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The glomerulus- a view from the outside- the podocyte

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Abstract

In the past decade, podocyte research has been greatly aided by the development of powerful new molecular, cellular and animal tools, leading to elucidation of an increasing number of proteins involved in podocyte function and identification of mutated genes in hereditary glomerulopathies. Accumulating evidence indicates that podocyte disorders may not only underlie these hereditary glomerulopathies but also play crucial role in a broad spectrum of acquired glomerular diseases. Genetic susceptibility, environmental influence and systemic responses are all involved in the mediation of the pathogenesis of podocytopathies. Injured podocytes may predisopose to further injury of other podocytes and other adjacent/distant renal cells in a vicious cycle, leading to inexorable progression of glomerular injury. The classic view is that podocytes have a limited ability to proliferate in the normal mature kidney. However, recent research in rodents has provided suggestive evidence for podocyte regeneration resulting from differentiation of progenitor cells within Bowman's capsule.

Keywords

podocyte; foot process effacement; slit diaphragms; hereditary proteinuria syndrome; acquired glomerular diseases; VEGF; progenitor cells; FSGS; diabetic nephropathy and kidney

1. INTRODUCTION

Podocytes are highly specialized epithelial cells that cover the outer layer of the glomerular basement membrane (GBM), playing a crucial role in regulation of glomerular function, and podocyte injury is an essential feature of progressive glomerular diseases (Mundel and Kriz, 1995). Since the late 1990's, studies using modern molecular and genetic techniques have increasingly extended our knowledge regarding the components and function of the podocyte and its role in congenital nephrotic syndromes (Tryggvason et al., 2006). Transmission electron microscopy has identified clear glomerular filtration barrier structures (Salmon et al., 2009). Human (Saleem et al., 2002) and rodent (Mundel et al., 1997, Mundel et al., 1997) differentiated podocyte culture techniques have allowed the study of podocytes *in vitro* (Shankland et al., 2007). In addition, the zebrafish glomerulus (Morello and Lee, 2002) as well the recent identification in Drosophila melanogaster of podocyte-like cells (the

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"nephrocyte") with remarkably conserved slit diaphragms (Chaib et al., 2008), offer simpler model organisms in which to study podocyte biology and podocyte-associated diseases.

Recent studies indicate that local podocyte damage can spread to induce injury in otherwise healthy podocytes and further affect both glomerular endothelial and mesangial cells, implying that even limited podocyte injury might initiate a vicious cycle of progressive glomerular damage (Ichikawa et al., 2005). Podocyte injury due to mutation or alteration of intracellular proteins unique to this cell type underlies the hereditary proteinuric syndromes but is also involved in wide spectrum of acquired glomerular diseases. Despite a dramatically increased knowledge of podocyte biology, mechanisms underlying functional and structural podocyte disturbances, especially "crosstalk" between podocytes and endothelial or other cells during renal diseases, still remain incompletely delineated (Shankland, 2006). A brief update of podocyte biology, the podocyte's pathogenic role in glomerular diseases and potential new therapeutic approaches are the subject of this review.

2. NEW ASPECTS IN PODOCYTE BIOLOGY

Podocytes are a highly differentiated cell with unique architecture. They are comprised of three major parts: cell body, major processes and foot processes. The foot processes of neighboring podocytes regularly interdigitate, leaving between them the filtration slits that are bridged by an extracellular structure, known as the slit diaphragm (Asanuma and Mundel, 2003). The slit diaphragm represents the only cell-cell contact between podocytes, while highly dynamic foot processes interposed to the slit diaphragm maintain podocyte structure to sustain the barrier function (Mundel and Shankland, 2002). Foot processes contain abundant microfilaments and modulate glomerular filtration (Ichimura et al., 2003), and the structure is maintained by an intricate actin cytoskeleton. Interference of actin cytoskeleton interactions with the slit diaphragm or the basal domain of foot processes itself will ultimately cause foot process effacement and proteinuria (Mundel and Shankland, 2002). Mutations in genes encoding slit diaphragm proteins result in proteinuria and nephrotic syndrome in both animal models and patients. The glomerular filtration barrier is traditionally considered as resulting from the fenestrated endothelial cells, glomerular basement membrane (GBM) and the slit diaphragm formed by the podocytes. Recently Salmon and his colleagues (Salmon et al., 2009) proposed adding two additional sites: the endothelial surface layer (ESL) and the subpodocyte space (SPS). ESL is a carbohydrate rich meshwork coating the luminal aspect of cytoplasmic and fenestral proteins of glomerular endothelial cells and may play an important role in glomerular permeability (Rostgaard and Qvortrup, 1997, Salmon et al., 2009). A new three-dimensional reconstruction of urinary spaces in the glomerular corpuscle using serial section transmission electron microscopy discovered that there are three interconnected but ultrastructurally distinct urinary spaces (Neal et al., 2007). SPS is bounded by the podocyte cell body and/or thin plate-like extensions above the podocyte cell body and under the glomerular filtration barrier, and SPSs cover 60% of the entire filterable surface area of the filtration barrier.

Newly discovered proteins that comprise the slit diaphragm junctional complex have been recently reviewed (Garg et al., 2007, Lowik et al., 2009, Tryggvason et al., 2006). They play a critical role in coordinating podocyte structure and function. Regardless of the debate concerning charge selectivity (Miner, 2008), GBM may be more than a fixed passive sieve (Salmon et al., 2009); in addition, podocytes are able to endocytose albumin, a process that appears to be statin sensitive (Eyre et al., 2007), and even to reverse filtration over a proportion of the glomeruli, suggesting a possible physiological role in the regulation of glomerular fluid flux across the glomerular barrier (Neal et al., 2007). New evidence has indicated that FcRn, an IgG and albumin transport receptor, is expressed in podocytes and

functions to internalize IgG from the GBM, so podocytes may play an active role in removing proteins from the GBM (Akilesh et al., 2008). Recent studies have also documented several polarity protein complexes in podocytes such as the partitioning defective 3 (PAR3), partitioning defective 6 (PAR6) and atypical protein kinase C complex and have suggested an essential role for normal podocyte morphology and differentiation, suggesting that polarity signaling pathways may be involved in the regulation of glomerular development, slit diaphragm targeting and apico-basolateral molecular distribution (Simons et al., 2009).

These findings indicate a close connection of podocytes with adjacent components within the glomerular filtration barrier, especially with endothelial cells (Eremina et al., 2007). Signaling pathways in the “crosstalk” between podocytes and other adjacent cells (such as endothelial and mesangial cells) could play an important role in normal glomerular physiology and in the progression of glomerular diseases.

3. MUTATIONS OF PODOCYTE COMPONENTS IN HEREDITARY PROTEINURIA SYNDROM

Mutations in podocyte components are associated with hereditary renal diseases. Since the slit diaphragm and associated proteins regulate podocyte actin dynamics, mutations can alter podocyte functions, leading to proteinuria. Cytoskeleton de-organization also disrupts podocyte integrity, and alterations in transcriptional factors can lead to altered expression of podocyte-specific proteins and result in aberrant podocyte function (Chugh, 2007). The list of hereditary proteinuria syndromes associated with the mutation of podocyte molecules in slit diaphragm, cytoskeleton and nuclear transcriptional factors (Table I) continues to expand.

In recent years, genetic analysis of congenital and early childhood-onset human nephrotic syndrome and gene manipulation in animal experiments has greatly expanded our knowledge of slit diaphragm proteins (Mundel and Shankland, 2002). Slit diaphragm molecules are critical in maintaining the filtration barrier of the kidney and preventing protein loss into the urine. In the 1990’s, positional cloning of the gene responsible for congenital nephritic syndrome of the Finnish type led to the identification of nephrin (Kestila et al., 1998), which directly links podocyte junctional integrity to actin cytoskeletal dynamics (Asanuma et al., 2007). Nephrin is a transmembrane protein with a large extracellular portion of eight immunoglobulin-like domains. Neighboring nephrin molecules extend toward each other from adjacent foot-processes and interact through homophilic dimerization to form a zipper-like arrangement. The gene (NPHS1) is located on chromosome 19 and encodes a 136 kDa protein product (Kestila et al., 1998). Subsequently, CD2-associated protein (CD2AP), an adaptor molecule involved in podocyte homeostasis was confirmed to be another slit diaphragm component responsible for congenital nephrotic syndrome in mice deficient in the protein (Shih et al., 1999). However, mutations of CD2AP in human do not exclusively cause focal segmental glomerulosclerosis (Wolf and Stahl, 2003). Mutation of a gene, NPH2, associated with autosomal recessive steroid-resistant nephrotic syndrome was mapped to 1q25-31 found to be exclusively expressed in the podocytes of fetal and mature kidney glomeruli; it encodes an integral membrane protein, podocin (Boute et al., 2000). Winn et al. and Reiser et al. (Reiser et al., 2005, Winn et al., 2005) reported the identification of a mutation in TRPC6, a member of the transient receptor potential superfamily of non-selective cation channels (Montell, 2005, Ramsey et al., 2006) in patients with an autosomal dominant pattern of adult onset FSGS. TRPC6 is expressed in podocytes and co-localizes with nephrin, podocin and CD2AP (Reiser et al., 2005). The calcium-dependent phosphorylation and disassembly of the slit diaphragm is believed to

underlie the pathogenic effects of TRPC6 mutations (Tiruppathi et al., 2002) (Schlondorff and Pollak, 2006).

In summary, the slit diaphragm represents a signaling platform that contributes to the regulation of podocyte function in health and disease (Benzing, 2004) (Huber and Benzing, 2005). An increasing number of proteins that comprise the slit diaphragm has been identified. Some proteins, such as FAT (Inoue et al., 2001, Jalanko et al., 2001), ZO-1(Kurihara et al., 1992), P-cadherin (Reiser et al., 2000) (Xu et al., 2005) and PLCE1 (Hinkes et al., 2006) have also been identified as SD components. All these proteins participate in intracellular signaling networks to support cytoskeletal organization, cell adhesion, and cell polarity; not surprisingly mutations in mice have shown effects on podocyte function and recent studies have indicated that PLCE1 mutations are a cause of congenital nephrotic syndrome in humans (Hinkes et al., 2006), although there may be additional genetic causes of FSGS (Gbadegesin et al., 2009).

The actin cytoskeleton anchors cell-cell contact and cell-matrix proteins, providing mechanical stability and a high dynamic capacity to respond to physical stress (Endlich and Endlich, 2006). Several human genetic diseases as well as transgenic mouse models provide evidence for a crucial role of the actin cytoskeleton in podocytes. *In vitro*, mutant alpha-actinin-4 binds filamentous actin (F-actin) more strongly than does wild-type alpha-actinin-4, an actin crosslinking protein. Mice with mutations in the gene encoding alpha-actinin-4 (ACTN4) develop autosomal dominant focal segmental glomerulosclerosis (Kos et al., 2003, Michaud et al., 2003). In human, mutations in ACTN4 cause or increase susceptibility to focal segmental glomerulosclerosis (Kaplan et al., 2000). Some other specific proteins may also play important roles in actin filament bundling in foot processes, such as synaptopodin (Asanuma et al., 2005), palladin (Parast and Otey, 2000) and the non-muscle myosin heavy chain II A (NMMHC-IIA), a cytoskeletal contractile protein. Human Myosin heavy chain 9 (MYH9) gene encodes NMMHC-IIA and is mainly expressed in podocytes and peritubular vessels in the mature kidney (Arrondel et al., 2002); its mutation is responsible for Fechtner's syndrome (nephritis, deafness, congenital cataracts, macrothrombocytopenia, and characteristic leukocyte inclusions) (Seri et al., 2000). New genetic evidence suggests that MYH9 gene alterations are associated with an increased risk for developing FSGS and hypertensive nephrosclerosis in African Americans (about two to four times greater risk of nondiabetic end stage renal diseases compared to European Americans) (Kao et al., 2008).

In summary, the highly dynamic foot processes of podocytes contain an actin-based contractile apparatus comparable to that of smooth muscle cells or pericytes. The convergence of multiple interconnected signaling pathways from the cell membrane of different foot process domains on the podocyte actin cytoskeleton involves not only actin binding proteins, but also its signaling pathway, such as Rho family GTPases. Mutations affecting several podocyte proteins lead to rearrangement of the actin cytoskeleton, disruption of the filtration barrier and development of proteinuric renal disease (Faul et al., 2007).

A growing numbers of podocyte-expressed transcriptional factors that regulate podocyte function under normal and disease conditions have been identified. Wilm’s tumour1 (WT-1), a zinc finger protein, was the first recognized gene that is a podocyte transcriptional factor linked with human renal diseases: constitutional mutations of the WT1 gene are found in most patients with Denys-Drash syndrome, or diffuse mesangial sclerosis, associated with pseudohermaphroditism and/or Wilms tumor (Barbaux et al., 1997, Jeanpierre et al., 1998). Varying degrees of loss of podocyte WT1 content (Barisoni et al., 1999) or gene mutations (Orloff et al., 2005) are noted in specific forms of focal glomerulosclerosis. The most

dramatic reduction in WT1 expression in human disease is seen in the collapsing variant of FSGS. Two WT1 associated proteins, WT1-interacting protein and brain acid soluble protein 1, are also expressed in the podocyte and function as corepressors of WT1 transcriptional factor activity. WT1-interacting protein monitors slit diaphragm protein assembly as part of a multiprotein complex, linking this specialized adhesion junction to the actin cytoskeleton, and shuttles into the nucleus after podocyte injury (Srichai et al., 2004). Mutations underlying the development of nail-patella syndrome have been linked to the LIM homeobox transcription factor 1β (Lmx1b) gene, which is expressed in podocytes (Dreyer et al., 1998) (McIntosh et al., 1998) (Vollrath et al., 1998). The Lmx1b protein appears to be particularly important during early embryonic development of the limbs, kidneys, and eyes. The findings in patients are corroborated by the fact that the inactivation of Lmx1b in mice also leads to a phenotype strongly resembling nail-patella syndrome (Chen et al., 1998, Sato et al., 2005) (Rohr et al., 2002). With continuing advancement in microarray array - based technology, large scale identification of additional target genes mediating podocyte-expressed transcriptional factors will soon be available (Chugh, 2007). It should also be noted that inherited defects in GBM and mitochondrial and lysosomal protein defects can also cause podocyte dysfunction, leading to glomerular diseases (Machuca et al., 2009, Moller et al., 2006).

4. THE ROLE OF PODOCYTE DISORDERS IN ACQUIRED GLOMERULAR DISEASES

Genotype-phenotype correlation and genetic molecular cloning have not only led to the discovery of the above mentioned gene mutations responsible for hereditary proteinuric syndrome but have also provided new insights into the potential role of podocyte disorders in non-congenital glomerular diseases. It is well known that podocytes are a major target in Minimal Change Disease and FSGS, and increasing evidence indicates that podocyte injury is also involved in a variety of other glomerular diseases, such as diabetic nephropathy, HIV nephropathy, membranous nephropathy and other acquired glomerular diseases (Mathieson, 2009).

Regardless of the etiology or pathologic classification, there are four major patterns of podocyte morphology alteration during glomerular diseases:

A. *Foot process effacement:* Foot process effacement represents an adaptive change in cell shape. Many factors may influence the actin cytoskeleton, including hypertrophy of the contractile apparatus, thereby reinforcing the supportive role of podocytes, mesangial support, glomerular pressure or impairment of GBM substructure and of podocyte-GBM-contacts (Shirato et al., 1996). In response, the podocyte actin cytoskeletion may be altered from parallel contractile bundles into a dense actin network (Drenckhahn and Franke, 1988). Foot process effacement requires the active reorganization of actin filaments (Shirato, 2002, Takeda et al., 2001). Loss of the foot processes of podocytes is characteristic of minimal change nephrotic syndrome and is also seen in many glomerulopathies associated with heavy proteinuria (Shirato, 2002).

B. *Apoptosis:* In nephrotic syndrome, foot process effacement is considered to be an early manifestation, which may be followed by a continuum of progressive podocyte damage characterized by vacuolization, pseudocyst formation, detachment of podocytes from the GBM and, finally, irreversible loss of podocytes (Kerjaschki, 1994). An apparent lack of podocyte regeneration following cell loss allows the denuded GBM to come into contact with Bowman’s capsule, resulting in synechiae formation, and initiating the development of a focally sclerotic lesion (Griffin et al., 2003) (Kriz et al., 1998). Depletion of podocytes is one of the

features in primary and secondary FSGS and may be mediated by a TGFβ - Smad, along with other signaling pathways (Schiffer et al., 2001).

C. *Arrested development:* The inability of differentiated podocytes to proliferate and repopulate the damaged glomerulus has been taken as a key factor in the progression of glomerular scarring (Kriz, 2003). In some cases, podocytes fail to complete maturation, accompanied by preserved proliferative activity, typical of immature phases of nephrogenesis. The glomeruli maintain an immature appearance with increased mesangial matrix, such as in diffuse mesangial sclerosis, as seen with WT-1 or PLCE1 defects (Barisoni et al., 2009). Based on the evidence that podocyte detachment from GBM was observed (Ng et al., 1984) and the degree of podocytopenia was related to the severity of glomerular dysfunction (Lemley et al., 2002) (Hara et al., 2007), the pathologic importance of podocytic injury has also been highlighted in IgA nephropathy, a disease characterized by mesangial proliferation and expansion (Lai et al., 2009).

D. *Dedifferentiation:* Podocytes originate from the metanephric mesenchyme and develop into postmitotic terminally differentiated epithelial cells (Kreidberg, 2003). In most glomerular diseases, podocytes do not proliferate (Mundel and Shankland, 2002) (Kriz et al., 1998). One exception is human immunodeficiency virus (HIV)-associated nephropathy, in which podocytes may dedifferentiate, and proliferate (Barisoni et al., 1999), resulting in collapsing focal segmental glomerulosclerosis with proliferation of epithelial cells in Bowman's space. Injured podocytes regress to a more immature state and re-engage the cell cycle (Griffin et al., 2003, Nagata et al., 2003). Podocyte dysfunction appears to be a direct result of HIV-1 protein expression, specifically Nef and Vpr as well as specific host factors (Lu et al., 2007).

As mentioned, podocyte injury underlies most forms of proteinuric kidney diseases (Pippin et al., 2009). Based on the etiologic factors and morphologic features, Barisoni et al recently created a taxonomy of diseases with podocyte injury, termed podocytopathies. Each of these morphologic entities needs then to be classified according to etiology as idiopathic, genetically transmitted, or reactive/secondary. The taxonomy does not include the cellular lesion and tip lesion. They re-organized podocyte diseases into four major types, all of which are associated with variable degrees of foot process effacement (Barisoni et al., 2009):

A. *Minimal change nephropathy*, by definition with normal morphology on light microscopy and preserved podocyte number;

B. *FSGS*, defined by segmental solidification of the tuft, occasionally accompanied by hyalinosis, foam cells or adhesion to the Bowman capsule, and decreased number of podocytes;

C. *Diffuse mesangial sclerosis*, defined by the presence of mesangial sclerosis with or without mild mesangial proliferation, and mildly increased proliferative activity of podocytes;

D. *Collapsing glomerulopathy*, where by definition the glomerular damage and podocyte number is substantially increased with pseudocrescent formation.

This taxonomy includes more glomerular diseases associated with disorder of podocytes than previous classifications (Thomas, 2009).

No matter what is the initiating mechanism, podocyte injury is involved in many forms of glomerular disease. Compared with the single gene mutation-induced congenital podocyte diseases, the pathogenesis for acquired podocytopathies is more complex, since a variety of

pathophysiological stimuli may induce or predispose to podocyte diseases, including the underlying genetic profile, immune-mediated stresses, metabolic derangements, drugs, toxins, infections, hemodynamic changes, growth factors, and cytokines, to name but a few. Acquired podocyte diseases in diabetic nephropathy, passive Heymann nephritis, puromycin aminonucleoside nephrosis, doxorubicin nephrosis, liopolysaccharide, crescentic glomerulonephritis, and protein overload nephropathy have been identified in rodent models (Pippin et al., 2009). Both genetic and environment factors may affect susceptibility to podocyte injury:

A. *Gene variants or alterations in gene regulation:* Altered podocyte gene expression has been identified in patients with various human renal diseases, including minimal change nephropathy, FSGS, IgA nephropathy, lupus nephritis, and diabetic nephropathy (Koop et al., 2003). In addition multiple studies have linked podocyte gene variants to altered expression in diverse sporadic nephropathies, although in both situations, it is still controversial whether these podocyte alterations are “causes” or “consequences” of podocyte injury. In some cases, the “second hit” or gene-gene and gene-environment interaction is essential for determination of complex nephropathy phenotypes (Papeta et al., 2009). For example, CD2AP haploinsufficient mice do not develop overt nephropathy but have increased susceptibility to experimental glomerular injury or develop nephropathy in conjunction with a null allele in either the synaptopodin gene or the *Fyn* proto-oncogene (Kim et al., 2003) (Huber et al., 2006). It has also been found that mice over-expressing COX-2 in podocytes were predisposed to injury by doxorubicin (adriamycin) (Cheng et al., 2007) or puromycin (Jo et al., 2007). A mendelian locus on chromosome 16 has been found to mediate susceptibility to doxorubicin nephropathy in mice (Zheng et al., 2005). Genetic susceptibility was also recognized in HIV-nephropathy (Rosenstiel et al., 2009). A survey of the podocyte transcriptional response to HIV1 associated nephropathy-predisposing alleles demonstrated the importance of underlying genotype and environment in interpreting the relationship of the gene expression profile to nephropathy (Papeta et al., 2009). In these circumstances, genetic susceptibility represents a compensated state that is unmasked upon exposure to additional genetic or environmental insults (Papeta et al., 2009).

B. *Systemic and environmental insults:* Recently Pippin et al. reviewed rodent models for acquired podocyte diseases that were induced by toxins and drugs (puromycin aminonucleoside, adriamycin, liopolysaccharide), immune alterations (both active and passive models) and protein overload (Pippin et al., 2009), suggesting a pathogenic role of environmental insults. Most components of the renin-angiotensin-system (RAS) exist in podocytes (Velez et al., 2007); podocytes are not only a local source of angiotensin II production, but are also a target for its deleterious effects (Durvasula and Shankland, 2006). In addition, altered RAS activity is a major mediator of hemodynamic influences on podocytes. Altered podocyte function is a characteristic of diabetic nephropathy (DN) (Kanwar et al., 2008) (Marshall, 2005) (Marshall, 2007. Hyperglycemia and haemodynamic abnormalities, oxidative stress are key factors underlying its pathogenesis. Advanced glycation end-products (AGEs) are heterogeneous groups of macromolecules that are normally formed non-enzymatically and their accumulation is implicated in the pathogenesis and progressive of DN (Bierhaus et al., 1998). Recently the AGEs receptor, RAGE, has been proposed as a biomarker and potential therapeutic target for DN (Ramasamy et al., 2009) (D'Agati et al., 2009). RAGE is a multi-ligand signal transduction receptor, belonging to the immunoglobulin superfamily. In the kidney RAGE is highly expressed on normal podocytes and is up-regulated in diabetic nephropathy, especially on podocytes

(Tanji et al., 2000). RAGE does not promote the uptake and removal of AGE, but AGE-ligation to RAGE induces inflammation through persistent activation of the proinflammatory transcription factor, nuclear factor kappa-B (NF-κB) (Bierhaus et al., 2005, Bierhaus and Nawroth, 2009). Protective effects of RAGE blockade or knockdown have been shown in diabetic animal models (Wendt et al., 2003) (Tan et al., 2007).

In response to patho-physiological stimuli, glomerular mesangial cells, podocytes and endothelial cells may undergo proliferation, de-differentiation, hypertrophy, senescence, apoptosis or necrosis. No matter where the injury initiated, these cells might crosstalk to each other during the disease progression. Here we will concentrate on the interaction between podocytes and endothelial or mesangial cells:

A. *Podocytes and endothelial cells: In situ* hybridization and immunohistochemical analyses define the podocyte as the site of glomerular VEGF production *in vivo*, while both glomerular endothelial cells and podocytes express VEGF receptors (Cui et al., 2004). VEGF (more accurately, its important subtype: VEGF-A) appears to be critical for the maintenance of capillary integrity, particularly in the glomerulus. In normal animals, systemic blockade of VEGF-A action is associated with endothelial cell damage, reduced nephrin expression and proteinuria (Sugimoto et al., 2003). VEGF-A is essential for kidney development, and loss of even one of the VEGF-A alleles in podocytes leads to glomerular capillary endothelial cell dysfunction and proteinuria. In contrast, podocyte over-expression of the longer splice VEGF A isoform, mouse VEGF 164, which contains a highly basic heparin-binding domain, leads to collapsing glomerulopathy and renal failure (Eremina et al., 2003). Up-regulated VEGF-A was reported in diabetes, and blockade of VEGF signaling ameliorates diabetic albuminuria in mice (Sung et al., 2006). Therefore, both deficiency and excess of VEGF appear to be detrimental to the physiological integrity of glomerular capillaries. Paracrine VEGF-A signaling occurs between podocytes and adjacent endothelial and mesangial cells, which express VEGF receptors 1 and 2 (Ferrara et al., 2003). Immuno-gold electron microscopic studies showed a clear concentration gradient of labeled VEGF particles from glomerulus to endothelial cells, with VEGF being clearly apparent on the endothelial side of the glomerular barrier (Guan et al., 2006). Recently Eremina et al reported that six patients treated with bevacizumab, a humanized monoclonal VEGF antibody developed glomerular disease characteristic of thrombotic microangiopathy (Eremina et al., 2008). This study along with the identical histological lesion induced by podocyte-specific deletion of VEGF in adult mice (Eremina et al., 2008) provides robust evidence for the effects of podocyte-derived VEGF on the adjacent glomerular endothelium in the mature glomerulus.

VEGF could be a potential activator of transient receptor potential ion channel (TRPC) (Schlondorff and Pollak, 2006), since it may induce the TRPC dependent calcium influx into endothelial cells and change in vascular permeability (Jho et al., 2005). Both podocytes and endothelial cells have angiotensin (AT) 1 and 2 receptors and RAGE. Angiotensin II signaling, AGE–RAGE interaction and ROS generation can stimulate podocyte VEGF mRNA expression (Okamoto et al., 2002) (Wendt et al., 2003). A number of other factors in the podocyte, such Nox4 (Brown and Griendling, 2009), Notch (Niranjan et al., 2009), CXCL12 (Sayyed et al., 2009), MCP-1 (Tesch, 2008), TGFβ (Barisoni and Mundel, 2003) and COX-2/prostaglandins (Pavenstadt, 2000) etc. are also potential candidates in mediating and signaling this interaction (Fig. 1).

B. *Podocytes and mesangial cells:* Three-dimensional reconstruction of glomeruli by electron microscopy provided physiologic evidence for “back-flow” across the GBM by increased renal perfusion pressure, which implied that growth factors and cytokines produced by the podocyte can access receptors on endothelial and mesangial cells (Neal et al., 2005) (D'Agati et al., 2009, Salmon et al., 2009). It has been shown that mesangial cells bear RAGE and VEGF and angiotensin receptors, especially under pathologic conditions. VEGF is also required for mesangial cell migration and survival (Eremina et al., 2006). There is evidence that the TGFβ - induced secretion of connective tissue growth factor and VEGF by podocytes acts as a paracrine regulatory mechanism on mesangial cells, which may cause mesangial matrix accumulation culminating in the development of glomerulosclerosis (Lee and Song, 2009). Podocyte-derived ROS and local podocyte RAS activation may also promote injury. On the other hand, TGFβ secreted as latent complexes by mesangial cells is stored in the mesangial matrix, from which soluble forms of latent TGFβ are released and localized to the podocyte surface in chronic glomerular disease (Lee and Song, 2009). Numerous mediators/ pathway may be involved in both podocytes and mesangial cells injury in response to hyperglycemia or glomerular hypertension, and they may contribute to the “crosstalk” between those cell types (Gruden et al., 2005).

4. CAN PODOCYTES BE REPAIRED?

Since the process from podocyte injury to sclerosis can be remarkably rapid, and the rate of progression depends upon the degree of initial podocyte injury (Ichikawa et al., 2005), exploration of novel therapeutic strategies to block this vicious cycle and enhance podocyte survival seems imperative. In the mature glomerulus, podocytes have a low level of DNA synthesis and do not readily proliferate under normal conditions (Marshall and Shankland, 2005). Traditionally podocyte proliferation is not considered to be a viable repair mechanism, although the ability to regenerate foot process architecture is an important component of repair in glomerular diseases (Quaggin and Kreidberg, 2008). Recent studies have raised the possibility that a population of stem cells might differentiate into, and replace, podocytes lost during injury or with normal aging. There is no evidence for one master stem cell in the kidney that can recapitulate development of all cell types (Little and Bertram, 2009). Although rare bone marrow-derived cells have been identified in the periphery of the glomerular tuft, there is not compelling evidence at present that bone marrow-derived stem cells play a significant role to repopulate the podocytes directly, and it has been argued that these cells simply act on an existing endogenous cell population, potentially a renal stem cell population, to repair renal architecture and function (Little and Bertram, 2009). Bussolati et al. (Bussolati et al., 2005) isolated potential progenitors from adult human kidney on the basis of expression of the stem cell marker CD133. Rodent research using careful immunohistochemistry and a transgenic animal model that differentially tagged the parietal epithelium vs. the glomerular visceral epithelium indicated the presence within the Bowman's capsule of podocyte progenitor cells that migrate over the basement membrane of the Bowman's capsule to ensure a constant re-supply of podocytes (Appel et al., 2009). Ronconi et al. isolated a $CD133^{+}$, $CD24^{+}$ population of cells from the Bowman's capsule of human kidneys and showed, upon reintroduction into an immuno-deficient animal model of renal damage, these cells contribute both to podocytes and to tubular epithelium. However, there is no definitive proof in either of these studies that these cells represent stem cells. Neither is there yet proof that podocyte localization in recipient xenotransplants is not due to fusion. However, these exciting results indicating that they are responsible for podocyte turnover is a revelation in nephrology (Ronconi et al., 2009, Sagrinati et al., 2006).

5. CONCLUSION AND PERSPECTIVE

In the past decade, there has been enormous progress in understanding the physiologic and pathophysiologic function of the podocyte. Development of powerful new molecular, cellular and animal tools has greatly enhanced our knowledge of podocyte biology and increased our understanding of underlying mechanisms of podocyte diseases. Podocytes are no longer considered to be simply a passive target but can also be a mediator of continuing glomerular injury (Fig.1). Finally, although highly differentiated podocytes have limited proliferative capacity under normal conditions, new experimental findings suggest a potential role in podocyte regeneration by progenitor cells residing within the Bowman's capsule, which may open a new era for the treatment of chronic glomerular diseases.

Cell facts

- Podocytes are highly differentiated cells with a unique architecture that includes a cell body, major processes and foot processes bridged by slit diaphragms (SD).
- Mutations in podocyte components are associated with hereditary renal diseases.
- Podocyte disorders also play a crucial role in a broad spectrum of acquired glomerular diseases.
- A potential role for podocyte regeneration may open a new era for the treatment of chronic glomerular diseases.

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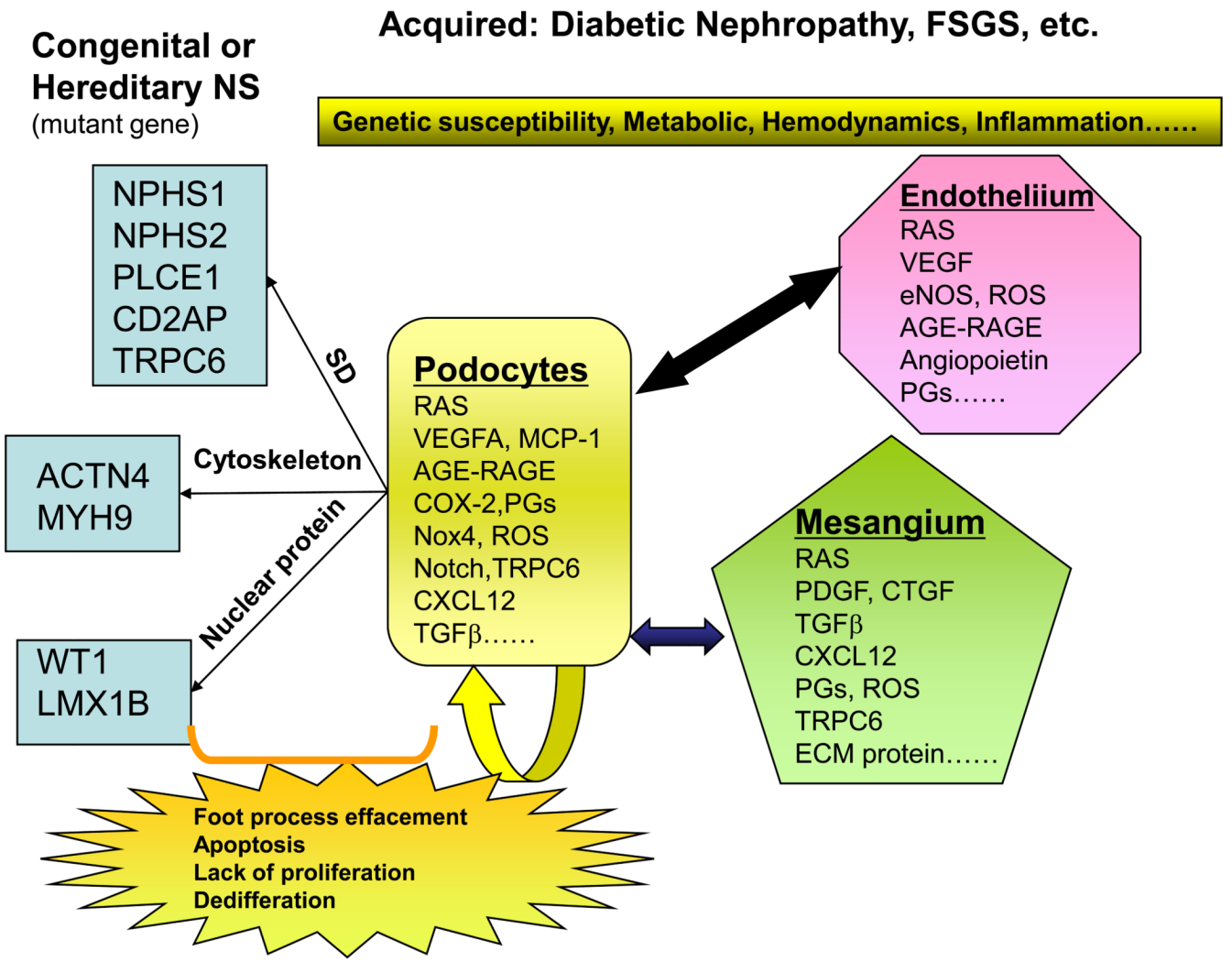

Fig. 1.

Podocyte disorders in hereditary and acquired proteinuria syndromes. Representative mutations linked to hereditary proteinuria syndromes are shown in the left. An individual's genetic profile may lead to an increased susceptibility to development of podocyte diseases; environmental factors, including metabolic, homodynamic, immune, infection and inflammatory alterations, could trigger the onset of the diseases. Injured podocytes could spread injury to the healthy ones and other adjacent/ distant cells, like endothelial and mesangial cells in a vicious cycle. Many molecules/proteins are involved in the "cross-talk" between cells during the disease progression. Injured podocytes may have foot process effacement and slit diaphragm alterations as an early manifestation of injury and subsequently undergo detachment, apoptosis, impaired proliferation and de-differentiation. SD: Slit diaphragm complex; RAS: renin-angiotensin system; AGE: Advanced glycation end-products; RAGE: receptor for AGEs; PGs: prostaglandins; ECM: extracellular matrix; FSGS: focal segmental glomerular sclerosis; NS: nephrotic syndrome.

Table I

Genetic glomerular diseases and their associated mutated podocyte genes

Gene	Protein	Associated Disease	Reference
Slit Diaphram			
NPHS1	Nephrin	Finnish type NS	(Kestila et al., 1998)
NPHS2	Podocin	Steroid-resistant NS	(Boute et al., 2000)
CD2AP	CD2 associated protein	NS in KO Mice	(Shih et al., 1999)
TRPC6	TRPC6	FSGS	(Winn et al., 2005) (Reiser et al., 2005)
PLCE1	Phospholipase Cε1	Early-onset NS with ESRD	(Hinkes et al., 2006)
Cytoskeleton			
ACTN4	α Actin 4	FSGS	(Kaplan et al., 2000)
MYH9	NMMHC-A	FSGS	(Kao et al., 2008)
Nuclear protein			
WT1	Wilms' tumor 1	Denys Drash syndrome	(Jeanpierre et al.,1998)
LMX1B	LIM-homeodomain protein	Nail-patella syndrome	(Rohr et al., 2002)

NS: nephritic syndrome; FSGS: focal segmental glomerular sclerosis; ESRD: end stage renal disease; KO: knock-out.