Diseases of the glomerular filter of the kidney are a leading cause of end-stage renal failure. Recent studies have emphasized the critical role of the slit diaphragm of podocytes for the size-selective filtration barrier of the kidney and revealed novel aspects of the mechanisms that lead to proteinuria, in both inherited and acquired diseases (1–4). Several critical structural protein components of the slit diaphragm have been identified. Recently, it has been speculated that these slit diaphragm proteins, in addition to their structural functions, participate in common signaling pathways. This review focuses on what is known about signaling at the slit diaphragm. It provides a snapshot of our current understanding of the signaling properties of slit diaphragm proteins and projects a framework for further studies necessary to delineate the function and dynamics of the slit diaphragm protein complex and the pathogenesis of nephrotic syndrome.

Ultrafiltration of plasma in the renal glomeruli is a major function of the kidney. The glomerular filter through which the ultrafiltrate has to pass consists of three layers: the fenestrated endothelium, the intervening glomerular basement membrane, and the epithelial podocyte foot processes. This filtration barrier behaves as a size-selective sieve restricting the passage of macromolecules on the basis of their size, shape, and charge (5–7). Although the glomerular filter is a primary target of a large number of progressive disorders that lead to chronic renal insufficiency, until recently, little was known about the importance of podocytes for establishing the size-selective filtration barrier of the kidney. The recent description of gene defects in hereditary nephrotic syndrome resulting in nephrotic syndrome and podocyte changes that resemble nephrin mutation (10). Because there is no case of nephrotic syndrome without major changes in podocyte morphology, it has been speculated for many years that the slit diaphragm is an important component of the glomerular filter (14).

A milestone in glomerular research was the cloning of nephrin by the Tryggvason group in 1998 together with its localization to the slit diaphragm of podocytes (15–18). This work suggested that nephrin is a critical structural component of the slit membrane and bridges the distance between interdigitating podocyte foot processes (3,9,19). Nephrin, encoded by NPHS1, the gene mutated in congenital nephrotic syndrome of the Finnish type, is a transmembrane adhesion protein of the Ig superfamily (Figure 1). Both humans and mice lacking nephrin are born without typical slit diaphragms and exhibit severe podocyte abnormalities and massive proteinuria already in utero (20,21).

Recently, several additional components of the slit diaphragm have been identified (22–25). Mutations in the genes encoding for these proteins cause severe podocyte changes and nephrotic syndrome. NPHS2, the gene responsible for a steroid-resistant form of nephrotic syndrome, was cloned by the Antignac group and encodes for podocin, a stomatin family membrane protein (23). Podocin almost exclusively localizes to the slit diaphragm of podocytes and interacts with the cytoplasmic tail of nephrin (26–28). Gene disruption in mice results in a severe congenital nephrotic syndrome (29). The cytoplasmic multi-adaptor protein CD2AP was cloned by the Shaw laboratory as a CD2-interacting protein in lymphocytes (30). CD2AP also interacts with nephrin and localizes to the cytoplasmic face of the slit diaphragm (31). It is interesting that mice completely lacking CD2AP die of massive proteinuria 6 wk after birth, suggesting a critical role for CD2AP in slit diaphragm function (22). Moreover, CD2AP haploinsufficiency seems to be linked to glomerular disease susceptibility both in mice and in humans, further supporting the critical role of CD2AP for the integrity of the glomerular filter (32,33). Donoviel et al. (24) identified neph1, another Ig superfamily protein (Figure 1) that localizes to the slit and causes congenital nephrotic syndrome in knockout mice. Neph1 is a member of a family of Ig adhesion molecules that are expressed in podocytes and interact with podocin (34). Recently, the adhesion protein and member of the protocadherin superfamily of proteins FAT1 was shown to localize to the slit membrane of podocytes (35). Targeted deletion of the fat1 gene in mice results in nephrotic syndrome and podocyte changes that resemble nephrin mutation (25).
The identification of these slit diaphragm proteins suggested that these proteins may serve important structural functions at the filtration slit necessary for establishing and maintaining an intact glomerular filter. However, accumulating evidence suggests that slit diaphragm proteins do not only serve structural functions setting up a size- and charge-selective filtration barrier but also may participate in common signaling pathways necessary to maintain the functional integrity of podocytes (27,36–38). This model proposes that the slit diaphragm protein complex is a highly dynamic protein complex that recruits signal transduction components and initiates signaling to regulate complex biologic programs in the podocyte, such as regulation of cytoskeletal rearrangements, polarized sorting and endocytosis, cell differentiation and suppression of proliferation, mechanotransduction, or podocyte viability.

**Proof of Principle: Nephrin and Neph1 Are Signaling Proteins**

Signal transduction is the process of converting extracellular signals into cellular responses. Transmission of an extracellular signal involves transmembrane proteins that have domains on both sides of the plasma membrane (Figure 2). The basic principle of signaling is that ligand binding on the extracellular side converts the receptor from an inactive to an active form. The process is called signal transduction because a signal has in effect been transduced across the membrane. In general, signal transduction systems are assembled through protein–protein interactions (39). This means that signaling events that are initiated at the plasma membrane control the reversible assembly of multiprotein complexes to regulate intracellular processes. Much of this regulation is achieved through attachment of phosphate groups to (phosphorylation) or cleavage of phosphate (dephosphorylation) from serine, threonine, or tyrosine residues of crucial protein substrates (40). Phosphorylation of these residues creates binding sites for modular phosphoprotein-binding domains such as Src homology 2 and phosphotyrosine-binding domains in the case of phosphotyrosine or 14-3-3, WW domains, forkhead-associated domains, and, tentatively, WD40 repeats and leucine-rich regions in the case of phosphoserine/phosphothreonine. Thus, phosphorylation connects proteins with their upstream kinases and downstream effectors to form multiprotein complexes (40,41).

Nephrin and neph1 are adhesion proteins and members of the Ig superfamily (Figure 1). In addition to their extracellular domains that are part of the slt membrane connecting interdigitating foot processes and a single transmembrane domain, these proteins contain a short cytoplasmic tail with a number of tyrosine residues that are predicted to serve as target for dynamic phosphorylation in vivo (27,34). Intriguing is that tyrosine phosphorylation at the cytoplasmic face of these proteins seems to be tightly regulated (37,38).
What is the protein (kinase) responsible for tyrosine phosphorylation of nephrin and neph1? A recent study demonstrated that the Src family nonreceptor protein tyrosine kinase Fyn directly binds to the cytoplasmic tail of nephrin and mediates nephrin phosphorylation \textit{in vitro} and \textit{in vivo} (43). It is interesting that targeted deletion of \textit{fyn} in mice with or without co-deletion of the tyrosine kinase gene \textit{yes} resulted in the loss of nephrin tyrosine phosphorylation, a severe podocyte dysfunction, foot process effacement, and proteinuria, suggesting that these abnormalities may be at least partially related to altered nephrin phosphorylation (43,46).

Moreover, it could be shown that nephrin and neph1 are signaling proteins and able to stimulate transcriptional activation in a model system (27,37). Nephrin and neph1 activate the transcription factor AP-1 via the stimulation of a mitogen-activated protein kinase module. Direct interaction of the tyrosine-phosphorylated cytoplasmic tail of nephrin with podocin dramatically facilitated nephrin signaling, whereas inhibition of tyrosine phosphorylation of the cytoplasmic tail of nephrin abrogated nephrin-mediated signal transduction (27). It is interesting that podocin-mediated augmentation of nephrin signaling required the direct interaction of the carboxy-terminal cytoplasmic domain of podocin with the cytoplasmic tail of nephrin (27,38). By contrast, in another study, neph1 signal transduction was augmented by direct interaction of the cytoplasmic tail of neph1 with the multiadaptor and scaffolding protein ZO-1 (37). Although derived from a model system, these studies provided the proof of principle that slit diaphragm proteins can initiate signal transduction.

**Intracellular Signaling Adaptors: The Functional Slit Diaphragm Complex Assembles through Dynamic Protein–Protein Interactions**

Signal transduction from cellular receptors requires intracellular adaptor proteins (Figure 3). Adaptor proteins are noncatalytic polypeptides that contain one or more protein interaction modules that mediate protein interactions (47). As described above, many of the protein interactions are regulated through phosphorylation and dephosphorylation of crucial protein and lipid substrates (40,48).

By screening phosphotyrosine-binding proteins for their in-

*Figure 3. Signaling at the slit diaphragm. Hypothetical signaling pathways involved in the regulation of podocyte biology and glomerular function. AKT, AKT/protein kinase B; Cbl, Casitas B-lineage lymphoma; Cort, cortactin; Endo, endophilin; MAPK, mitogen-activated protein kinase family; Syn, synaptotagmin; TRP, hypothetical TRP channel.*
teraction with the tyrosine-phosphorylated cytoplasmic tail of nephrin, the protein p85 was the first SH2 domain-containing protein to be identified that binds to the tyrosine-phosphorylated cytoplasmic tail of nephrin in vivo (36). p85 is the regulatory subunit of class Ia phosphoinositide 3-OH (PI3) kinase. PI3 kinase activity is responsible for the phosphorylation of lipids at the inner leaflet of the plasma membrane (49). Recruitment of the regulatory p85 subunit to the cytoplasmic tail of nephrin induced the activation of the p110 catalytic subunit, which converts the membrane lipid phosphatidylinositol-4,5-biphosphate to phosphatidylinositol-3,4,5-triphosphate. Thus, lipids at the cytoplasmic side of the filtration slit are phosphorylated by nephrin-activated PI3 kinase, which may initiate a cascade of events in the podocyte foot process (36).

Signaling proteins with pleckstrin-homology (PH) domains accumulate at sites of PI3 kinase activation by directly binding to these phosphorylated lipids. These proteins themselves regulate a variety of crucial cellular programs such as cell survival, actin cytoskeletal dynamics, endocytosis, and cell metabolism (49). Of particular interest in the podocyte is the PH domain-containing serine-threonine kinase AKT (36). Other PH domain proteins that are activated by PI3 kinase and could play a role in podocyte biology include GDP-GTP exchange factors for Rac and ARF6 and protein tyrosine kinases of the Bruton’s tyrosine kinase (Btk) and Tec family. Binding of PI3 kinase–generated phospholipids to the PH domain of AKT leads to the translocation and activation of AKT. Among a wealth of effects, AKT activity has been found to be required for the growth factor–dependent survival of a wide variety of cell types ranging from fibroblasts to neurons by blocking apoptosis (50). Consequently, nephrin-mediated activation of PI3 kinase and AKT activity has been shown to inhibit podocyte apoptosis and to increase the threshold for podocyte cell death induced by apoptotic stimuli (36).

However, nephrin is not the only slit diaphragm protein to associate with p85 and activate PI3 kinase. Recently, it was demonstrated that CD2AP directly interacts with p85 (36). Together with nephrin, CD2AP strongly activates PI3 kinase in podocytes. Targeted disruption of the cd2ap gene dramatically reduces AKT activity in podocytes and is associated with an increased susceptibility to podocyte apoptosis (36). These findings are particularly interesting in the context of the pathogenic steps that lead to glomerulonephrosis (51–54). Podocyte death and podocyte depletion have been proposed as hallmarks of both primary and secondary forms of glomerulonephrosis for many years and are now considered a key step in the development of progressive renal disease (51,55–57). Thus, the structural and functional integrity of the slit diaphragm proteins and signaling at the slit diaphragm may be required for the inhibition of apoptosis and for cell survival in podocytes. In support of this hypothesis, cd2ap+/− heterozygous mice are haploinsufficient and develop severe glomerular changes at 9 mo of age with a histologic pattern similar to that in human focal segmental glomerulosclerosis (32,33).

Although the underlying mechanism of CD2AP-mediated PI3 kinase activity at the molecular level is not completely understood, recent evidence suggests that by directly interacting with several target proteins, CD2AP may orchestrate PI3 kinase effectors to amplify efficient PI3 kinase signaling (T. Benzing, unpublished data). In analogy to CIN85, CD2AP may also be involved in the recycling and endocytosis of transmembrane receptors (e.g., nephrin), thereby regulating signal transduction from the slit diaphragm (32,58). An additional function of the PI3 kinase downstream effector AKT is to repress collagenase expression and to induce the synthesis of laminin and type IV collagen chains (59,60); both are key components of the glomerular basement membrane. Because basement membrane abnormalities are involved in the development of several forms of proteinuria, it is tempting to speculate that AKT activation may contribute to the synthesis and/or maintenance of an intact glomerular basement membrane. These data further support the concept that signal transduction at the slit diaphragm is critical for podocyte function, viability, and integrity of the glomerular filter.

It’s All about Location: Signaling at the Slit Diaphragm Needs a Lipid Raft Surrounding

As mentioned above, nephrin-mediated signaling is facilitated by the direct interaction with the NPHS2 gene product podocin (27). Podocin, a member of the stomatin protein family with a short amino terminal domain, a transmembrane region, and a cytosolic carboxyl terminal domain, is exclusively expressed in podocytes of the developing and mature glomeruli and predicted to form a membrane-associated hairpin-like structure with the N- and C-terminal domains facing the cytosolic side of the slit diaphragm (26). A functional interaction of nephrin with podocin was indirectly confirmed in patients with hereditary nephrotic syndrome. In an interesting study, Koziell et al. (61) could show a functional interrelationship between NPHS1 and NPHS2, the genes encoding for nephrin and podocin. However, until recently, the question remained how podocin by directly interacting with nephrin may facilitate nephrin signaling. Some light has been shed on the mechanism through which podocin can augment nephrin signaling by a recent study that demonstrated that podocin-mediated recruitment of nephrin to so-called lipid raft microdomains of the plasma membrane is required for efficient nephrin signaling (38).

Multiple pieces of evidence suggest that the plasma membrane of the filtration slit has a special lipid composition (28,43,44,62). Lipid rafts are specialized microdomains of the plasma membrane with a unique lipid content and a concentrated assembly of signal transduction molecules (63). Rafts have been proposed to form platforms for many important cellular processes, such as polarized sorting of membrane proteins and signal transduction (64–66). Mundel and coworkers (28,44) could show that podocin is a lipid raft–associated protein at the filtration slit. Subsequently, Huber et al. (38) demonstrated that podocin serves to recruit nephrin into lipid raft microdomains. Lipid raft targeting of nephrin was required for the proper initiation of nephrin signaling. Disease-causing podocin mutations failed to target nephrin to rafts and lost their ability to augment nephrin signal transduction (38).
Thus, not only the protein components but also a correct lipid composition of the plasma membrane at the slit diaphragm is important for proper signal transduction at the filtration slit.

**Talking about the Ligands: What Can We Learn from Model Organisms?**

As detailed above, the basic principle of signal transduction is that ligand binding on the extracellular side converts the receptor (in our case, nephrin) from an inactive to an active form. Consequently, an important question is, “What could be the ligand that binds to the extracellular domain of the proteins at the slit diaphragm inducing the activation of signaling cascades as described above?” Early work suggested that nephrin may engage in homophilic interactions (16). Moreover, cross-linking of nephrin molecules was sufficient to induce an increase in tyrosine phosphorylation of the cytoplasmic tail of nephrin (45). Although subsequent studies confirmed homophilic binding of nephrin molecules (67–69), these homophilic interactions may not be the only interactions occurring *in vivo*. Recently, neph1 was shown to serve as a binding partner of the extracellular domain of nephrin (67,69,70). Although these interactions were surprisingly promiscuous, these data suggested that *cis* and *trans* interactions involving at least nephrin and neph1 Ig superfamily proteins are required to set up an intact slit diaphragm structure and induce efficient signal transduction. The identification of neph1 led to the description of a family of nep proteins in humans and mice (neph1, neph2, neph3/filtrin), all expressed in the podocyte (34,71). Whether these proteins act as additional ligands of nephrin at the filtration slit is not clear to date.

These data are strongly supported by experimental results derived from various model organisms. Nephrin and nep proteins can be found in different species ranging from worm and fly to mice and humans. Although the fruit fly *Drosophila melanogaster* and the nematode *C. elegans* lack structures comparable to a mammalian kidney glomerulus, some cells engage in specialized cell–cell contacts that closely resemble the specialized cell junction of podocytes. The *Drosophila* homologues of nephrin (hibris [*hbs*] and sticks-and-stones [*sns*]) interact with homologues of mammalian neph1 (dumbfounded [*duf*] and roughest/irreC [*rsl*]) (72–74) to engage in intimate cell junctions that are required for myoblast fusion during embryonic muscle development. During skeletal muscle development and regeneration after injury, mononucleated myoblasts fuse to form multinucleated muscle fibers. This process of myoblast fusion is amenable to genetic dissection in the fly, in which muscle formation involves a well-defined temporospatial sequence of events that are remarkably conserved also in mammalian myogenesis. Recognition and fusion require the formation of intense cell–cell contacts, so-called prefusion complexes, that are based on nep and nephrin proteins and comparable to the slit diaphragm cell junctions of podocytes (75–77). Loss of one of the nephrin or nep homologues in this system disrupts the cellular program required for myoblast fusion. Intriguing is that *in vivo* mapping of the functional protein domains required for myoblast fusion revealed that the intracellular domain mediates their activity (77), suggesting that intact signal transduction is required for the proper function of these proteins.

In agreement with this concept, *syg-1*, the *C. elegans* homologue of *neph3*, has been shown to be required as a guidepost signal in neuronal synapse formation in *C. elegans* (78), a process that also requires tightly regulated signal transduction events. Thus, from these data, the concept is emerging that members of the neph and nephrin protein families form specialized cell junctions that are involved in pathfinding, orientation, formation of prefusion complexes, and the intimate organization of cell extensions in various cells and organisms, including the mammalian kidney. All of these programs are strictly dependent on intracellular signaling networks.

**Hanging on a Scaffold: The Role of Actin Cytoskeleton and PDZ Domain Proteins in the Organization of Signaling Proteins at the Filtration Slit**

Although many of the key proteins of the slit diaphragm have now been identified, the fundamental question remains how the different proteins are organized at this specialized cell junction. Given the fluid nature of plasma membranes, restriction of podocyte proteins to the slit diaphragm protein complex at the base of the filtration slit requires anchoring mechanisms. Obviously, this restriction is a critical prerequisite for the maintenance of a sieve as well as efficient signal transduction at the filtration slit. In addition to the function of podocin, which recruits nephrin into specialized lipid raft microdomains of the plasma membrane at the slit diaphragm, two crucial mechanisms seem to be important for the assembly of slit diaphragm components. First, it has been shown that slit diaphragm proteins are associated with the cortical actin cytoskeleton in the podocyte *in vitro* and *in vivo* (79–81). This interaction seems at least in part to be mediated by CD2AP (82). Each foot process is equipped with a microfilament-based contractile apparatus composed of actin, myosin-II, α-actinin, talin, paxillin, and vinculin (83–85). The slit diaphragm protein complex is linked to the actin cytoskeleton and seems to modify actin dynamics. CD2AP has been shown to associate with WASp, the Arp2/3 complex, the actin-capping protein CAPZ, and cortactin, proteins involved in actin filament assembly (86–88). Actin fiber formation is a highly dynamic process that is governed by continuous assembly and disassembly of filaments. It is well known that the dynamics of the submembranous actin meshwork of podocytes is profoundly changed in effaced foot processes (1). The current belief is that loss of the organized structure of the actin cytoskeleton in podocytes is a prerequisite for podocyte foot process effacement and proteinuria. These findings assign a central role to the submembranous actin cytoskeleton for maintaining the stability of the podocyte’s shape and the integrity of the slit diaphragm protein complex. Moreover, it seems that loss of the integrity of the slit diaphragm complex has a dramatic effect on the actin cytoskeleton leading to foot process effacement and proteinuria (1). Work by the Shimizu, Salant, and Chugh
groups showed that injection of antisera directed against the extracellular domains of nephrin or nep1 results in rapidly developing proteinuria, disorganization of the actin cytoskeleton, and foot process effacement (70,89–91). The critical importance of an intact submembranous actin skeleton is highlighted by the fact that mutations in the actin-bundling protein α-actinin-4 have been detected in an autosomal dominant hereditary form of focal segmental glomerulosclerosis (92). Patients with mutations in the ACTN4 gene as well as mice with targeted disruption of ACTN4 or transgenic overexpression of a mutated form of α-actinin-4 display effaced podocyte foot processes and a steroid-resistant form of focal segmental glomerulosclerosis (93,94). Although a critical role of signaling at the slit diaphragm for active actin remodeling and the maintenance of the podocyte structure is highly conceivable, little is known about the effectors of slit diaphragm proteins involved in transmitting these signals to the actin meshwork (95,96). It is interesting that α-actinin-4 has been shown to bind to densin-180 in the postsynaptic density in neurons (97). Densin-180 has recently been localized to the slit diaphragm of podocytes by Holthöfer et al. (98) and may provide one important link of slit diaphragm proteins to the actin cytoskeleton.

The second anchoring mechanism that restricts podocyte proteins to the slit diaphragm protein complex is binding to scaffolding proteins. The first of these scaffolding proteins localized to the cytoplasmic face of the filtration slit by Farquhar and colleagues (42,99) was a protein called zonula occludens 1 (ZO-1). ZO proteins are membrane-associated multidomain proteins that are usually localized at sites of intercellular junctions. They contain several protein interaction modules, namely three PDZ domains, a Src homology 3 (SH3) domain, and a guanylate kinase (GUK) domain (100). PDZ domains are protein-binding modules that recognize short peptide motifs within their protein targets (101). In most cases, the last three to five residues at the extreme carboxy terminus of a transmembrane protein represent the target sequence. Genetic evidence from invertebrate systems demonstrates a role for ZO proteins in facilitating signal transduction, and evidence from vertebrate systems demonstrates a structural role in organizing transmembrane protein complexes (102,103). In a recently published functional study, it was shown that ZO-1 directly binds to the cytoplasmic tail of neph proteins (37). This interaction was mediated by the first PDZ domain of ZO-1 and the last three amino acids of the carboxy terminal domain of neph proteins and induced a dramatic increase in tyrosine phosphorylation of the cytoplasmic tail of neph1. Thus, in addition to clustering neph proteins, ZO-1 alters the phosphorylation state of Neph1 and its ability to induce signal transduction. It has been suggested that ZO-1 in addition to its signaling function interacts with the actin cytoskeleton and components of the paracellular seal (104). Although the functional implications of ZO-1/actin association have not yet been established in vivo, ZO-1 could link Neph1 and its associated binding proteins to the actin cytoskeleton and contribute to the organization of the foot processes of podocytes. It is interesting to note that the interaction of the cytoplasmic tail of neph1 with PDZ domain proteins seems to be regulated by phosphorylation of a critical threonine residue (C. Reinhardt, T.B. Huber, T. Benzing, unpublished data), which suggests that the specificity for PDZ domain binding at the slit diaphragm is regulated by signaling events.

**Signaling Effectors: Highway to He(alth)**

How can we put all of this together? In this article, I have summarized data suggesting that signaling at the slit diaphragm is critical for the regulation of podocyte function, maintenance of foot process structure, and possibly podocyte survival (Figure 3). Although many aspects of this concept have yet to be addressed in various animal models, recent studies clearly indicate that nephrin and neph proteins are signaling proteins. However, the regulation of dynamics and kinetics of signaling is completely unclear. The recent generation of mouse strains that allow for podocyte-specific gene targeting will greatly aid the study of signaling in vivo (105–107).

It is reasonable to speculate that the slit diaphragm protein complex is highly dynamic. Protein components of the complex are endocytosed, recycled, and returned back to the cell surface. In this regard, it is conceivable that nephrin or neph1 molecules that enter the complex may be dephosphorylated and inactive. Interaction with their respective ligand at the slit diaphragm may then induce tyrosine phosphorylation and initiation of signaling. This could be a way of sensing repair and turnover of slit diaphragm components. In conjunction with ion channels, this system could also serve to monitor pressure at the filtration slit (108,109). It is interesting to note that the closest homologue of podocin in C. elegans, a stomatin family protein called MEC-2, is involved in mechanosensation in the worm (110). Thus, it is tempting to speculate that podocin has similar functions in the mammalian kidney.

An interesting question is whether podocyte foot processes are able to regulate the width of the filtration slit, slit diaphragm permeability, and glomerular ultrafiltration. Although experimental data are almost completely lacking, it seems that this could be the case. The slit diaphragm is a robust structure with a fairly constant width. However, it is increasingly appreciated that the width may vary and that the slit diaphragm has to be partially elastic and highly dynamic in nature (3,111). In addition to acting as a molecular sieve, it has been suggested that the slit diaphragm may impose substantial resistance to liquid flow across the glomerulus (112). Thus, fine tuning of the width of the slit diaphragm may have an impact on the hydraulic resistance and thus contribute to the regulation of glomerular ultrafiltration and permeability of the filter.

It is clear that the slit diaphragm is not the only membrane domain where signaling takes place in the podocyte. Recent experimental evidence suggests a critical role for integrin signaling at the sole of the podocyte foot process (113), for growth factors such as vascular endothelial growth factor (114) or basic fibroblast growth factor (115), protein tyrosine phosphatases (116), and chemokines (117,118) in podocyte development and glomerular pathophysiology.

However, it is clearly more and more appreciated that (1) the slit diaphragm protein complex does not only serve as static molecular sieve but rather is a highly dynamic functional
protein complex and (2) signaling at the slit diaphragm may be critical for maintaining the integrity of the podocyte architecture and the function of the glomerular filter of the kidney. A better understanding of the mechanisms involved in signal transduction at the slit diaphragm will definitively provide valuable insights into important aspects of glomerular diseases in general. Progress in research on podocyte biology and signaling will greatly help to improve our understanding of the pathophysiology not only of inherited but also of the more common acquired diseases, namely minimal change disease, membranous nephropathy and diabetic nephropathy. From this perspective, at some point patients will benefit from the progress that has been made in the exciting field of podocyte cell biology and signal transduction.

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References


of unique carboxyl-terminal motifs by distinct PDZ domains. 


