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Cells in focus

The glomerulus – a view from the outside – the podocyte

Huifang Cheng*, Raymond C. Harris

Division of Nephrology, Departments of Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA

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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.

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.

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 1990s, 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., 1997a,b) 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 "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,

* Corresponding author at: Division of Nephrology, S3223 MCN, Vanderbilt University School of Medicine, Nashville, TN 37232-2372, USA. Tel.: +1 615 322 7572.
E-mail address: huifang.cheng@vanderbilt.edu (H. Cheng).

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Table 1
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' tumor1	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.

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 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 syndrome

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 1) 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 1990s, 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,