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Human Genome & Diseases: Review

Focal and segmental glomerulosclerosis

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Abstract. An increasing cause of end-stage renal disease is the pathological lesion focal and segmental glomerulosclerosis (FSGS). FSGS is characterized by proteinuria and frequently nephrotic syndrome with ensuing renal failure. The etiology remains unknown in the majority of individuals. The idiopathic form of FSGS is most common; however, secondary forms of FSGS do exist. There is a form of FSGS that is fulminant that frequently recurs after renal transplantation with an estimated frequency of approximately 30%, suggesting that the pathogenesis is not solely a result of intrinsic kidney disease. Recently, hereditary forms of the disease were recognized as well as those associated with other congenital syndromes. Known genetic causes of the hereditary form of this disease have been suggested to account for upwards of 18% of cases. This review will address recent discoveries of the genetic mechanisms of hereditary FSGS and the current interpretations of their interactions at the slit diaphragm.

Keywords. Familial focal segmental glomerulosclerosis, familial nephropathy, genetics, kidney; hereditary, TRPC6, podocin, nephrin, ACTN4.

Introduction

End-stage renal disease (ESRD) is a substantial cause of morbidity and mortality worldwide. A recent review of the available data suggests that focal and segmental glomerulosclerosis (FSGS) is a considerable cause of ESRD, accounting for up to 20% of dialysis patients [1, 2]. FSGS has been reported in all ethnicities; however, it accounts for 50% of unexplained nephrotic syndrome in blacks [3]. The diagnosis of FSGS requires the presence of areas of glomerular sclerosis and tuft collapse that are both focal (some glomeruli are affected but not all) and segmental (a segment of the glomerulus is affected). The clinical hallmarks include proteinuria, nephrotic syndrome and frequently the progressive loss of renal function. Segmental hyalinosis, glomerular deposits that are positive for immunoglobulin M and/or C3 by immunofluorescence microscopy as well as epithelial cell foot process effacement by electron microscopy are often seen but not required to make the diagnosis.

While the idiopathic form of FSGS is most common, secondary FSGS can occur in association with reflux nephropathy, obesity, HIV infection and sickle cell disorder as well as other medical conditions [4–6]. Recently, autosomal dominant and recessive forms of FSGS have been described as well as those associated with congenital syndromes [5, 7–16]. It is now thought that perhaps up to 18% of FSGS cases are due to familial disease [17]. Substantial progress has been made over the last decade by advances in molecular genetics technology and mapping, including high-throughput genotyping for genomic screening, that provide powerful tools for the analysis of renal diseases [7]. These insights have promoted additional understanding of the biologic basis of FSGS and podocyte structure, and function through the identification and understanding of genetic mutations associated with various familial forms.

The etiology of FSGS remains unknown in a majority of cases. There is an estimated recurrence rate of FSGS in

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approximately 30–40% of renal transplant patients, which suggests that the pathogenesis is not exclusively the result of intrinsic kidney disease. A 'circulating factor' that causes recurrent FSGS has been widely reported; however, the precise identification has not been made [18]. Steroid therapy is the principal treatment for idiopathic FSGS. However, the response rate is estimated at 30–50% at 10 years, with the persistence of nephrotic range proteinuria and the majority still reaching ESRD [19]. Findings from the North American FSGS Trial suggest better outcomes when cyclosporine (CsA) is combined with prednisone in individuals with steroid-resistant FSGS; the combination of these two drugs caused a greater reduction in proteinuria and longer preservation of kidney function [20]. The disparity in response of this disease process supports the existence of varying biologic mechanisms [19, 21]. Effective patient care will necessitate a greater understanding of the underlying pathogenetic mechanisms.

Current understanding of known genetic mutations

Nephrin

Studies of Mendelian forms of FSGS have provided some very useful insights into the pathophysiological mechanisms of this disease. Congenital nephrotic syndrome of the Finnish type (i.e. Finnish nephropathy), an autosomal recessive disease, characterized by massive proteinuria *in utero*, was initially described in 1956 by Hallman and colleagues [22]. While congenital nephrotic syndrome (CNF) is found predominately in Finns, it has been described in other ethnic groups in North America and Europe. Of interest, it also exists among Mennonites in Lancaster County, Pennsylvania [23]. Clinically, there is massive proteinuria *in utero* and up to 20–30 g/day of urinary protein. The mortality rate is high unless prompt treatment with nephrectomy and renal replacement therapy is initiated. A genome-wide linkage analysis localized the causative gene to chromosome 19q13.1 with the subsequent identification of disease-causing mutations in the nephrin gene (*NPHS1*) [24, 25].

Numerous mutations have been identified in the 26-kb gene [26]. Nephrin is in the immunoglobulin (Ig) superfamily and is a transmembrane adhesion molecule that localizes to signaling domains known as lipid rafts within the slit diaphragm of the podocyte [27–29]. It has been demonstrated to play a role in regulating signaling pathways [30, 31].

Two mutations termed Fin major (deletion at nucleotides 121 and 122 leading to a frameshift) and Fin minor (premature stop codon at amino acid 1109) cause 95% of the observed disease. As such, screening for these alleles in carriers is effective for early diagnosis. Recurrence of CNF can occur in 20–25% of children after transplantation; this recurrence is thought to be caused by anti-glomerular and anti-nephrin antibodies [32, 33].

Targeted disruption of the nephrin gene in mouse models for CNF mimic the human disease Also, interestingly, injection of mice with monoclonal antibodies to nephrin, such as mAb 5–1-6, produce massive amounts of proteinuria [34]. These antibodies are directed toward the extracellular domain of nephrin, highlighting the importance of nephrin and the slit diaphragm in the regulation of glomerular permselectivity. As has long been postulated, the importance of nephrin as a link in signaling pathways of the podocyte was recently illustrated [35]. These investigators found that the cytoplasmic tail of nephrin has conserved tyrosine-based motifs which bind Nck, an adaptor protein involved in signal transduction from receptor tyrosine kinases [34, 35]. When the Nck adaptor proteins were selectively deleted from podocytes in transgenic mice, the mice displayed growth abnormalities, albuminuria and failure of embryonic foot process formation and differentiation consistent with a CNF phenotype.

Podocin

Steroid-resistant nephrotic syndrome (SRNS) is another autosomal recessive form of nephrotic syndrome. *NPHS2*, located on chromosome 1q25-q31, is the gene that contains the causative mutations [36]. The onset of the disease is between 3 months and 5 years of age and has rapid progression to ESRD. Recurrence after renal transplantation is rare but appears to be highly dependent on the specific mutation. Pathology findings are also diverse, with descriptions ranging from minimal change to mesangial proliferation with IgM deposition to FSGS [37]. *NPHS2* mutations have now been widely reported in both autosomal recessive disease and in individuals with sporadic adult-onset nephrotic syndrome.

The gene product, podocin, is an integral 383-amino acid membrane protein of approximately 42 kD. In the kidney, it is exclusively expressed in podocytes [38]. *NPHS2* is part of the stomatin protein family, and has a single membrane domain forming a hairpin-like structure, with cytosolic N- and C-terminal domains [39]. Podocin has been localized to the base of the foot processes on either side of the slit diaphragm [39]. It is associated with lipid rafts and oligomerizes in the slit diaphragm forming membrane invaginations. It then appears to recruit nephrin and CD2-associated protein (*CD2AP*) to these microdomains [40]. Podocin also acts as a structural protein, helping to form and align the slit diaphragm [41]. Mice deficient in podocin develop proteinuria and die soon after birth from kidney failure caused by mesangial sclerosis [42]. Certain mutations in podocin are thought to cause a failure of podocin to recruit nephrin to lipid rafts, either because of retention in the endoplasmic reticulum or inability to associate with lipid rafts in the plasma membrane [43].

Alpha-actinin 4

Alpha-actinin 4 (*ACTN4)* mutations cause hereditary FSGS in an autosomal dominant pattern. Autosomal dominant FSGS is typically a disease of adults, with widely variable age of onset, severity and progression to ESRD. Through linkage analysis, the first reported locus for autosomal dominant FSGS mapped to chromosome 19q13, with the subsequent identification of *ACTN4* [44, 45]. *ACTN4* is one of four actinin genes, and a member of the spectrin gene superfamily. It encodes a 100-kDa actin-binding protein that is involved in binding actin to the cell membrane. It is expressed in a wide range of tissues; however, it appears to be very highly expressed in podocytes. Mutated *ACTN4* binds filamentous actin more strongly *in vitro* than wild type, thus suggesting a role for *ACTN4* in the regulation of the podocyte cytoskeleton [45].

ACTN4-deficient mouse models had a lower survival rate, severe progressive proteinuria and podocyte foot process effacement [46]. For unclear reasons, despite the widespread expression of this gene, no other tissue abnormalities were observed. Recently, mutant *ACTN4* was shown to form large protein aggregates [47]. Additionally, when mutated, the *ACTN4* was less dynamic. The authors of these studies suggest that these protein aggregates are toxic to podocytes over time, as in diseases like Alzheimer's or Huntington's. Another proposal suggests that there is increased degradation of mutated *ACTN4*. Interestingly, the aforementioned dominant and recessive models demonstrate the importance of the *ACTN4* gene to normal kidney function.

Transient receptor potential cation channel 6

There is considerable genetic heterogeneity and pathogenesis of the autosomal dominant forms of nephrotic syndrome that cause FSGS. The most recently reported disease-causing mutation for hereditary FSGS is the transient receptor potential cation channel 6 (*TRPC6*) [48]. In this particular subset of families, affected individuals present in their third or fourth decade with high-grade proteinuria. Sixty percent of these individuals progress to ESRD disease within 10 years. A genomic screen performed in a New Zealand kindred mapped the locus of the disease to chromosome 11q21-22 [1]. Previously reported mutations in familial disease such as *NPHS1*, *NPHS2* and *ACTN4* have emphasized the importance of cytoskeletal and structural proteins in proteinuric kidney diseases. This is the first ion channel shown to cause a hereditary nephrotic syndrome and FSGS.

The TRP channels have been implicated in varied biological functions such as mechanosensation, ion homeostasis, cell growth and PLC-dependent calcium entry into cells. All of the TRP channels are six-transmembrane-spanning proteins that assemble as tetramers to form cation pores [49]. *TRPC6* is a 100-kDa protein with intracellular N and C termini; the fifth and sixth transmembrane domains form tetramers that line the pore of the ion channel. The *TRPC3,6,7* subfamily appear to co-assemble when heterologously expressed. Most TRP channels are not highly selective to cations and permit Na^+ as well as Ca^{2+} entry into cells. *TRPC6* is the most Ca^{2+} selective of the *TRPC3,6,7* subfamily. Additionally, *TRPC6* can be activated via the G protein-coupled receptor (GPCR) pathway. The mutation in this family was found in the first ankyrin repeat (P112Q) of *TRPC6*. Ankyrin-binding repeats in the N terminus are frequent elements in many TRP channels and modulate protein:protein interactions. The P112Q *TRPC6* mutation causes an increase in calcium influx into cells, with the hypothesis that this results in disrupted glomerular cell function or causes apoptosis [48]. Interestingly, stimulation by angiotensin II (AII) also causes higher peak intracellular Ca^{2+} changes in $TRPC6^{P112Q}$-transfected cells. AII acting through its AT1 receptor plays a critical role in the generation of proteinuria and progression of kidney injury.

Additional work has corroborated findings implicating *TRPC6* in the pathogenesis of autosomal dominant FSGS. Pollak and colleagues [50] found *TRPC6* mutations in five additional families. Two of these families were associated with an increase in calcium influx. This suggests that multiple mechanisms involving *TRPC6* abnormalities exist, which may result in dysregulation of the ion channel, or altered interaction with other slit diaphragm proteins. The exploration for interactions of *TRPC6* with the other known causes of hereditary FSGS and nephrotic syndromes as well as alterations in cellular signaling is an area deserving further study.

Discussion

Glomerular sclerosis is the final common pathway for a variety of kidney diseases such as diabetes mellitus and systemic lupus erythematosus. Abnormalities in the highly specialized glomerular podocyte such as foot process effacement and slit diaphragm alterations are common to all forms of nephrotic syndrome. Significant advances in understanding podocyte structure and function as well as protein interactions at the slit diaphragm have been made in recent years. The above-named genes highlight the heterogeneity of this pathological process.

Figure 1 is a diagram of our current understanding of the molecular composition of the podocyte foot process. Nephrin molecules from adjacent foot processes help form the porous slit diaphragm. The nephrin molecules interact with each other to form an ultrafilter structure creating the main size-selective filter barrier in the kidney [51]. Nephrin is also involved in signaling cascades

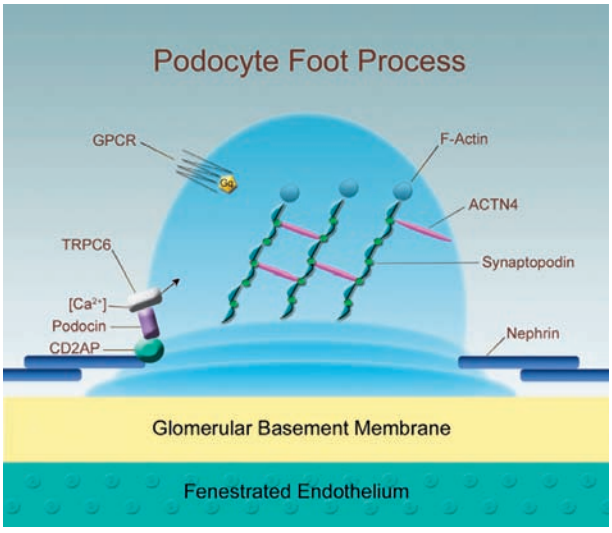

Figure 1. Proposed scheme of the podocyte foot process cytoskeleton. As illustrated by hereditary nephrotic syndromes, disruption of podocyte structure or signaling pathways involving the various podocyte proteins can lead to reorganization of the actin cytoskeleton and foot process effacement as seen in focal segmental glomerulosclerosis. TRPC6, transient receptor potential cation channel 6; ACTN4, alpha-actinin 4; CD2-AP, CD2-associated protein; F-actin, filamentous actin; GPCR, G protein-coupled receptor.

via phosphorylation of tyrosine in the intracellular cytoplasmic tail by Src kinase [52]. *CD2AP*, an intracellular protein, connects the cytoplasmic domain of nephrin to the cytoskeleton. The C terminus of podocin associates with *CD2AP* and nephrin at the slit diaphragm [39, 40]. Alpha-actinin 4 stabilizes the actin cytoskeleton by cross-linking actin filaments (F-actin).

It has been well established that mutations in nephrin, podocin, *CD2AP* [53] and alpha-actinin 4 cause proteinuria and nephrotic syndrome. What remains unanswered is whether treatment in individuals with hereditary nephrotic syndromes and FSGS should be tailored to specific gene mutations. We know that the vast majority of individuals with podocin mutations do not respond to steroids [54]. However, no prospective randomized controlled trials (RCTs) have been undertaken to specifically examine this question. There are reports that suggest treatment with chemo- or immunotherapy may delay the progression of ESRD in individuals with hereditary FSGS [55, 56]. While hereditary forms of these diseases certainly do not account for the majority of individuals, screening individuals with sporadic forms of familial nephrotic syndromes and FSGS for disease-specific mutations will help to increase the utility of future prospective RCTs aimed at predicting drug responsiveness. Additionally, it will provide an accurate estimate of the prevalence of mutations in the sporadic population. By understanding genotype/phenotype correlations, one may be able to apply pharmacogenetics to maximize efficacy and minimize drug toxicity. Potential novel therapeutic avenues may also be developed.

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