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Human genetics of nephrotic syndrome and the quest for precision medicine

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Abstract

Purpose of review—In this review, we take a combined membrane biologist's and geneticist's view of the podocyte, to examine how genetics have informed our understanding of membrane receptors, channels and other signaling molecules affecting podocyte health and disease.

Recent findings—An integral part of the kidney, the glomerulus is responsible for the kidney's filter function. Within the glomerulus, the podocyte is a unique cell serving a critically important role: it is exposed to signals from the urinary space in Bowman's capsule, it receives and transmits signals to/from the basement membrane upon which it elaborates, and it receives signals from the vascular space with which it also communicates, thus exposed to toxins, viruses, chemicals, proteins and cellular components or debris that flow in the blood stream. Our understanding of how podocytes perform their important role has been largely informed by human genetics, and the recent revolution afforded by exome sequencing has brought a tremendous wealth of new genetic data to light.

Summary—Genetically defined, rare/orphan podocytopathies, as reviewed here, are critically important to study as they may reveal the next generation targets for precision medicine in nephrology.

Keywords

actin cytoskeleton; calcium; TRPC5; arhgdia; arhgap24

Introduction: The podocyte at the center of glomerular function

The kidney glomerulus works hard with every cardiac cycle to filter blood into an ultrafiltrate that will ultimately become urine. The glomerulus consists of a glomerular tuft and Bowman's capsule and the basic unit of the glomerular tuft is a single capillary. The glomerular basement membrane (GBM) provides the primary structural scaffold for the

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Conflict of interest

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glomerular tuft. Endothelial and smooth muscle-like mesangial cells providing capillary support are located inside the GBM, while podocytes are attached to the outer aspect of the GBM. There are therefore four resident cell types in the glomerulus: endothelial cells, mesangial cells, parietal epithelial cells of Bowman's capsule, and podocytes[1].

Podocytes are pericyte-like cells with a complex cellular organization consisting of a cell body, major processes and foot processes (FPs). Podocyte FPs elaborate into a characteristic interdigitating pattern with foot processes of neighboring podocytes, forming in between the filtration slits that are bridged by the glomerular slit diaphragm (SD)[1]. Podocyte FPs and the interposed SD cover the outer aspect of the GBM and play a major role in establishing the selective permeability of the glomerular filtration barrier, which explains why podocyte injury is typically associated with marked albuminuria associated with the nephrotic syndrome [1].

Podocytes are highly differentiated cells with limited capability to undergo cell division in the adult and the loss of podocytes is a hallmark of progressive kidney disease. The function of podocytes is largely based on the dynamic regulation of their complex cell architecture, in particular the FP structure[1]. Over the past two decades, there has been a growing understanding of the role of specific proteins, which affect critical podocyte functions, a scientific area largely driven by human genetics and the technological advances in the field of genomics [1]. Here we aim to provide insight into the genetics of nephrotic syndrome, which have taught us much of what we know about what regulates podocyte structure and function in health and disease.

Podocyte injury is the hallmark of proteinuria and glomerular disease

The common feature in many forms of human and experimental glomerular disease, such as minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranous glomerulopathy (MGN), diabetic nephropathy (DN), and lupus nephritis [2, 3], is podocyte injury. The best-characterized pattern of injury involves a reorganization of the FP actin cytoskeleton, which leads to FP effacement and SD disruption [4, 5]. The transformation of the actin cytoskeleton from parallel contractile bundles [6] into a dense mesh, and loss of the normal interdigitating FP pattern leads to proteinuria [3].

The sequence of events that mediates FP effacement and proteinuria (Fig. 1) follows a canonical pattern, which results over time in further phenotypic changes such as podocyte hypertrophy and ultimately podocyte death (Fig. 1). Many laboratories and many years of hard work have revealed certain patterns of injury including: i) changes in SD structure or function [7, 8], ii) interference with the GBM or the podocyte:GBM interaction [9-15], iii) dysregulation of podocyte calcium homeostasis [16-21] iv) *de novo* dysfunction of the podocyte actin cytoskeleton [5, 20-27] v) modulation of the negative surface charge of podocytes [28-30], vi) activation of innate immunity pathways such as B7-1/CD80 signaling [31-34], vii) upregulation of CatL-mediated proteolysis [35-39] and viii) disturbances in the transcriptional regulation of podocyte function [40]. Early podocyte injury is reversible, if the actin cytoskeleton is repaired, allowing FPs to ramify once again into their interdigitating pattern (Fig. 1). However, sustained, chronic podocyte injury can lead to the

loss of glomerular function and ultimately kidney failure. Therefore strategies to preserve podocytes must be at the center of any and all targeted, precision medicine approaches to treat nephrotic syndrome and other glomerular diseases [41, 42].

The SD: a signaling complex revealed through human genetics

The podocyte SD is a complex signal transduction unit with characteristics of a modified adherens junction spanning the 30-50 nm wide filtration slits [43]. The extracellular portion of the SD is made up of rod-like units, thought to be composed of the extracellular domains of various transmembrane proteins such as nephrin and FAT [44]. These rods are connected by a linear bar, forming a zipper-like pattern, which leaves pores with the same size as or smaller than albumin [44]. The SD's cytoplasmic portion contains a region of detergent resistant [44] electron dense material, which is reminiscent of the highly insoluble specialization of the submembranous actin cytoskeleton in neurons known as the postsynaptic density (PSD) [45]. The PSD is known to contain multiple receptors and ion channels linked through a multitude of adaptor proteins to the cytoskeletal core, forming a large protein network [46]. Similarly, at the SD, we have now learned that IgG like molecules such as nephrin[47], ion channels such as TRPCs [48], receptors[16], integrins[49] and other membrane proteins are connected to actin via a variety of adaptor and effector proteins[1]. The dysruption of SD structure or function is a common theme in many kidney diseases arising at the level of the podocyte [50]. The SD is thought to function as a key sensor for and regulator of the adaptations in FP shape and length [47, 51]. For example, the movement of each FP needs to be precisely coordinated with the FPs of neighboring podocytes to ensure the integrity of the filtration barrier. This is likely to be achieved through functional coupling of opposed FPs, which generates signaling cascades on both ends of the SD. Simply put, this multiprotein network likely serves a far more complex role as a signaling platform, rather than a simple physical sieve[1].

A broadly studied membrane protein of the SD, the one which has allowed us to best understand this intricate cellular structure, is nephrin [47]. Mutations in the NPHS1 gene encoding for nephrin have been identified as the cause of congenital nephrotic syndrome of the Finnish type [52]. Nephrin has a single transmembrane domain, a short intracellular tail and a long, immunoglobulin-like extracellular moiety, which is thought to align parallel to the extracellular domains of neighboring nephrin molecules. Through its intracellular domain, nephrin is connected to the actin cytoskeleton by several adapter proteins and plays a pivotal part in the regulation of podocyte actin dynamics [24, 51]. Among others (reviewed in detail in [51]), a recently discovered signaling pathway couples nephrin to the actin cytoskeleton via the adaptor protein Nck [25, 53, 54]. After nephrin phosphorylation by Fyn [8], Nck binds to phospho-nephrin and N-WASP [25, 53], activating the Arp2/3 complex, a major regulator of actin dynamics [24, 25, 51, 53]. Recent work has also shown that Fyn phosphorylation of nephrin promotes activation of phosphoinositide 3 kinase (PI3K) and Rac1 activity [55]. Proteosomal degradation of Nck1 was also shown to regulate RhoA activity in podocytes, thus once again linking nephrin to the actin cytoskeleton[54].

Another essential protein of the SD is podocin, a protein encoded by the gene NPHS2, which is associated with steroid-resistant nephrotic syndrome (SRNS), often with a variable

onset of disease ranging from infancy to adulthood, and severe proteinuria resistant to corticosteroids [4, 56-58]. Through immune electron microscopy, it has shown that podocin localizes to the podocyte FP membrane at the insertion site of the slit diaphragm[47]. Podocin interacts with two other important components of the SD, which were revealed by human genetics, namely the adaptor molecule CD2AP and nephrin, thus serving in the structural organization of the SD[47].

Human genetics reveal the causes of podocyte injury leading to disease

Human genetics, and the genomic revolution afforded by deep sequencing technology in recent years in particular, have fueled our progress toward a molecular understanding of the SD and the modulators of FP architecture. In the last fifteen years, human genetic studies revealed that mutations in genes encoding nephrin [52], podocin [58], phospholipase C epsilon [59], coenzyme Q10 biosynthesis monooxygenase 6 (CoQ6) [60], aarF domain containing kinase 4 (ADCK4) [61], or Arhgdia [62] give rise to early onset proteinuria. Due to rapid exome sequencing and analysis, the list at this time is growing at an ever-faster rate. Of note, all these mutations are either direct or indirect regulators of the podocyte actin cytoskeleton, with the exception of CoQ6 and ADCK4, which appear to regulate mitochondrial CoQ10 biosynthesis, but nevertheless appear to be required for proper cytoskeletal dynamics during podocyte migration [60, 61].

The podocyte actin cytoskeleton theme continues with adult-onset familial diseases such as focal segmental glomerulosclerosis (FSGS), which is associated with mutations in genes encoding α-actinin 4 [5], CD2AP [63], INF2 [64], TRPC6 [48, 65, 66], Arhgap24 [67], anillin [68] and synaptopodin [69]. Even mutations in LMX1b, a transcription factor for collagen, result in podocyte cytoskeletal abnormalities due to impaired cell adhesion to the abnormal GBM [70]. Similarly, mutations in Laminin β2, another component of the GBM, lead to podocyte injury and proteinuria [71]. Finally, recent exome sequencing as well as a whole-genome linkage analysis revealed *MYO1E* mutations, encoding for a mutant form of non-muscle class I myosin, in childhood proteinuric disease and FSGS [72, 73].

Mouse genetic studies have revealed that additional proteins regulating the plasticity of the podocyte actin cytoskeleton such as Rho GDIα [74], podocalyxin [75], FAT1 [76], Nck1/2 [25, 53, 54], synaptopodin [77, 78] and cofilin [79] are also of critical importance for sustained function of the glomerular filtration barrier. Most impressively, all these mutations, whether mouse or human, appear to coalesce to specific and distinct signaling modules or compartments, with podocyte actin regulation rising to the top of all pathways dysregulated by genetic causes of nephrotic syndrome.

Beyond familial causes of nephrotic syndrome, human genomics applied to large population studies have revealed common variations in a number of genes that predispose or confer susceptibility to proteinuric kidney disease. These gene polymorphisms are not yet directly linked to podocyte-specific defects, but this is an area of active research. A large locus containing numerous genes was recently identified in African American populations [80, 81]. Initial studies revealed *MYH9* as a likely gene candidate in this locus. This was an attractive hypothesis given previous work showing that *MYH9* is responsible for two genetic

causes of proteinuria, known as Epstein and Fechtner syndromes [82]. Interestingly, further work revealed that the likely candidate gene conferring risk for kidney disease is *APOL1*. The gene encodes Apolipoprotein L1, a molecule previously known for its trypanolytic properties, which confer an evolutionary advantage for its prevalence in an African American population [83]. More recent work has begun to unravel the role of APOL1 in kidney disease progression [84-86], in what may be the first example of a sophisticated Genome Wide Association Study (GWAS) approach for the identification of a tractable target for kidney disease therapeutics. Furthermore, common variations in *GPC5* encoding glypican 5 also associate with acquired nephrotic syndrome [87]. Further work is likely to reveal how we can best utilize this knowledge to diagnose and treat patients with nephrotic syndrome.

Conclusions

A central mission for modern medicine is the development of precision therapeutics. In recent years, cancer therapies have been clearly at the leading edge of this effort, while nephrology has unfortunately lagged behind most other fields on the path to precision medicine [41]. As reviewed here, rather than defining diseases based on symptoms (nephrotic syndrome), we can now use genomics to provide molecular definitions for diseases (for example, Rac1-activating mutation-mediated nephrotic syndrome as in patients with Arhgdia [62] or Arhgap24 [67] mutations), which can in turn guide our therapies, hoping to avoid unnecessary toxicities and complications. Much work lies ahead, however, as we attempt to develop precise, genetically inspired therapies, which will allow us in nephrology to fulfill a timely quest for precision medicine.

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Key Points

- Human genetics have revealed the podocyte as essential to filter barrier function in the kidney

- The orthogonal convergence of genetics and cell biology provide the best available rationale for targeted treatments for proteinuric kidney disease.

- Human mutations reveal the regulation of the podocyte actin cytoskeleton as a top priority target for future precision medicines for nephrotic syndrome

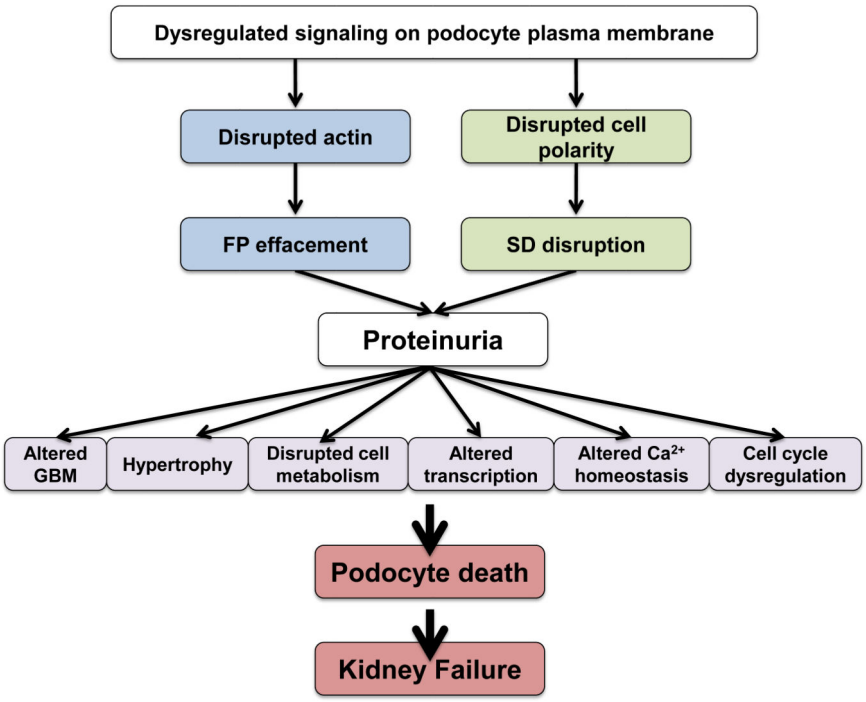

Figure 1. Dysregulated podocyte signaling causes proteinuria and ultimately kidney failure

Dysregulated signaling at the plasma membrane may lead to morphological changes that are reversible. Therefore, proteinuria may arise, with FP effacement, but if the upstream injurious signals are reversed, the cell morphology can revert back to physiologic patterns. Persistence of podocyte injury is manifest in the activation of cellular processes that lead to irreversible changes such as loss of adhesion to the GBM, cell hypertrophy, changes in transcription, disrupted metabolic pathways, aberrant calcium signaling and cell cycle dysregulation. These irreversible changes can cause podocyte death. The resulting loss of podocytes will ultimately lead to irreversible glomerulosclerosis and kidney failure.