Cheng A, Tremblay ML. Modulation of insulin signaling by protein tyrosine phosphatases. J Mol Med (Berl) 2000; 78:473-82; PMID:11140373; http://dx.doi.org/10.1007/s001090000141

115. Zabolotny JM, Bence-Hanulec KK, Stricker-Krongrad A, Haj F, Wang Y, Minokoshi Y, Kim YB, Elmquist JK, Tartaglia LA, Kahn BB, et al. PTP1B regulates leptin signal transduction in vivo. Dev Cell 2002; 2:489-95; PMID:11970898; http://dx.doi.org/10.1016/S1534-5807(02)00148-X

116. Bourdeau A, Dubé N, Tremblay ML. Cytoplasmic protein tyrosine phosphatases, regulation and function: the roles of PTP1B and TC-PTP. Curr Opin Cell Biol 2005; 17:203-9; PMID:15780598; http://dx.doi.org/10.1016/j.ceb.2005.02.001

117. Liu F, Chernoff J. Protein tyrosine phosphatase 1B interacts with and is tyrosine phosphorylated by the epidermal growth factor receptor. Biochem J 1997; 327:139-45; PMID:9355745

118. Haj FG, Markova B, Klaman LD, Bohmer FD, Neel BG. Regulation of receptor tyrosine kinase signaling by protein tyrosine phosphatase-1B. J Biol Chem 2003; 278:739-44; PMID:12424235; http://dx.doi.org/10.1074/jbc.M210194200

119. McCole DF, Truong A, Bunz M, Barrett KE. Consequences of direct versus indirect activation of epidermal growth factor receptor in intestinal epithelial cells are dictated by protein-tyrosine phosphatase 1B. J Biol Chem 2007; 282:13303-15; PMID:17339316; http://dx.doi.org/10.1074/jbc.M700424200

120. Balsamo J, Leung T, Ernst H, Zanin MK, Hoffman S, Lilien J. Regulated binding of PTP1B-like phosphatase to N-cadherin: control of cadherin-mediated adhesion by dephosphorylation of beta-catenin. J Cell Biol 1996; 134:801-13; PMID:8707857; http://dx.doi.org/10.1083/jcb.134.3.801

121. Sheth P, Seth A, Atkinson KJ, Gheyi T, Kale G, Giorgianni F, Desiderio DM, Li C, Naren A, Rao R. Acetaldehyde dissociates the PTP1B-E-cadherin-beta-catenin complex in Caco-2 cell monolayers by a phosphorylation-dependent mechanism. Biochem J 2007; 402:291-300; PMID:17087658; http://dx.doi.org/10.1042/BJ20060665

122. Nakamura Y, Patrushev N, Inomata H, Mehta D, Urao N, Kim HW, Razvi M, Kini V, Mahadev K, Goldstein BJ, et al. Role of protein tyrosine phosphatase 1B in vascular endothelial growth factor signaling and cell-cell adhesions in endothelial cells. Circ Res 2008; 102:1182-91; PMID:18451337; http://dx.doi.org/10.1161/CIRCRESAHA.107.167080

123. Grinnell KL, Chichger H, Braza J, Duong H, Harrington EO. Protection against LPS-induced pulmonary edema through the attenuation of protein tyrosine phosphatase-1B oxidation. Am J Respir Cell Mol Biol 2012; 46:623-32; PMID:22180868; http://dx.doi.org/10.1165/rcmb.2011-0271OC

124. Winter MC, Shasby S, Shasby DM. Compromised E-cadherin adhesion and epithelial barrier function with activation of G protein-coupled receptors is rescued by Y-to-F mutations in beta-catenin. Am J Physiol Lung Cell Mol Physiol 2008; 294:L442-8; PMID:18083766; http://dx.doi.org/10.1152/ajplung.00404.2007

125. Sachs N, Sonnenberg A. Cell-matrix adhesion of podocytes in physiology and disease. Nat Rev Nephrol 2013; 9:200-10; PMID:23338211; http://dx.doi.org/10.1038/nrneph.2012.291
126. Aoudjit L, Jiang R, Lee TH, New LA, Jones N, Takano T. Podocyte Protein, Nephrin, Is a Substrate of Protein Tyrosine Phosphatase 1B. J Signal Transduct 2011; 2011:376543. doi: 10.1155/2011/376543.
127. Cool DE, Tonks NK, Charbonneau H, Walsh KA, Fischer EH, Krebs EG. cDNA isolated from a human T-cell library encodes a member of the protein-tyrosine-phosphatase family. Proc Natl Acad Sci U S A 1989; 86:5257-61; PMID:2546150; http://dx.doi.org/10.1073/pnas.86.14.5257
128. Tiganis T, Bennett AM. Protein tyrosine phosphatase function: the substrate perspective. Biochem J 2007; 402:1-15; PMID:17238862; http://dx.doi.org/10.1042/BJ20061548
129. Galic S, Hauser C, Kahn BB, Haj FG, Neel BG, Tonks NK, Tiganis T. Coordinated regulation of insulin signaling by the protein tyrosine phosphatases PTP1B and TCPTP. Mol Cell Biol 2005; 25:819-29; PMID:15632081; http://dx.doi.org/10.1128/MCB.25.2.819-829.2005
130. Bettaieb A, Liu S, Xi Y, Nagata N, Matsuo K, Matsuo I, Chahed S, Bakke J, Keilhack H, Tiganis T, et al. Differential regulation of endoplasmic reticulum stress by protein tyrosine phosphatase 1B and T cell protein tyrosine phosphatase. J Biol Chem 2011; 286:9225-35; http://dx.doi.org/10.1074/jbc.M110.186148; PMID:21216966
131. Tiganis T. PTP1B and TCPTP--nonredundant phosphatases in insulin signaling and glucose homeostasis. FEBS J 2013; 280:445-58; http://dx.doi.org/10.1111/j.1742-4658.2012.08563.x; PMID:22404968
132. Lorenzen JA, Dadabay CY, Fischer EH. COOH-terminal sequence motifs target the T cell protein tyrosine phosphatase to the ER and nucleus. J Cell Biol 1995; 131:631-43; PMID:7593185; http://dx.doi.org/10.1083/jcb.131.3.631
133. Ibarra-Sánchez MJ, Simoncic PD, Nestel FR, Duplay P, Lapp WS, Tremblay ML. The T-cell protein tyrosine phosphatase. Semin Immunol 2000; 12:379-86; PMID:10995584; http://dx.doi.org/10.1006/smim.2000.0220
134. Lam MH, Michell BJ, Fodero-Tavoletti MT, Kemp BE, Tonks NK, Tiganis T. Cellular stress regulates the nucleocytoplasmic distribution of the protein-tyrosine phosphatase TCPTP. J Biol Chem 2001; 276:37700-7; PMID:11479308; http://dx.doi.org/10.1074/jbc.M105128200
135. Tiganis T, Bennett AM, Ravichandran KS, Tonks NK. Epidermal growth factor receptor and the adaptor protein p52Shc are specific substrates of T-cell protein tyrosine phosphatase. Mol Cell Biol 1998; 18:1622-34; PMID:9488479
136. Mattila E, Pellinen T, Nevo J, Vuoriluoto K, Arjonen A, Ivaska J. Negative regulation of EGFR signalling through integrin-alpha1beta1-mediated activation of protein tyrosine phosphatase TCPTP. Nat Cell Biol 2005; 7:78-85; PMID:15592458; http://dx.doi.org/10.1038/ncb1209
137. van Vliet C, Bukczynska PE, Puryer MA, Sadek CM, Shields BJ, Tremblay ML, Tiganis T. Selective regulation of tumor necrosis factor-induced Erk signaling by Src family kinases and the T cell protein tyrosine phosphatase. Nat Immunol 2005; 6:253-60; PMID:15696169; http://dx.doi.org/10.1038/ni1169
138. Simoncic PD, Lee-Loy A, Barber DL, Tremblay ML, McGlade CJ. The T cell protein tyrosine phosphatase is a negative regulator of janus family kinases 1 and 3. Curr Biol 2002; 12:446-53; PMID:11909529; http://dx.doi.org/10.1016/S0960-9822(02)00697-8
139. ten Hoeve J, de Jesus Ibarra-Sanchez M, Fu Y, Zhu W, Tremblay M, David M, Shuai K. Identification of a nuclear Stat1 protein tyrosine phosphatase. Mol Cell Biol 2002; 22:5662-8; PMID:12138178; http://dx.doi.org/10.1128/MCB.22.16.5662-5668.2002
140. You-Ten KE, Muise ES, Itié A, Michaliszyn E, Wagner J, Jothy S, Lapp WS, Tremblay ML. Impaired bone marrow microenvironment and immune function in T cell protein tyrosine phosphatase-deficient mice. J Exp Med 1997; 186:683-93; PMID:9271584; http://dx.doi.org/10.1084/jem.186.5.683
141. Heinonen KM, Nestel FP, Newell EW, Charette G, Seemayer TA, Tremblay ML, Lapp WS. T-cell protein tyrosine phosphatase deletion results in progressive systemic inflammatory disease. Blood 2004; 103:3457-64; PMID:14726372; http://dx.doi.org/10.1182/blood-2003-09-3153
142. Wiede F, Chew SH, van Vliet C, Poulton IJ, Kyparissoudis K, Sasmono T, Loh K, Tremblay ML, Godfrey DI, Sims NA, et al. Strain-dependent differences in bone development, myeloid hyperplasia, morbidity and mortality in ptpn2-deficient mice. PLoS One 2012; 7:e36703; http://dx.doi.org/10.1371/journal.pone.0036703; PMID:22590589
143. Hassan SW, Doody KM, Hardy S, Uetani N, Cournoyer D, Tremblay ML. Increased susceptibility to dextran sulfate sodium induced colitis in the T cell protein tyrosine phosphatase heterozygous mouse. PLoS One 2010; 5:e8868; PMID:20111595; http://dx.doi.org/10.1371/journal.pone.0008868
144. Anderson CA, Boucher G, Lees CW, Franke A, D'Amato M, Taylor KD, Lee JC, Goyette P, Imielinski M, Latiano A, et al. Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. Nat Genet 2011; 43:246-52; http://dx.doi.org/10.1038/ng.764; PMID:21297633
145. Todd JA, Walker NM, Cooper JD, Smyth DJ, Downes K, Plagnol V, Bailey R, Nejentsev S, Field SF, Payne F, et al.; Genetics of Type 1 Diabetes in Finland; Wellcome Trust Case Control Consortium. Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes. Nat Genet 2007; 39:857-64; PMID:17554260; http://dx.doi.org/10.1038/ng2068
146. Smyth DJ, Plagnol V, Walker NM, Cooper JD, Downes K, Yang JH, Howson JM, Stevens H, McManus R, Wijmenga C, et al. Shared and distinct genetic variants in type 1 diabetes and celiac disease. N Engl J Med 2008; 359:2767-77; PMID:19073967; http://dx.doi.org/10.1056/NEJMoa0807917
147. Scharl M, Paul G, Weber A, Jung BC, Docherty MJ, Hausmann M, Rogler G, Barrett KE, McCole DF. Protection of epithelial barrier function by the Crohn's disease associated gene protein tyrosine phosphatase n2. Gastroenterology 2009; 137:2030-40, e5; PMID:19818778; http://dx.doi.org/10.1053/j.gastro.2009.07.078
148. Scharl M, McCole DF, Weber A, Vavricka SR, Frei P, Kellermeier S, Pesch T, Fried M, Rogler G. Protein tyrosine phosphatase N2 regulates TNFα-induced signalling and cytokine secretion in human intestinal epithelial cells. Gut 2011; 60:189-97; PMID:21115548; http://dx.doi.org/10.1136/gut.2010.216606
149. Yu AS, Cheng MH, Angelow S, Günzel D, Kanzawa SA, Schneeberger EE, Fromm M, Coalson RD. Molecular basis for cation selectivity in claudin-2-based paracellular pores: identification of an electrostatic interaction site. J Gen Physiol 2009; 133:111-27; PMID:19114638; http://dx.doi.org/10.1085/jgp.200810154
150. Weber CR, Raleigh DR, Su L, Shen L, Sullivan EA, Wang Y, Turner JR. Epithelial myosin light chain kinase activation induces mucosal interleukin-13 expression to alter tight junction ion selectivity. J Biol Chem 2010; 285:12037-46; PMID:20177070; http://dx.doi.org/10.1074/jbc.M109.064808
151. McCole DF. Regulation of epithelial barrier function by the inflammatory bowel disease candidate gene, PTPN2. Ann N Y Acad Sci 2012; 1257:108-14; PMID:22671596; http://dx.doi.org/10.1111/j.1749-6632.2012.06522.x
152. Rhee I, Veillette A. Protein tyrosine phosphatases in lymphocyte activation and autoimmunity. Nat Immunol 2012; 13:439-47; PMID:22513334; http://dx.doi.org/10.1038/ni.2246
153. Yang Q, Co D, Sommercorn J, Tonks NK. Cloning and expression of PTP-PEST. A novel, human, nontransmembrane protein tyrosine phosphatase. J Biol Chem 1993; 268:17650; PMID:8349645
154. Garton AJ, Flint AJ, Tonks NK. Identification of p130(cas) as a substrate for the cytosolic protein tyrosine phosphatase PTP-PEST. Mol Cell Biol 1996; 16:6408-18; PMID:8887669
155. Davidson D, Veillette A. PTP-PEST, a scaffold protein tyrosine phosphatase, negatively regulates lymphocyte activation by targeting a unique set of substrates. EMBO J 2001; 20:3414-26; PMID:11432829; http://dx.doi.org/10.1093/emboj/20.13.3414
156. Garton AJ, Tonks NK. PTP-PEST: a protein tyrosine phosphatase regulated by serine phosphorylation. EMBO J 1994; 13:3763-71; PMID:7520867
157. Espejo R, Rengifo-Cam W, Schaller MD, Evers BM, Sastry SK. PTP-PEST controls motility, adherens junction assembly, and Rho GTPase activity in colon cancer cells. Am J Physiol Cell Physiol 2010; 299:C454-63; PMID:20519451; http://dx.doi.org/10.1152/ajpcell.00148.2010
158. Souza CM, Davidson D, Rhee I, Gratton JP, Davis EC, Veillette A. The phosphatase PTP-PEST/PTPN12 regulates endothelial cell migration and adhesion, but not permeability, and controls vascular development and embryonic viability. J Biol Chem 2012; 287:43180-90; PMID:23105101; http://dx.doi.org/10.1074/jbc.M112.387456
159. Krueger NX, Streuli M, Saito H. Structural diversity and evolution of human receptor-like protein tyrosine phosphatases. EMBO J 1990; 9:3241-52; PMID:2170109
160. Fachinger G, Deutsch U, Risau W. Functional interaction of vascular endothelial-protein-tyrosine phosphatase with the angiopoietin receptor Tie-2. Oncogene 1999; 18:5948-53; PMID:10557082; http://dx.doi.org/10.1038/sj.onc.1202992
161. Bäumer S, Keller L, Holtmann A, Funke R, August B, Gamp A, Wolburg H, Wolburg-Buchholz K, Deutsch U, Vestweber D. Vascular endothelial cell-specific phosphotyrosine phosphatase (VE-PTP) activity is required for blood vessel development. Blood 2006; 107:4754-62; PMID:16514057; http://dx.doi.org/10.1182/blood-2006-01-0141
162. Nawroth R, Poell G, Ranft A, Kloep S, Samulowitz U, Fachinger G, Golding M, Shima DT, Deutsch U, Vestweber D. VE-PTP and VE-cadherin ectodomains interact to facilitate regulation of phosphorylation and cell contacts. EMBO J 2002; 21:4885-95; PMID:12234928; http://dx.doi.org/10.1093/emboj/cdf497
163. Nottebaum AF, Cagna G, Winderlich M, Gamp AC, Linnepe R, Polaschegg C, Filippova K, Lyck R, Engelhardt B, Kamenyeva O, et al. VE-PTP maintains the endothelial barrier via plakoglobin and becomes dissociated from VE-cadherin by leukocytes and by VEGF. J Exp Med 2008; 205:2929-45; PMID:19015309; http://dx.doi.org/10.1084/jem.20080406
164. Vestweber D. Relevance of endothelial junctions in leukocyte extravasation and vascular permeability. Ann N Y Acad Sci 2012; 1257:184-92; PMID:22671605; http://dx.doi.org/10.1111/j.1749-6632.2012.06558.x
165. Sui XF, Kiser TD, Hyun SW, Angelini DJ, Del Vecchio RL, Young BA, Hasday JD, Romer LH, Passaniti A, Tonks NK, et al. Receptor protein tyrosine phosphatase micro regulates the paracellular pathway in human lung microvascular endothelia. Am J Pathol 2005; 166:1247-58; PMID:15793303; http://dx.doi.org/10.1016/S0002-9440(10)62343-7

166. Broermann A, Winderlich M, Block H, Frye M, Rossaint J, Zarbock A, Cagna G, Linnepe R, Schulte D, Nottebaum AF, et al. Dissociation of VE-PTP from VE-cadherin is required for leukocyte extravasation and for VEGF-induced vascular permeability *in vivo*. J Exp Med 2011; 208:2393-401; PMID:22025303; http://dx.doi.org/10.1084/jem.20110525
167. Hermiston ML, Zikherman J, Zhu JW. CD45, CD148, and Lyp/Pep: critical phosphatases regulating Src family kinase signaling networks in immune cells. Immunol Rev 2009; 228:288-311; PMID:19290935; http://dx.doi.org/10.1111/j.1600-065X.2008.00752.x
168. Takahashi T, Takahashi K, St John PL, Fleming PA, Tomemori T, Watanabe T, Abrahamson DR, Drake CJ, Shirasawa T, Daniel TO. A mutant receptor tyrosine phosphatase, CD148, causes defects in vascular development. Mol Cell Biol 2003; 23:1817-31; PMID:12588999; http://dx.doi.org/10.1128/MCB.23.5.1817-1831.2003
169. Zhu JW, Brdicka T, Katsumoto TR, Lin J, Weiss A. Structurally distinct phosphatases CD45 and CD148 both regulate B cell and macrophage immunoreceptor signaling. Immunity 2008; 28:183-96; PMID:18249142; http://dx.doi.org/10.1016/j.immuni.2007.11.024
170. Takahashi T, Takahashi K, Mernaugh R, Drozdoff V, Sipe C, Schoecklmann H, Robert B, Abrahamson DR, Daniel TO. Endothelial localization of receptor tyrosine phosphatase, ECRTP/DEP-1, in developing and mature renal vasculature. J Am Soc Nephrol 1999; 10:2135-45; PMID:10505690
171. Ostman A, Yang Q, Tonks NK. Expression of DEP-1, a receptor-like protein-tyrosine-phosphatase, is enhanced with increasing cell density. Proc Natl Acad Sci U S A 1994; 91:9680-4; PMID:7937872; http://dx.doi.org/10.1073/pnas.91.21.9680
172. Grazia Lampugnani M, Zanetti A, Corada M, Takahashi T, Balconi G, Breviario F, Orsenigo F, Cattelino A, Kemler R, Daniel TO, et al. Contact inhibition of VEGF-induced proliferation requires vascular endothelial cadherin, beta-catenin, and the phosphatase DEP-1/CD148. J Cell Biol 2003; 161:793-804; PMID:12771128; http://dx.doi.org/10.1083/jcb.200209019
173. Koch S, Tugues S, Li X, Gualandi L, Claesson-Welsh L. Signal transduction by vascular endothelial growth factor receptors. Biochem J 2011; 437:169-83; PMID:21711246; http://dx.doi.org/10.1042/BJ20110301
174. Carmeliet P, Lampugnani M-G, Moons L, Breviario F, Compernolle V, Bono F, Balconi G, Spagnuolo R, Oosthuyse B, Dewerchin M, et al. Targeted deficiency or cytosolic truncation of the VE-cadherin gene in mice impairs VEGF-mediated endothelial survival and angiogenesis. Cell 1999; 98:147-57; PMID:10428027; http://dx.doi.org/10.1016/S0092-8674(00)81010-7
175. Chabot C, Spring K, Gratton JP, Elchebly M, Royal I. New role for the protein tyrosine phosphatase DEP-1 in Akt activation and endothelial cell survival. Mol Cell Biol 2009; 29:241-53; PMID:18936167; http://dx.doi.org/10.1128/MCB.01374-08
176. Spring K, Chabot C, Langlois S, Lapointe L, Trinh NT, Caron C, Hebda JK, Gavard J, Elchebly M, Royal I. Tyrosine phosphorylation of DEP-1/CD148 as a mechanism controlling Src kinase activation, endothelial cell permeability, invasion, and capillary formation. Blood 2012; 120:2745-56; PMID:22898603; http://dx.doi.org/10.1182/blood-2011-12-398040
177. Sallee JL, Burridge K. Density-enhanced phosphatase 1 regulates phosphorylation of tight junction proteins and enhances barrier function of epithelial cells. J Biol Chem 2009; 284:14997-5006; PMID:19332538; http://dx.doi.org/10.1074/jbc.M901901200
178. Rao RK, Basuroy S, Rao VU, Karnaky KJ Jr., Gupta A. Tyrosine phosphorylation and dissociation of occludin-ZO-1 and E-cadherin-beta-catenin complexes from the cytoskeleton by oxidative stress. Biochem J 2002; 368:471-81; PMID:12169098; http://dx.doi.org/10.1042/BJ20011804
179. Gebbink MF, Zondag GC, Koningstein GM, Feiken E, Wubbolts RW, Moolenaar WH. Cell surface expression of receptor protein tyrosine phosphatase RPTP mu is regulated by cell-cell contact. J Cell Biol 1995; 131:251-60; PMID:7559782; http://dx.doi.org/10.1083/jcb.131.1.251
180. Aricescu AR, Hon WC, Siebold C, Lu W, van der Merwe PA, Jones EY. Molecular analysis of receptor protein tyrosine phosphatase mu-mediated cell adhesion. EMBO J 2006; 25:701-12; PMID:16456543; http://dx.doi.org/10.1038/sj.emboj.7600974
181. Gebbink MF, Zondag GC, Wubbolts RW, Beijersbergen RL, van Etten I, Moolenaar WH. Cell-cell adhesion mediated by a receptor-like protein tyrosine phosphatase. J Biol Chem 1993; 268:16101-4; PMID:8393854
182. Mourton T, Hellberg CB, Burden-Gulley SM, Hinman J, Rhee A, Brady-Kalnay SM. The PTPmu protein-tyrosine phosphatase binds and recruits the scaffolding protein RACK1 to cell-cell contacts. J Biol Chem 2001; 276:14896-901; PMID:11278757; http://dx.doi.org/10.1074/jbc.M010823200
183. Johnson KG, Van Vactor D. Receptor protein tyrosine phosphatases in nervous system development. Physiol Rev 2003; 83:1-24; PMID:12506125
184. Ensslen-Craig SE, Brady-Kalnay SM. PTP mu expression and catalytic activity are required for PTP mu-mediated neurite outgrowth and repulsion. Mol Cell Neurosci 2005; 28:177-88; PMID:15607952; http://dx.doi.org/10.1016/j.mcn.2004.08.011
185. Bianchi E, Bender JR, Blasi F, Pardi R. Through and beyond the wall: late steps in leukocyte transendothelial migration. Immunol Today 1997; 18:586-91; PMID:9425737; http://dx.doi.org/10.1016/S0167-5699(97)01162-6
186. Koop EA, Lopes SM, Feiken E, Bluyssen HA, van der Valk M, Voest EE, Mummery CL, Moolenaar WH, Gebbink MF. Receptor protein tyrosine phosphatase mu expression as a marker for endothelial cell heterogeneity; analysis of RPTPmu gene expression using LacZ knock-in mice. Int J Dev Biol 2003; 47:345-54; PMID:12895029
187. Chagnon MJ, Uetani N, Tremblay ML. Functional significance of the LAR receptor protein tyrosine phosphatase family in development and diseases. Biochem Cell Biol 2004; 82:664-75; PMID:15674434; http://dx.doi.org/10.1139/o04-120
188. Pulido R, Serra-Pagès C, Tang M, Streuli M. The LAR/PTP delta/PTP sigma subfamily of transmembrane protein-tyrosine-phosphatases: multiple human LAR, PTP delta, and PTP sigma isoforms are expressed in a tissue-specific manner and associate with the LAR-interacting protein LIP.1. Proc Natl Acad Sci U S A 1995; 92:11686-90; PMID:8524829; http://dx.doi.org/10.1073/pnas.92.25.11686
189. Chien PN, Ryu SE. Protein tyrosine phosphatase σ in proteoglycan-mediated neural regeneration regulation. Mol Neurobiol 2013; 47:220-7; PMID:22956273; http://dx.doi.org/10.1007/s12035-012-8346-x
190. Persson C, Sjöblom T, Groen A, Kappert K, Engström U, Hellman U, Heldin CH, den Hertog J, Ostman A. Preferential oxidation of the second phosphatase domain of receptor-like PTP-alpha revealed by an antibody against oxidized protein tyrosine phosphatases. Proc Natl Acad Sci U S A 2004; 101:1886-91; PMID:14762163; http://dx.doi.org/10.1073/pnas.0304403101
191. Wallace MJ, Batt J, Fladd CA, Henderson JT, Skarnes W, Rotin D. Neuronal defects and posterior pituitary hypoplasia in mice lacking the receptor tyrosine phosphatase PTPsigma. Nat Genet 1999; 21:334-8; PMID:10080192; http://dx.doi.org/10.1038/6866
192. Muise AM, Walters T, Wine E, Griffiths AM, Turner D, Duerr RH, Regueiro MD, Ngan BY, Xu W, Sherman PM, et al. Protein-tyrosine phosphatase sigma is associated with ulcerative colitis. Curr Biol 2007; 17:1212-8; PMID:17614280; http://dx.doi.org/10.1016/j.cub.2007.06.013
193. Wagner J, Gordon LA, Heng HH, Tremblay ML, Olsen AS. Physical mapping of receptor type protein tyrosine phosphatase sigma (PTPRS) to human chromosome 19p13.3. Genomics 1996; 38:76-8; PMID:8954782; http://dx.doi.org/10.1006/geno.1996.0594
194. Rioux JD, Silverberg MS, Daly MJ, Steinhart AH, McLeod RS, Griffiths AM, Green T, Brettin TS, Stone V, Bull SB, et al. Genomewide search in Canadian families with inflammatory bowel disease reveals two novel susceptibility loci. Am J Hum Genet 2000; 66:1863-70; PMID:10777714; http://dx.doi.org/10.1086/302913
195. Batt J, Cutz E, Fladd C, Rotin D. Apparent normal lung architecture in protein tyrosine phosphatase-sigma-deficient mice. Am J Physiol Lung Cell Mol Physiol 2003; 284:L214-23; PMID:12471016
196. Müller T, Choidas A, Reichmann E, Ullrich A. Phosphorylation and free pool of beta-catenin are regulated by tyrosine kinases and tyrosine phosphatases during epithelial cell migration. J Biol Chem 1999; 274:10173-83; PMID:10187801; http://dx.doi.org/10.1074/jbc.274.15.10173
197. Marrs JA, Nelson WJ. Cadherin cell adhesion molecules in differentiation and embryogenesis. Int Rev Cytol 1996; 165:159-205; PMID:8900959; http://dx.doi.org/10.1016/S0074-7696(08)62222-6
198. Huber O, Bierkamp C, Kemler R. Cadherins and catenins in development. Curr Opin Cell Biol 1996; 8:685-91; PMID:8939663; http://dx.doi.org/10.1016/S0955-0674(96)80110-4
199. Becker KF, Atkinson MJ, Reich U, Becker I, Nekarda H, Siewert JR, Höfler H. E-cadherin gene mutations provide clues to diffuse type gastric carcinomas. Cancer Res 1994; 54:3845-52; PMID:8033105
200. Birchmeier W, Hülsken J, Behrens J. E-cadherin as an invasion suppressor. Ciba Found Symp 1995; 189:124-36; discussion 136-41, 174-6.
201. Scharl M, Rudenko I, McCole DF. Loss of protein tyrosine phosphatase N2 potentiates epidermal growth factor suppression of intestinal epithelial chloride secretion. Am J Physiol Gastrointest Liver Physiol 2010; 299:G935-45; PMID:20689057; http://dx.doi.org/10.1152/ajpgi.00106.2010