Review Article

Understanding podocytopathy and its relevance to clinical nephrology

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ABSTRACT

Podocytopathies are the most common group of glomerular disorder leading to proteinuria. On the basis of pathophysiology, light microscopic and ultrastructural evaluation, the podocytopathies include minimal change disease, diffuse mesangial sclerosis, focal segmental glomerulosclerosis and collapsing glomerulopathy. The present review summarizes the basic etiopathogenesis of podocytopthies, highlights the common genetic and acquired factors in its causation, puts forth various diagnostic modalities and discusses the role of emerging agents or treatment.

Key words: Collapsing glomerulopathy, diffuse mesangial sclerosis, focal segmental glomerulosclerosis, minimal change disease, podocytopathy, proteinuria

Introduction

Recent years have seen the emergence of a plethora of research in the field of podocyte biology and podocytopathies. Decoding the complex molecular language of basic research is a major challenge. The present review aims at the analysis of current literature and underscores the importance of basic understanding of podocyte biology in the routine practice. This review will provide an insight to the pathobiology of podocytopathies, mechanism of podocyte injury, phenotypic variations of podocytes, and the diagnostic and therapeutic agents available till date.

Definition

Podocytopathies are the group of glomerular diseases in which proteinuria is attributed to damage or dysfunction of podocytes.[1,2]

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Pathobiology of Podocytes

Podocyte is a terminally differentiated cell with specialized functions owing to its unique structural and functional properties. The functions of podocytes include: (1) regulation of glomerular permselectivity;[3] (2) maintenance of structural integrity of the glomerulus;[4] (3) remodeling the glomerular basement membrane (GBM);[5] (4) endocytosis of filtered proteins;[6] (5) counteracting the intracapillary hydrostatic pressure; (6) secretion of vascular endothelial growth factor required for proper functioning;[7] and (7) production of platelet-derived growth factor, which has trophic properties for neighboring mesangial cells.[8]

The functional or structural alteration in the podocytes may be due to inherited or acquired factors [Table 1].[9] With the increase in the identification of specific defects, the idiopathic group is becoming smaller.

Barisoni *et al*. proposed that podocytes react to injurious stimuli in limited manner, which may include: (1) phenotype modification as foot process effacement, with no alteration in podocytes number; (2) apoptosis and loss of podocyte; (3) developmental arrest accompanied by mild proliferative activity; and (4) dedifferentiation and re-entrance into the cell cycle with marked proliferative activity.

Thus, four histological patterns of podocytopathies are identified: (1) minimal change nephropathy (MCN), if

Table 1: Abnormality and or dysfunction of various intrinsic and extrinsic factors associated with podocytopathies

Intrinsic factors	Extrinsic factors
Transcriptional regulators: WT1, PAX-2, WTIP, LIM homeobox transcription factor 1β	**Infections:** Circulating viral protein, lipopolysaccharides
Alteration of slit diaphragm complex: Nephrin, podocin, CD2AP, FAT-1, FAT-2, ZO-1 Cytoskeletal abnormality: ACTN-4 mutation	**Toxic:** Medication (pamidronate, interferon), toxin (puromycin aminonucleoside, adriamycin)
Luminal and abluminal proteins: α-β dystroglycans, podocalyxin, TRPC6	**Lymphokine or other host protein:** IFN-α, IFN-β, FSGS permeability factor, TGF-β
Cytoplasmic proteins: PLCε1 Mitochondria: tRNA mutation, COQ2 mutation	**Mechanical:** Obesity, hyperfiltration, acute ischemia associated with thrombotic microangiopathy
Metabolic: Fabry's, SCARB2/ LIMP-2	**Immunologic:** Lupus, IgA nephropathy, membranous nephropathy
Extracellular matrix: LAMB2	**Metabolic:** Diabetes Miscellaneous: Stress induced induction of CD80

WT1: Wilms tumor 1, WTIP: Wilms tumor 1 interacting protein, TGF-β: Transforming growth factor beta, FSGS: Focal segmental glomerulosclerosis, IFN-α: Interferon-alpha, IFN-β: Interferon-beta, PLCε1: Phospholipase Cε1, LAMB2: Laminin beta 2, LIMP-2: Lysosomal integral membrane protein type 2, TRPC6: Transient receptor potential cation channel 6, ZO-1: Zonula occludens 1

the number of podocytes per glomerulus is unchanged; (2) focal segmental glomerulosclerosis (FSGS), if there is podocytopenia; (3) diffuse mesangial sclerosis (DMS), where low proliferative index has been described; and (4) collapsing glomerulopathy (CG), if there is marked proliferation.[9]

Mechanisms of Injury in the Primary Podocytopathies

Role of transcriptional regulators

Wilms tumor 1 (WT1), a zinc finger protein, regulates podocyte differentiation. All renal progenitor cells express WT1 during early development, but on nephron maturation it is confined to podocytes. Altered WT1 protein content or *WT1* gene mutation are noted in genetic or acquired forms of podocytopathies, such as steroid-resistant FSGS,[10] DMS,[11] and CG.[12]

PAX2, is another transcriptional regulator related to WT1, which regulates early kidney development. As the glomerulus matures the expression of PAX2 decreases, while that of WT1 increases. Persistent expression of PAX2 is implicated in the development of nephrotic syndrome in humans as well as experimental models.[13]

Another important transcription factor in causation of podocytopathies is LIM homeobox transcription factor 1β (Lmx1b). It is mutated in patients of nail-patella syndrome.[14] It regulates the expression of *COL4A3* and *COL4A4* genes, and podocin encoding gene *NPHS2*. Thus, the mutation of Lmx1b is associated with abnormal collagen deposition in the GBM, alteration in slit diaphragm and development of mesangial and segmental sclerosis.[15]

The Notch signaling is important in podocyte cell fate determination during early embryogenesis. Waters *et al*. through their experimental model showed that the constitutive Notch signaling is deleterious, leading to altered podocyte function, proteinuria and glomerulosclerosis.[16] Role of Wnt pathway in the causation of podocytopathies is still debated.

Altered components of the slit diaphragm complex

The discovery of NPHS1 gene, encoding nephrin by Kestila *et al*. was the stepping stone in the direction of establishing the role of slit diaphragm component in causation of nephrotic syndrome.[17] The NPHS1 mutation was found to be responsible for congenital nephrotic syndrome of Finnish type. The discovery of NPHS1 was closely followed by the identification of another slit diaphragm component protein podocin encoded by NPHS2. Mutated NPHS2 was first described in patients with steroid resistant nephrotic syndrome.[18] The various components of the slit diaphragm are shown in Figure 1.

Abnormal assembly or function of the actin-based cytoskeleton

The α4-actinin gene, ACTN4, encodes a protein, which links the cell membrane to the cytoskeleton. The mutation of ACTN4 leads to autosomal dominant familial FSGS.[19] The peculiarity of ACTN4 mutation associated nephrotic syndrome is that the manifestation of disease is relatively late. Thus, it can be hypothesized a second "hit" is necessary to disrupt the cytoskeletal apparatus even if α4-actinin is mutated.[20]

Expression and localization of membrane (abluminal and luminal side) proteins

α3β1-integrin and the dystroglycan complex are important component involved in cell matrix interaction.[21] The loss of these anchoring factors decrease cell adhesion which may cause podocyte detachment and loss, resulting in podocytopenia and FSGS.

The importance of extracellular matrix in regulating cell adhesion and foot process can be inferred from the fact that patients of Alport disease eventually develop FSGS.

Regele *et al*. in their study found that in MCN, protein expression of α-dystroglycan was reduced by 75% and

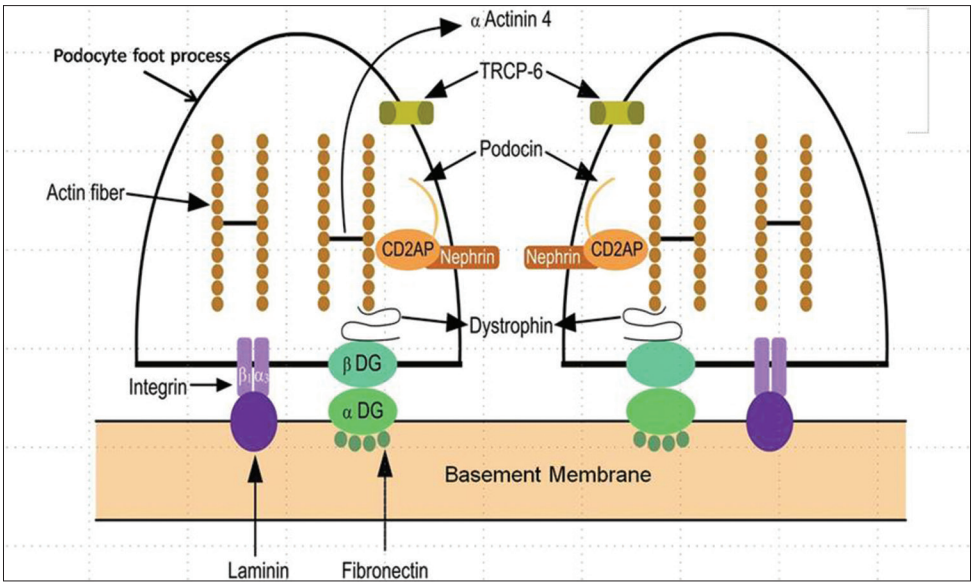

Figure 1: Slit diaphragm. The schematic diagram shows that the molecular complex of nephrin, podocin and CD2AP forms a specialized junction between podocyte foot processes. α-Actinin four cross-links various actin filaments. The interaction between α3β1 and dystroglycans with laminin and fibronectin, respectively help in stabilization of podocyte interaction with glomerular basement membrane. Transient receptor potential cation channel 6 (TRCP6), regulates intracellular calcium in podocytes

that of β-dystroglycan, by 50%, whereas expression of both dystroglcyans was normal or slightly increased in FSGS.[22]

The canonical transient receptor potential cation channel 6 (TRPC6), is located in the luminal side of the podocyte cell membrane, the mutated form of this protein is identified in the cases of FSGS.[23,24] Though, the mechanism by which it causes FSGS is not clear, it possibly causes a gain of function and increased intracellular calcium.

Podocalyxin is a cell membrane sialoprotein, which imparts a negative charge to podocyte cell membrane. Podocalyxin dysruption or neutralization of its negative charge may results in dissociation of the cell membrane from the cytoskeleton and foot process effacement.[25]

Dysfunction of cytoplasmic proteins

Phospholipase Cε1 (PLCε1) encoded by PLCE-1 regulates many G-protein-coupled receptors. It has an important role in the development of nephron. Lack of PLCε1 causes impairment of normal nephron development and leads to reduced nephrin and podocin expression. In childhood nephrotic syndrome the truncated mutation of PLCE1, may lead to DMS.[26] In "idiopathic" DMS the commonest genetic abnormality is truncating mutation of PLCε1.[27]

Mitochondrial injury

Mitochondrial injury has been described as both primary or secondary process in nephrotic syndrome.[28-32] The mechanism by which mitochondrial injury causes podocytopathic effects is still elusive. The various proposed mechanisms are: (1) Mitochondria are pivotal for cell motility through their interaction, with outer membrane protein zyxin and with the actin cytoskeleton. Thus, mitochondrial abnormality may lead to effacement in a cytoskeleton-dependent manner.[33] (2) These are mediators of apoptotic stimuli, which is proposed to cause development of segmental sclerosis.

Metabolic diseases

The lysosomal storage diseases like Fabry disease, due to mutation in gene encoding α-galactosidase A (α-GAL A) and action myoclonus-renal failure, due to a mutation in a gene encoding a lysosomal protein (SCARB2/LIMP-2) lead to FSGS.[34] The exact mechanism is still obscure however, two major processes proposed are: (1) Defective activity of α-GAL A in Fabry's results in accumulation of globotriaosylceramide in endothelial cells of the microvasculature which may further lead to chronic ischemic changes, leading to podocyte damage and death. (2) Accumulation of globotriaosylceramide in podocytes may be directly lethal to these postmitotic cells.

Extracellular matrix protein

Basement membrane protein laminin β2 encoded by LAMB2 gene is implicated in the causation of congenital nephrotic syndrome. Laminin β2 is a major BM constituent that play important roles in cell adhesion, proliferation, differentiation and migration.[35]

Inducible B7-1 in the Pathogenesis of Podocytopathies

CD80 (also known as B7-1) is a 53 kD membrane associated protein. In the immune system, it is located on B-lymphocytes and antigen presenting cells where it acts as a costimulatory receptor with role in T-cell activation.[36] In the glomerulus, it is localized exclusively in podocytes under stress conditions.[25,36] Puromycin induced CD80 activation in cultured podocytes has been shown to attenuate nephrin expression and results in foot process effacement.[37] The role of CD80 in podocyte pathobiology was studied by Reiser *et al*. in an experimental model where lipopolycaccharide injection in mice, resulted in increased expression of CD80 in podocytes and proteinuria, while no proteinuria occurred in CD80 knockout mice. Studies by Garlin *et al*. indicate that urinary excretion of CD80 could be used to differentiate between patients with the relapsed minimal change disease and FSGS. Yu *et al*. have recently found that CD80-positive podocytes have a reduced capacity to attach to the surrounding matrix through β1 integrin.[38] They found that CD80-positive podocytes change their morphologic characteristics, leading to podocyte foot processes detachment from the GBM and thus proteinuria.

Epithelial Mesenchymal Transition - Does it has Role in Pathogenesis of Podocytopathies?

The loss of epithelial phenotype with gain of mesenchymal characters has recently been implicated in pathogenesis of podocytopathies. The loss of epithelial markers such as P-cadherin, ZO-1, and nephrin, and the acquisition of mesenchymal markers such as FspI, desmin, collagen I and fibronectin by injured podocyte support the notion of podocyte epithelial mesenchymal transition (EMT). Since P-cadherin, ZO-1, and nephrin are important slit diaphragm component,[39] their loss has detrimental effect on the mature podocyte and leads to its dedifferentiation and loss of integrity of the slit diaphragm.

Podocytes normally produce type IV collagen and laminin, the major components of the GBM. By producing the interstitial matrix components, type I collagen and fibronectin, podocytes adapt to a mesenchymal phenotype after injury, which profoundly change their functions. One interesting observation is the striking induction of matrix metallopeptidase 9 (MMP-9) expression in injured podocytes. As the specific substrates for MMP-9 are type IV collagen and laminin,[40] elevation of the secreted MMP-9 would inevitably cause the remodeling of GBM.

Diagnosis of Podocytopathies

Morphological

The four types of podocytopathies diagnosed on light microscopic [Figure 2] and ultrastructural analysis [Figure 3] include: (1) Minimal change disease; (2) FSGS; (3) DMS; and (4) CG.

MCN is usually characterized by normal light microscopy picture. On ultrastructural examination, there is extensive podocyte foot process effacement, condensation of the actin-based cytoskeleton against the "sole" of the podocyte and there is microvillous transformation.

In FSGS, there is segmental solidification of the glomerular tuft with accumulation of extracellular matrix, often with an adhesion (synechia) between the capillary tuft and Bowman's capsule. Hyalinosis and foam cells also can be present.

DMS is characterized by mesangial expansion due to extracellular matrix protein accumulation. It is often accompanied by podocyte hypertrophy and mild hyperplasia.

Collapsing glomerulopathy is defined by the presence of segmental capillary tuft collapse (wrinkling and folding) in at least 1 glomerulus, in association with podocyte hypertrophy and/or hyperplasia.

Immunohistochemistry

Danilewiczn *et al*. showed diminished immunoexpression of podocalyxin and its significant correlation with the level of proteinuria in FSGS patients.[41] Nowicka *et al*. studied immunohistochemical expression of the podocyte-associated proteins, particularly ezrin, podocalyxin, synaptopodin, and nephrin in glomeruli with and without signs of immaturity. They found that in cases of diffuse mesangial proliferation with signs of immaturity, podocytes situated in the central region of the glomerulus were negative for podocyte associated proteins such as ezrin, podocalyxin, synaptopodin, and nephrin, while immunopositivity was observed in the outer continuous "layer" of podocytes. They attributed unfavorable clinical course of DMS and steroid resistant FSGS to glomerular immaturity, which may be a consequence of decreased immunohistochemical expression of cytoskeleton-specific proteins.[42]

Circulating biomarkers

The possibility of circulating factor in the causation of FSGS was speculated as it frequently reoccurs shortly after renal transplant and often develops as a de novo disease in the transplanted kidney.[43] The major advancement in this

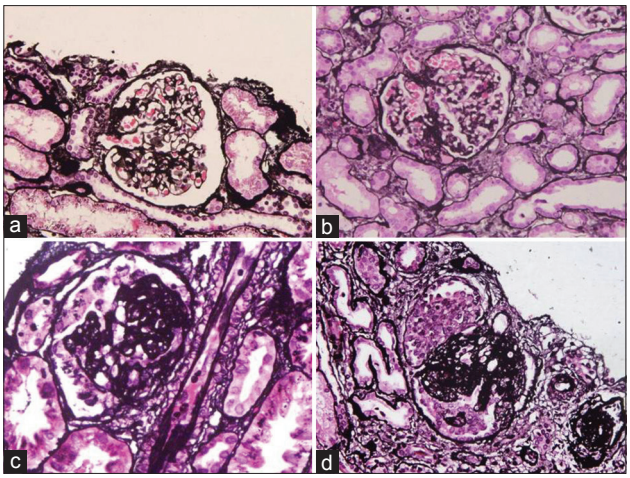

Figure 2: (a) Photomicrograph shows minimal change disease. Glomerulus appears normal by light microscopy (silver methanamine, x200). (b) Focal segmental glomerulosclerosis: There is segmental sclerosis characterized by increase in mesangial matrix and obliteration of capillary lumina (silver methanamine, x200). (c) Diffuse mesangial sclerosis: There is dense sclerosis with obliteration of capillary tuft (silver methanamine, x200). (d) Collapsing glomerulopathy: There is collapse of glomerular tuft and hyperplasia of overlying visceral epithelial cells. An occasional resorption droplets are also noted (silver methanamine, x200)

direction was the discovery by Wei *et al*. of a circulating permeability factor, soluble urokinase-type plasminogen activator receptor (suPAR) linked to the development of FSGS in humans and mice.[44] These authors demonstrated the elevated plasma suPAR levels in two third of FSGS patients. The higher levels of suPAR correlated with the higher rate of recurrence of FSGS in transplanted kidneys and the plasmapheresis led to remission of disease in recurrent FSGS cases. The suPAR binds and activates β3 integrins, which in turn leads to altered podocyte foot process dynamics, with dysregulation of its shape and function.[44] Though the source of suPAR is still under investigation inflammatory cells including neutrophill, monocyte and T cells are speculated as the source.[44] The discovery of suPAR as the diagnostic tool and a therapeutic target for FSGS is still under investigation but seem promising.[44]

Urine biomarkers

The search of suitable urinary biomarkers is imperative as a noninvasive tool for the diagnosis of podocytopathies. Though none of the podocyte restricted proteins have translated to the level of routine diagnostics, an array of proteins have been found to be indicator of podocyte injury such as nephrin, podocin, podocalyxin, CR1, CD80, synaptopodin, GLEPP-1, mindin, alpha 3 integrin, CD59, and WT1 protein. These proteins can be detected by various methods like immunofluorescent staining, western blot, enzyme-linked immunosorbent assay (ELISA), flow cytometry, and mass spectrometry.[45]

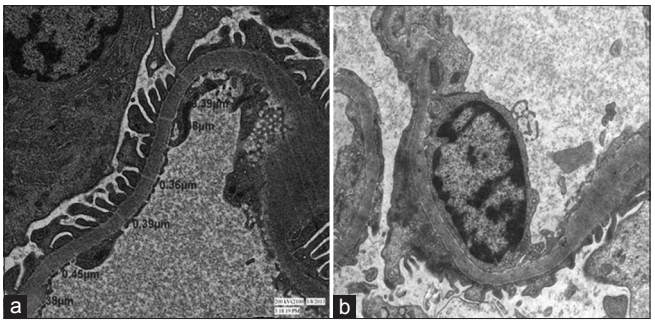

Figure 3: (a) Transmission electron microscope photomicrograph shows a normal podocyte foot process (x2100). (b) Minimal change disease with extensive foot process effacement with microvillus transformation. Glomerular basement membrane is normal and there are no electron dense deposits (x2100)

Furthermore, polymerase chain reaction can be used to quantify podocyte specific messenger ribonucleic acid (mRNA) in the urine sample of patients with glomerular diseases.[46-50]

Mutation analysis

Though a whole array of genetic defects are implicated in the causation of hereditary nephrotic syndrome, seven main genes implicated in the causation of nonsyndromic podocytopathies are NPHS1, NPHS2, CD2AP, PLCE1, ACTN4, TRPC6, and INF2.[17-19,24,26,51,52] The proteins encoded by these genes are nephrin, podocin, CD2AP, PLCε1, α-actinin4, TRPC6 and a member of the formin family of actin-regulating proteins, respectively. The inheritance pattern of CD2AP, ACTN4, TRPC6, and INF2 are autosomal dominant, while that of NPHS-1, NPHS-2 and PLCE1 are autosomal recessive. In a review of hereditary nephrotic syndrome Benoit *et al*. have suggested that in patients with nonsyndromic congenital nephrotic syndrome, the first gene to be screened for the evidence of genetic mutation should be NPHS1 gene. This gene should also be tested in all infants with nephrotic syndrome with typical proximal tubular radial dilatation on renal biopsy.

However, in patients with infantile nephrotic syndrome showing MCD or FSGS the first gene to be tested should be NPHS-2 followed by NPHS-1. In cases where the renal biopsy reveals DMS the genetic testing of WT1 and PLCE1 genes is warranted.

Emerging Treatment Options According to the Understanding of Podocytopathies

Stabilization of actin cytoskeleton

Stabilization of actin cytoskeleton of podocytes has emerged as an important off target mechanism of Rituximab. It is now being widely used in the recurrent FSGS after kidney transplant. The mechanism of action is believed

to be due to its binding to acid sphingomyelinase-like phosphodiesterase 3b protein (SMPDL-3b), a putative acid-sphingomyelinase (ASMase). It thus protects the podocyte from the down-regulatory effects of recurrent FSGS sera on SMPDL-3b and ASMase.[53]

The therapeutic effect of cyclosporine in podocytopathies has been believed to be via nonimmune mechanism. The cyclosporine causes inhibition of calcineurin, which helps in the preservation of synaptopodin: 14-3-3β interaction and maintenance of podocyte stress fibers.[54]

Yu *et al*. have found that abatacept (an inhibitor of B7-1) cures patients with severe nephrotic syndrome due to primary FSGS or recurrent FSGS after transplantation by ameliorating CD80 induced changes in podocyte morphology.

Agents for the replenishment of podocytes in podocytopenic conditions

This particular approach may be useful in podocytopenic condition like FSGS. Fibroblast growth factors are investigated agent in this area.[55]

Agents for podocyte replacement

The division inhibitors in conjunction with agents leading to cell differentiation may be useful therapeutic agent in podocytopathies associated with cell proliferation like CG.

The role of cyclin-dependent kinase inhibitors and glycogen synthetase kinase-3 inhibitors is being studied in this direction.[56]

Conclusion

With new insight in the pathobiology of podocytes various non-invasive methods of screening are emerging. The frequency of true idiopathic cases is decreasing and will continue to decrease as we learn more about the pathobiology of the podocytopathies. Mutational screening in the steroid resistant nephrotic syndrome may obviate the need of immunosuppression in the patients with genetic structural defects in podocytes. Not only this, the understanding of the podocyte structure and function will pave way for the better targeted therapy with less systemic side effects.

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